Overview
- Review background on CRE and testing issues in clinical labs
- Review criteria for submitting isolates for confirmatory test
- Laboratory reports and interpretation of results
- Share preliminary results of MDCH confirmation testing to date
- Questions

CRE Update 2013: CRE Confirmation Testing in Michigan
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Spread of Carbapenem-Resistant Enterobacteriaceae in US
http://www.cdc.gov/hai/organisms/cre/TrackingCRE.html

CRE: Issues with Laboratory Detection
- CRE = Carbapenem-Resistant Enterobacteriaceae
- Bacteria produce enzyme (carbapenemase) – hydrolyzes antibiotics ("super" Beta-lactamases – worse than ESBL)
  - KPC
  - NDM
  - VIM, IMP…?
- Bacteria that produce enzyme do not always test resistant to carbapenems using current FDA interpretive breakpoints and common Antimicrobial Susceptibility Testing (AST) methods. (Some CRE test as "S"
- Sensitivity of detection varies by which carbapenem is tested

CRE: Issues with Laboratory Detection
- CLSI* recommends different breakpoints
- Now 2 sets of acceptable breakpoints
- Same MIC value has different interpretation (S, I or R) depending on which set used
- Laboratories using commercial systems and automated instruments [Microscan, Vitek, Phoenix] for AST must use FDA-cleared breakpoints, unless they do their own validation studies for CLSI bkpts
- Identification of a carbapenemase in isolates that test susceptible to carbapenems creates problems in reporting results

*CLSI = Clinical and Laboratory Standards Institute

MIC Interpretive Breakpoints
Current FDA, “Old” CLSI (2009)

<table>
<thead>
<tr>
<th>Antimicrobial</th>
<th>S (ug/mL)</th>
<th>I (ug/mL)</th>
<th>R (ug/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Imipenem</td>
<td>&lt;=4</td>
<td>8</td>
<td>&gt;=16</td>
</tr>
<tr>
<td>Meropenem</td>
<td>&lt;=4</td>
<td>8</td>
<td>&gt;=16</td>
</tr>
<tr>
<td>Ertapenem</td>
<td>&lt;=2</td>
<td>4</td>
<td>&gt;=8</td>
</tr>
<tr>
<td>Doripenem</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>
CLSI Changed breakpoints in June 2010

<table>
<thead>
<tr>
<th>Antimicrobial</th>
<th>S</th>
<th>I</th>
<th>R</th>
<th>S</th>
<th>I</th>
<th>R</th>
</tr>
</thead>
<tbody>
<tr>
<td>Imipenem</td>
<td>&lt;=4</td>
<td>8</td>
<td>&gt;=16</td>
<td>&lt;=1</td>
<td>2</td>
<td>&gt;=4</td>
</tr>
<tr>
<td>Meropenem</td>
<td>&lt;=4</td>
<td>8</td>
<td>&gt;=16</td>
<td>&lt;=1</td>
<td>2</td>
<td>&gt;=4</td>
</tr>
<tr>
<td>Ertapenem</td>
<td>&lt;=2</td>
<td>4</td>
<td>&gt;=8</td>
<td>&lt;=0.5</td>
<td>1</td>
<td>&gt;=2</td>
</tr>
<tr>
<td>Doripenem</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>&lt;=1</td>
<td>2</td>
<td>&gt;=4</td>
</tr>
</tbody>
</table>

Further CLSI Recommendations
- For labs not switching to new breakpoints:
  - Add Modified Hodge Test to detect carbapenemase producers that test “S” when using old breakpoints:
    - Ertapenem = 2
    - Imipenem, Meropenem = 2-4
- And in 2012: If using old breakpoints and MHT positive, change all carbapenems to R if values fall within ranges:
  - Ertapenem = 2-4
  - Imipenem, Meropenem = 2-8

Modified Hodge Test

2010: CLSI recommends addition of MHT to detect CRE that test susceptible

Lab Survey 2012 (n=49)
Additional testing performed on suspect CRE

Criteria for Isolates if laboratory is using FDA breakpoints
- Look at instrument results for Enterobacteriaceae isolates (no Pseudomonas, no Acinetobacter)
- If carbapenem I or R, submit to MDCH lab for CRE confirmatory testing
- If carbapenem = S, look at numerical MIC value(s):

Criteria for MDCH CRE confirmatory testing of Enterobacteriaceae using OLD (2010 or CLSI) or FDA (2012 or old) carbapenem breakpoints

- Look at instrument results (Vitek®, Microscan®, Phoenix™)
- Check MIC values of carbapenems. Are any of the following true?
  - Imipenem MIC is = 2 or 4 ug/ml
  - Meropenem MIC is = 2 or 4 ug/ml
  - Ertapenem MIC is = 1 or 2 ug/ml
- Perform MHT (Modified Hodge Test)
- Submit isolate to MDCH lab for CRE confirmation

**If your laboratory is not doing the MHT, we encourage you to do so.**
Criteria for isolates if laboratory is using “newer” CLSI breakpoints

Enterobacteriaceae reported out as I or R by automated instrument

Submit to MDCH lab for CRE confirmation

January 2013

MIC
MHT +
KPC or NDM-1

What to Submit

• Pure culture on agar slant (no plates!)
• Copy of lab results (MIC, MHT)
• Any species of Enterobacteriaceae that fits criteria
  • E coli
  • Klebsiella
  • Enterobacter
  • Citrobacter
  • NOT Pseudomonas
  • NOT Acinetobacter

What to Submit

• E coli
• Klebsiella
• Enterobacter
• Citrobacter
• Serratia
• Proteus*
• Providencia*
• Morganella*
• NOT Pseudomonas
• NOT Acinetobacter

*These species have intrinsic resistance to Imipenem.
Suspect CRE if other carbapenems are I or R.

Use the most current version of our DCH 0583 requisition form

Use the most current version of our DCH 0583 requisition form

It’s still 2 pages

MDCH homepage

Click here

MDCH homepage

MDCH homepage

Click here

Prevent Disease – Promote Wellness – Improve Quality of Life

Prevent Disease – Promote Wellness – Improve Quality of Life

Prevent Disease – Promote Wellness – Improve Quality of Life

Prevent Disease – Promote Wellness – Improve Quality of Life
We also Need Your Results

- Identification and AST
- Instrument printout preferred
  - Especially if using cascade/suppressed reporting algorithms
  - Need carbapenem and 3rd generation cephalosporin results
- Modified Hodge test result – record “MHT Pos” or “MHT Neg” on test req or your instrument printout

Testing at MDCH

- Gram Stain
- Confirm organism ID (after subculture for fresh growth)
- Reference method MIC
  - (CLSI broth microdilution using frozen panels)
- Modified Hodge Test
- PCR for KPC and NDM-1 genes as indicated by results of above testing

Reporting

- KPC PCR result
  - KPC (blaKPC) gene DNA Detected
  - KPC (blaKPC) gene DNA Not Detected
- NDM-1 PCR result
  - NDM (blaNDM) gene DNA Detected
  - NDM (blaNDM) gene DNA Not Detected
- “Unsatisfactory” if amplification is inhibited (after repeat testing)

MDCH using 2012 CLSI breakpoints

Results to Date 3/29/2013

- Number Isolates submitted = 104
- Reported 99, including 13 that did not meet criteria and were not tested by PCR (5 pending)
- 86 isolates met criteria and were tested by PCR
- Number KPC positive = 34 / 86 = 41% positivity
- 34 / 35 KPC positive were Modified Hodge Test positive at MDCH
KPC positive* isolates (N=35)

KPC Positive isolates (N=35) confirmed by PCR

KPC Positive isolates (% of total tested per species)

Positive Isolates/ No. tested by Region

KPC Positive isolates by source

KPC positive isolates by source

MIC Values in KPC Positive Isolates MDCH Data – 2012 CLSI breakpoints

Ertapenem MIC Values in KPC Positive Isolates MDCH Data 2012 CLSI breakpoints
Discrepant Results
• 43 isolates matched everything - ID, MHT results (where provided) and MIC values within +/- one twofold dilution
• Two isolates with MHT difference only
• Eight isolates = different identifications
  • 1 MHT discrepant
  • 1 MIC value discrepant
  • 1 everything mismatched (wrong bug sent?)
• Twenty-three isolates with 1 drug MIC >= 2 twofold dilutions difference
• Ten isolates with 2 drugs MIC >= 2 twofold dilutions difference
• Two isolates with 3 drugs >= 2 twofold dilutions difference

Discrepancies in ID

<table>
<thead>
<tr>
<th>Clinical Lab ID</th>
<th>MDCH ID</th>
<th>Other discrepancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>E. coli</td>
<td>Ps. aeruginosa</td>
<td>Not tested</td>
</tr>
<tr>
<td>GNR</td>
<td>Acinetobacter sp.</td>
<td>Not tested</td>
</tr>
<tr>
<td>GNR</td>
<td>Klebsiella sp.</td>
<td>None</td>
</tr>
<tr>
<td>K. pneumoniae</td>
<td>P. mirabilis</td>
<td>None</td>
</tr>
<tr>
<td>C. freundii complex</td>
<td>E. coli</td>
<td>None</td>
</tr>
<tr>
<td>E. coli</td>
<td>C. freundi</td>
<td>ceftazidime (16, 64)</td>
</tr>
<tr>
<td>C. freundii</td>
<td>C. gattii</td>
<td>MHT (Pos, Neg)</td>
</tr>
<tr>
<td>E. cloacae</td>
<td>E. coli</td>
<td>All results</td>
</tr>
</tbody>
</table>

Beta lactam MIC values in KPC positive isolates
MDCH Data 2012 CLSI breakpoints

<table>
<thead>
<tr>
<th>MIC Value in ug/mL</th>
<th>Cefoxitin</th>
<th>Ceftriaxone</th>
<th>Aztreonam</th>
<th>R breakpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cefoxitin</td>
<td>6 isolates</td>
<td>I to Cefotaxim</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Beta lactam MIC values in KPC negative isolates
MDCH Data 2012 CLSI breakpoints

<table>
<thead>
<tr>
<th>MIC Value in ug/mL</th>
<th>Cefoxitin</th>
<th>Ceftriaxone</th>
<th>Aztreonam</th>
</tr>
</thead>
</table>
Questions

• We are using the FDA breakpoints. Should we change S or I cefoxitin (i.e., cephapirin) results on KPC positives?
• "KPC+ isolates should test R to cefoxitin. It would be safe to change I or S to R if MHT pos. If this is happening for multiple isolates from multiple patients then there should be concern about inaccurate test results either from the instrument or the MHT." Dr. Jean Patel, CDC

Questions

• Should we send repeat isolates from the same patient if from a different source or date of admission?
• When can we quit sending our isolates?
• Is there an easier method for doing surveillance cultures?
• Is there PACE credit for the webinar?

Thank you!