Laboratory Detection and Reporting of CRE

June 6, 2014
Featured Presenters

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Director, Collaborative Research Unit
Cook County Health & Hospitals System

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Rush University Medical Center

The opinions, viewpoints, and content presented in this webinar may not represent the position of the Illinois Department of Public Health
Laboratory Detection and Reporting of CRE

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Loyola University Medical Center
pschrecken@lumc.edu
Learning Objectives

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

1. Describe mechanisms of carbapenem resistance

2. List criteria to be used for screening laboratory isolates for CRE

3. Describe the procedure, interpretation and application of the Hodge Test and MBL Etest.

4. List the pitfalls of susceptibility testing for the detection of CRE

5. Prepare appropriate comments for reporting CRE
# Financial Disclosures

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<thead>
<tr>
<th>Type of Affiliation/Financial Interest</th>
<th>Name of Commercial Interest</th>
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<tr>
<td>Salaried Employee</td>
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<td>Stocks/Stock Options</td>
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<tr>
<td>Independent contractor/Speaker’s Bureau</td>
<td>bioMerieux, Cubist, Forest Laboratories, Hardy Diagnostics, Merck, Remel, Siemens</td>
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<td>Consultant/Advisory Committees</td>
<td>Abbott Molecular, BioFire, Forest Laboratories, Quidel, Thermo Fisher Scientific, Theravance</td>
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<td>Research Grants</td>
<td>Abbott Molecular, Becton-Dickinson, BioFire, bioMerieux, Cepheid, Siemens</td>
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</table>
Penicillin nucleus

Cephalosporin nucleus
The β-lactam family of antibiotics

- **Penicillins**
  - Benzylpenicillin
  - Methicillin
  - Ampicillin
  - Carbenicillin
  - Mezlocillin
  - Ticarcillin

- **Cephalosporins**
  - Cephalothin 1st
  - Cefamandole 2nd
  - Cefuroxime 2nd
  - Cefotaxime 3rd
  - Ceftazidime 3rd
  - Ceftriaxone 3rd
  - Cefepime 4th

- **Cephamycins**
  - Cefoxitin
  - Cefotetan
  - Cefmetazole

- **Carbapenems**
  - Imipenem
  - Meropenem
  - Ertapenem
  - Doripenem

- **Monobactams**
  - Aztreonam
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>
<th>Cephalosporins</th>
<th>Cephamycins</th>
<th>Carbapenems</th>
<th>Monobactams</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzyl-penicillin</td>
<td>Cephalothin 1\textsuperscript{st}</td>
<td>Cefoxitin</td>
<td>Imipenem</td>
<td>Aztreonam</td>
</tr>
<tr>
<td>Methicillin</td>
<td>Cefamandole 2\textsuperscript{nd}</td>
<td>Cefotetan</td>
<td>Meropenem</td>
<td></td>
</tr>
<tr>
<td>Ampicillin</td>
<td>Cefuroxime 2\textsuperscript{nd}</td>
<td>Cefmetazole</td>
<td>Ertapenem</td>
<td></td>
</tr>
<tr>
<td>Carbenicillin</td>
<td>Cefotaxime 3\textsuperscript{rd}</td>
<td></td>
<td>Doripenem</td>
<td></td>
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<tr>
<td>Mezlocillin</td>
<td>Ceftazidime 3\textsuperscript{rd}</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ticarcillin</td>
<td>Ceftriaxone 3\textsuperscript{rd}</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cefepime 4\textsuperscript{th}</td>
<td></td>
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ESBLs hydrolyze all
Penicillins
Cephalosporins
Monobactams
The β-lactam family of antibiotics

- **Penicillins**
  - Benzylpenicillin
  - Methicillin
  - Amoxicillin
  - Carbenicillin
  - Ticarcillin

- **Cephalosporins**
  - Cephalothin 1st
  - Cefamandole 2nd
  - Cefuroxime 2nd
  - Cefotaxime 3rd
  - Ceftazidime 3rd
  - Ceftriaxone 3rd

- **Cephamycins**
  - Cefoxitin
  - Cefotetan
  - Cefmetazole

- **Carbapenems**
  - Imipenem
  - Meropenem
  - Ertapenem
  - Doripenem

- **Monobactams**
  - Aztreonam

ampCs hydrolyze all Penicillins, Cephalosporins except 4th generation (cefepime), Cephamycins, Monobactams
The β-lactam family of antibiotics

<table>
<thead>
<tr>
<th>Penicillins</th>
<th>Cephalosporins</th>
<th>Cephamycins</th>
<th>Carbapenems</th>
</tr>
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<tr>
<td>Benzyl-penicillin</td>
<td>Cephalothin 1&lt;sup&gt;st&lt;/sup&gt;</td>
<td>Cefoxitin</td>
<td>Imipenem</td>
</tr>
<tr>
<td>Methicillin</td>
<td>Cefamandole 2&lt;sup&gt;nd&lt;/sup&gt;</td>
<td>Cefotetan</td>
<td>Meropenem</td>
</tr>
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<td>Ampicillin</td>
<td>Cefuroxime 2&lt;sup&gt;nd&lt;/sup&gt;</td>
<td>Cefmetazole</td>
<td>Ertapenem</td>
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<tr>
<td>Carbenicillin</td>
<td>Cefotaxime 3&lt;sup&gt;rd&lt;/sup&gt;</td>
<td></td>
<td>Doripenem</td>
</tr>
<tr>
<td>Mezlocillin</td>
<td>Ceftazidime 3&lt;sup&gt;rd&lt;/sup&gt;</td>
<td></td>
<td></td>
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<td>Ceftriaxone 3&lt;sup&gt;rd&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cefepime 4&lt;sup&gt;th&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Metallo BL hydrolyze all**  
**Penicillins**  
**Cephalosporins**  
**Cephamycins**  
**Carbapenems**

Monobactams

Aztreonam
### The β-lactam family of antibiotics

<table>
<thead>
<tr>
<th>Penicillins</th>
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<th>Cephamycins</th>
<th>Carbapenems</th>
<th>Monobactams</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzyl-penicillin</td>
<td>Cephalothin 1(^{st})</td>
<td>Cefoxitin</td>
<td>Imipenem</td>
<td>Aztreonam</td>
</tr>
<tr>
<td>Methicillin</td>
<td>Cefamandole 2(^{nd})</td>
<td>Cefotetan</td>
<td>Meropenem</td>
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<tr>
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<td></td>
<td>Doripenem</td>
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<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cefepime 4(^{th})</td>
<td></td>
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</tbody>
</table>

**KPCs hydrolyze all**
- Penicillins
- Cephalosporins
- Cephamycins
- Carbapenems
- Monobactams
Carbapenems

• By way of review the following antibiotics are classified as carbapenems
  ◆ Ertapenem
  ◆ Doripenem
  ◆ Imipenem
  ◆ Meropenem
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
## Carbapenemases in the U.S.

<table>
<thead>
<tr>
<th>Molecular Class</th>
<th>Carbapenemase</th>
<th>Found in:</th>
<th>Some Key Features</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A</strong></td>
<td>KPC</td>
<td><em>K. pneumoniae</em> and other Enterobacteriaceae</td>
<td>Some are chromosomal (NmcA, Sme, IMI-1, SFC-1) others are plasmid encoded (KPC, IMI-2, GES). All hydrolyze carbapenems and are partially inhibited by clavulanic acid</td>
</tr>
<tr>
<td></td>
<td>SME</td>
<td><em>S. marcescens</em></td>
<td></td>
</tr>
<tr>
<td></td>
<td>also IMI, NMCA, GES</td>
<td>Enterobacteriaceae</td>
<td></td>
</tr>
<tr>
<td><strong>B</strong></td>
<td>Metallo beta-lactamases (IMP, VIM, GIM, SPM, NDM-1)</td>
<td>*S. maltophilia, P. aeruginosa, Enterobacteriaceae, Acinetobacter,</td>
<td>Hydrolyze all β-lactams except aztreonam. Activity inhibited by EDTA but not by clavulanic acid</td>
</tr>
<tr>
<td><strong>D</strong></td>
<td>OXA</td>
<td><em>Acinetobacter baumannii</em>, Enterobacteriaceae</td>
<td>OXA-48 first reported in Turkey in 2003. Not inhibited by EDTA or clavulanic acid</td>
</tr>
</tbody>
</table>

When to Suspect a Carbapenemase

- Enterobacteriaceae – especially K. pneumoniae that are resistant to extended-spectrum cephalosporins:
  - Carbapenemase-producing Enterobacteriaceae test resistant to extended-spectrum cephalosporins
  - KPC producers show variable susceptibility to cefotetan, cefoxitin, and cefepime
  - Metallo-β-lactamas producers show variable susceptibility to aztreonam
Strategy for Laboratory Detection of Carbapenemases

• CLSI Screening Criteria for KPCs (M100-S-19 Jan 2009)
  ◆ Disk zone of < 22 mm for ertapenem or meropenem
  ◆ MIC of >1 μg/ml for imipenem, ertapenem or meropenem

• CLSI Confirmatory Test (M100-S19, Jan 2009)
  ◆ Modified Hodge Test

• 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
Imipenem disk showing susceptible zone but many break-through colonies

Ertapenem
Etest showing many break-through colonies
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.

*Anderson KF et al. JCM 2007 Aug;45(8):2723-5.*
Carba NP Test for Carbapenemase Production

- Isolated colonies (lyse / centrifuge)
- Hydrolysis of imipenem
- Detected by change in pH of indicator (red to yellow/orange)
- Rapid <3h
- Microdilution plate or microtube method


“a” tubes – Solution A
“b” tubes Solution A + imipenem

(slide courtesy Janet Hindler)
Enterobacteriaceae (CRE)

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.
Rosco Diagnostica IMI/EDTA Disks
MBL Etest bioMerieux

EDTA Etest = Pos

IMI alone = 19 mm

Meropenem Etest

IMI + EDTA = 27 mm
KPC - Questions

• If I have detected KPC-production, should I change susceptible carbapenem results to resistant?
  ◆ If using old CLSI carbapenem breakpoints:
    • Isolates that are MHT positive and have an ertapenem MIC of 2-4 ug/mL, imipenem MIC of 2-8 ug/mL, or meropenem MIC of 2-8 ug/mL, Report carbapenems as resistant
  ◆ If using new CLSI carbapenem breakpoints
    • Report MIC, interpret with new breakpoints

(CLSI Jan 2011 M100-S21, p. 55)
Enterobacteriaceae - Revised Carbapenem Breakpoints (MIC μg.ml)

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<tr>
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<tr>
<td></td>
<td>Susc</td>
<td>Int</td>
</tr>
<tr>
<td>Doripenem</td>
<td>-</td>
<td>-</td>
</tr>
<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>
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</table>

Special CLSI M100-S20-U Supplement published June 2010 with Enterobacteriaceae Tables with these new breakpoints

* Ertapenem BP revised in CLSI document M100-S22 Jan 2012

CLSI M100-S20-U. Table 2A
## Enterobacteriaceae - Revised Carbapenem Breakpoints (disk mm)

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<tr>
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<tr>
<td></td>
<td>Susc</td>
<td>Int</td>
</tr>
<tr>
<td>Doripenem</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ertapenem*</td>
<td>≥ 19</td>
<td>16-18</td>
</tr>
<tr>
<td>Imipenem</td>
<td>≥ 16</td>
<td>14-15</td>
</tr>
<tr>
<td>Meropenem</td>
<td>≥ 16</td>
<td>14-15</td>
</tr>
</tbody>
</table>

*Ertapenem BP revised in CLSI document M100-S22 Jan 2012*

Special CLSI M100-S20-U Supplement published June 2010 with Enterobacteriaceae Tables with these new breakpoints

**CLSI M100-S20-U. Table 2A**
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 Resistant Enterobacteriacea (CRE) and implementation of infection control practices are necessary to limit spread
CDC Definition of CRE (Carbapenem Resistant Enterobacteriaceae)

- Enterobacteriaceae that are:
  - **Nonsusceptible** to one of the following carbapenems: doripenem, meropenem, or imipenem AND
  - **Resistant** to all of the following 3rd-generation cephalosporins that were tested: ceftriaxone, cefotaxime, and ceftazidime. (Note: All three of these antimicrobials are recommended as part of the primary or secondary susceptibility panels for Enterobacteriaceae)

http://www.cdc.gov/hai/organisms/cre/
CDC Definition of CRE

• *Klebsiella* spp. and *E. coli* that meet the CRE definition are a priority for detection and containment in all settings; however, other *Enterobacteriaceae* (e.g., *Enterobacter* species) might also be important in some regions.

• For bacteria that have intrinsic imipenem nonsusceptibility (i.e., *Morganella morganii*, *Proteus* spp., *Providencia* spp.), requiring nonsusceptibility to carbapenems other than imipenem as part of the definition might increase specificity.

http://www.cdc.gov/hai/organisms/cre/
Imipenem vs. Proteeeae

• MIC$_{90}$S of imipenem are $\leq 1$ ug/mL for most Enterobacteriaceae, but are 4-8 ug/mL for Proteeeae and therefore may test non-susceptible to imipenem using the new CLSI/FDA breakpoints

• 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

• Meropenem, doripenem and ertapenem are not affected and will test in susceptible range in absence of a carbapenemase (eg. KPC)

Villar HE et al JAC 1997, 40:365-370
Neuwirth C, et al. 1995, 36:335-342
Imipenem Disclaimers

• FDA Indications for imipenem: *Acinetobacter* spp., *Citrobacter* spp., *Enterobacter* spp., *E. coli*, *M. morganii*, *P. vulgaris*, *Prov. rettgeri*, *Prov. stuartii*, *P. aeruginosa*, *Serratia* spp., including *S. marcescens*

• Note: there is no FDA indication for imipenem and *P. mirabilis*

• Consider not reporting imipenem results for *P. mirabilis*
Detect and Protect

• CDC is funding some states who are testing the use of “Detect and Protect” strategies to find germs causing healthcare-associated infections (HAI) and prevent their spread.

• Detect and Protect strategies include: Tracking CRE, including use of the National Healthcare Safety Network (NHSN), and Prevention activities, such as those found in CDC guidelines and HAI prevention toolkits.

http://www.cdc.gov/hai/organisms/cre/
In response to the CRE public health threat, IDPH has amended the Control of Communicable Diseases Code (77 Ill. Adm. Code 690) Rules (see addendum) to require reporting of CREs to IDPH.

All hospitals, hospital-affiliated clinical laboratories, independent or free-standing laboratories, longer-term care facilities, and long-term acute care hospitals in Illinois will be required to report CRE isolates that meet surveillance criteria to IDPH through a tool called the XDRO registry, effective November 1, 2013.
Report CRE Isolates to XDRO Registry with one of following test results:

1. Molecular test (e.g., PCR) specific for carbapenemase

   OR

2. Phenotypic test (e.g., Modified Hodge) specific for carbapenemase production

   OR

3. For *E. coli* and *Klebsiella* species only: non-susceptible to ONE of the carbapenems (doripenem, meropenem, or imipenem) AND resistant to ALL third generation cephalosporins tested (ceftriaxone, cefotaxime, and ceftazidime).

Report 1st CRE event per patient per encounter
Why labs should continue to perform MHT and EDTA Inhibition Test on isolates that test NS to carbapenems

- Knowing the resistance mechanism is important
- The following cases demonstrate 3 different mechanisms of carbapenem resistance. Some require changes in antibiotic reporting, some require infection control notification, some require reporting to XDRO registry, 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), currently vent dependent
  ◆ Chronic foley catheter
  ◆ Diabetes mellitus type 2
  ◆ ESRD
• Exam:
  ◆ Afebrile
  ◆ Multiple decubitus ulcers (sacrum, spine, right leg)
  ◆ Urine is grossly dirty
Patient History

- Concerned that septic => Pan-cultures
  - Urine: *Klebsiella*…
  - Spot Indole Neg
**Oxidase**

- **Type:** Gram Negative General Susceptibility 143 (GNS-143)
- **Status:** Final
- **Elapsed Time:** 13 hours
- **Organism:** Klebsiella pneumoniae
- **Source:** Manual

### Demographics:

<table>
<thead>
<tr>
<th>Drug</th>
<th>MIC</th>
<th>Instrument</th>
<th>Expert</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ampicillin</td>
<td>&gt;=32</td>
<td>R</td>
<td></td>
</tr>
<tr>
<td>Ampicillin/Sulbactam</td>
<td>&gt;=32</td>
<td>R</td>
<td></td>
</tr>
<tr>
<td>Piperacillin/Tazobactam</td>
<td>&gt;=128</td>
<td>R</td>
<td></td>
</tr>
<tr>
<td>Cefazolin</td>
<td>&gt;=32</td>
<td>R</td>
<td></td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>&gt;=64</td>
<td>R</td>
<td></td>
</tr>
<tr>
<td>Ceftazidime</td>
<td>&gt;=32</td>
<td>R</td>
<td></td>
</tr>
<tr>
<td>Cefepime</td>
<td>B</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aztreonam</td>
<td>&gt;=32</td>
<td>R</td>
<td></td>
</tr>
<tr>
<td><strong>Imipenem</strong></td>
<td>&lt;=4</td>
<td>S</td>
<td></td>
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<tr>
<td>Gentamicin</td>
<td>4</td>
<td>S</td>
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<tr>
<td>Tobramycin</td>
<td>&gt;=16</td>
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<td>Trimeth-sulfa</td>
<td>&gt;=320</td>
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<tr>
<td>Nitrofurantoin</td>
<td>64</td>
<td>I</td>
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</tbody>
</table>

**ESBL**

- **Expert:** Negative

**MIC values in mcg/ml (M1) Wait for All**

The presence of other Beta-lactamases (e.g. AmpC, IRT) may mask ESBL production.
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 ........
# Carbapenemases in the U.S.

<table>
<thead>
<tr>
<th>Molecular Class</th>
<th>Carbapenemase</th>
<th>Found in:</th>
<th>Some Key Features</th>
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<tr>
<td>A</td>
<td>KPC</td>
<td><em>K. pneumoniae</em> and other Enterobacteriaceae</td>
<td>Some are chromosomal (NmcA, Sme, IMI-1, SFC-1) others are plasmid encoded (KPC, IMI-2, GES). All hydrolyze carbapenems and are partially inhibited by clavulanic acid</td>
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<tr>
<td></td>
<td>SME</td>
<td><em>S. marcescens</em></td>
<td></td>
</tr>
<tr>
<td></td>
<td>also IMI, NMCA, GES</td>
<td>Enterobacteriaceae</td>
<td></td>
</tr>
</tbody>
</table>
| B               | Metallo beta-lactamases | *S. maltophilia*  
*P. aeruginosa*, Enterobacteriaceae, *Acinetobacter*, | Hydrolyze all β-lactams except aztreonam. Activity inhibited by EDTA but not by clavulanic acid |
|                 | OXA           | *Acinetobacter baumannii*, Enterobacteriaceae | OXA-48 first reported in Turkey in 2003. Not inhibited by EDTA or clavulanic acid |

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.”

• REPORT TO XDRO REGISTRY
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 ß-lactamase. Isolates may become resistant to all cephalosporins after initiation of therapy. Avoid ß-lactam-inhibitor drugs”
- **DO NOT REPORT TO XDRO REGISTRY**
Case 3

• Patient is a 40 Y.O. male paraplegic who traveled to New Delhi India for a surgical procedure. 3-4 months after returning to the U.S. patient presents to outpatient center in Chicago with multiple decubitus ulcers and urinary tract infection. Urine collected from foley cath is submitted for culture.
## MicroScan Report - Case 3

### Panel Data

**Biotype:**
73115012

**Organism Identification:**

<table>
<thead>
<tr>
<th>Organism</th>
<th>% Probability</th>
<th>Footnotes</th>
<th>Special Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>E. coli</td>
<td>99.99</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Biochemical Results: (Biochemicals that are bolded and underlined are atypical for the first choice organism)

- GLU + RAF - INO - URE - LYS + TDA - CIT - CL4 - ACE - K4 + P4 +
- SUC + RHA + ADO - H2S - ARG - ESC - MAL - CF8 + CET - NIT + TAR -
- SOR + ARA + MEL + IND + ORN + VP - ONPG + OXI - FD64 - OFIG + TO4 +

MIC Results: (Antimicrobics marked with "Ø" are suppressed from Long and Short Format Patient Reports)

<table>
<thead>
<tr>
<th>AM</th>
<th>A/S</th>
<th>P/T</th>
<th>CFZ</th>
<th>CAX</th>
<th>CAZ</th>
<th>CPE</th>
<th>MER</th>
<th>GM</th>
<th>Ø TE</th>
<th>TO</th>
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<th>AK</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;16</td>
<td>&gt;16/8</td>
<td>&gt;64</td>
<td>&gt;16</td>
<td>&gt;32</td>
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<th>IMP</th>
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</tr>
</tbody>
</table>

**Extra Tests:** ESBL -
Case 3. 12 Disk
Case 3 - Modified Hodge Test
Rosco Diagnostica IMI/EDTA Disks
MBL Etest bioMerieux

Case 3 EDTA Etest = Pos

IMI alone = 19 mm

Meropenem Etest

IMI + EDTA = 27 mm
And the Answer is ..........
# Carbapenemases in the U.S.

<table>
<thead>
<tr>
<th>Molecular Class</th>
<th>Carbapenemase</th>
<th>Found in:</th>
<th>Some Key Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
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<td></td>
</tr>
<tr>
<td>B</td>
<td>Metallo beta-lactamases (IMP, VIM, GIM, SPM, NDM-1)</td>
<td><em>S. maltophilia</em> <em>P. aeruginosa</em>, Enterobacteriaceae, <em>Acinetobacter</em>,</td>
<td>Hydrolyze all β-lactams except aztreonam. Activity inhibited by EDTA but not by clavulanic acid.</td>
</tr>
<tr>
<td>D</td>
<td>OXA</td>
<td><em>Acinetobacter baumannii</em>, Enterobacteriaceae</td>
<td>OXA-48 first reported in Turkey in 2003. Not inhibited by EDTA or clavulanic acid.</td>
</tr>
</tbody>
</table>

NDM-1
New Class B: Metallo-β-Lactamases

• First reported in Swedish patient of Indian origin traveled to New Delhi, acquired a urinary tract infection caused by NDM-1-producing *K. pneumoniae*

• MBLs hydrolyze all β-lactams, including carbapenems, penicillins, extended-spectrum cephalosporins, but not aztreonam

• MBLs pose a serious threat in terms of infection control because of their high mobility

• MBLs require zinc for enzymatic activity which is not diminished by serine β-lactamase inhibitors but is inhibited by EDTA and other chelators of divalent cations


Courtesy Brandi Limbago, CDC
# MicroScan Report

## Panel Data

### Biotype:
73115012

### Organism Identification:

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(Biochemicals that are bolded and underlined are atypical for the first choice organism)

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<th>ACE</th>
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(Antimicrobics marked with "Ø" are suppressed from Long and Short Format Patient Reports)

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### Extra Tests:
ESBL -
# Enterobacteriaceae - Revised Carbapenem Breakpoints (MIC $\mu$g.ml)

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</thead>
<tbody>
<tr>
<td></td>
<td>Susc</td>
<td>Int</td>
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<tr>
<td>Doripenem</td>
<td>-</td>
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<tr>
<td>Ertapenem</td>
<td>$\leq 2$</td>
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<td>Imipenem</td>
<td>$\leq 4$</td>
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</tr>
<tr>
<td>Meropenem</td>
<td>$\leq 4$</td>
<td>8</td>
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</tbody>
</table>

*CLSI. Performance Standards for Antimicrobial Susceptibility Testing: Twentieth Informational Supplement (June 2010 Update). CLSI document M100-S20-U. Wayne, PA; 2010*
Patient Report Case 3

• 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 EDTA Inhibition Test – probable MBL type. Implement infection control measures according to facility”

• REPORT TO XDRO REGISTRY
Carbapenem-Resistant Enterobacteriaceae (CRE): Submitting Samples to IDPH

• IDPH and CDC want to prioritize sample submission of CRE isolates other than KPC for further (genotypic) testing.

• At a minimum, prior to submission, labs should confirm ID, ensure pure cultures, and repeat resistance testing, with a different method if possible, to confirm resistance patterns.

• Submit likely MBL-producing CRE isolates to IDPH
Carbapenem-Resistant Enterobacteriaceae (CRE): Submitting Samples to IDPH

- Likely MBL-producing CRE isolates:
  1) Must exhibit carbapenem resistance (I or R to imipenem, doripenem, or meropenem using updated breakpoints) and resistance (R) to all tested third-generation cephalosporins

  **AND**

  2) Must have phenotypic testing suggesting MBL (e.g. + MBL Etest or + multi-disk test) OR, if phenotypic testing not done, be isolated from a patient with international travel in last 6 months or epidemiologic link to a patient with non-KPC CRE.
QUESTIONS?

Oh, crap! Was that TODAY?
XDRO Registry
for Laboratories

June 2014

Michael Lin, MD MPH
William Trick, MD
Chicago CDC Prevention Epicenter
Objectives

1. Review epidemiology and registry data (2 slides)

2. XDRO registry website orientation
CRE in Chicagoland

<table>
<thead>
<tr>
<th>Facility type</th>
<th>CRE colonization prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Short stay acute care hospitals (adult ICUs)</td>
<td>3%</td>
</tr>
<tr>
<td>Long term acute care hospitals (LTACHs)</td>
<td>30%</td>
</tr>
</tbody>
</table>

• CRE common in some Chicago healthcare facilities, particularly LTACHs

• Data suggest that skilled nursing facilities with ventilated patients have rates similar to LTACHs

Lin et al. CID, 2013. 57(9): 1246-1252.
Since Nov. 2013, average 2-3 patients reported per day
XDRO registry website: orientation and updates
Carbapenem-resistant Enterobacteriaceae (CRE) are extremely drug resistant organisms (XDR0s) that have few treatment options and high mortality rates. CRE are increasingly detected among patients in Illinois, including acute and long term care healthcare facilities.

In response to the CRE public health threat, the Illinois Department of Public Health (IDPH) has guided development an infection control tool called the XDRO registry. The purpose of the XDRO registry is two-fold:

1. **Improve CRE surveillance:** The first CRE-positive culture per patient stay must be reported to the XDRO registry.
2. **Improve inter-facility communication:** Healthcare facilities can query the XDRO registry to see whether a patient has been previously reported as CRE-positive.

**For access to the XDRO registry, click here**

**UPDATES**

IL CRE Detect and Protect Campaign. More...

CRE are reportable to IDPH via the XDRO registry. Links: [IDPH letter to facilities, September 2013](#Reporting rule]

XDRO registry orientation webinar [Slides](#)[Recordings]

CDC guidance on control of CRE: [The 2012 Toolkit]

**As of November 1, 2013, the XDRO registry is open for CRE submissions and queries.**

View FAQs: [FAQs PDF]
Welcome to the IDPH Web Portal

From here, you can:

- Find all your public health related information at one secure site.
- Join online communities to share files, discussions, calendars and more.
- Access Web-based applications.

To access the IDPH Web Portal, users must be running Internet Explorer 6.0 or higher. Some portal applications may not function properly with other browsers such as Mozilla Firefox.

Current Users: click here to access the portal: Login

I need to...

Register for a Portal Account

Contact Customer Service Center
1-800-366-8768

For assistance with IDPH portal access and web-based application support, contact the Customer Service Center at 1-800-366-8768, Option 1, then Option 1 for password reset assistance or Option 7 to reach support personnel for the Department of Public Health.

Please indicate to the CSC staff that you are an IDPH Health Alert Network (portal) user when placing the call to ensure you are routed to the correct support staff to resolve the problem. Include your name, phone number, and specific application name, detail of the issue and error messages, if any, in your description of the problem to ensure efficient resolution.
Registration Page: New Users

First name: *
Last name: *
Password: *
Confirm password: *
Title: *
Organization: *
Department: *
Work address: *
City: *
State: *
ZIP code: *
E-mail: *
Confirm E-mail: *
Work phone #: *
Cell phone #: *
Pager #: *
FAX #: *
Supervisor’s name: *
Purpose for registration: 

Please check the appropriate box(es) below to request access to restricted applications.

- Beach Monitoring System
- Cancer Registry System
- EMS Licensing System
- Environmental Health Licensing System
- Food Service Sanitation Manager Certification
- Genetic Counselling System
- HAN Alert Notification Recipient
- HAN Alert Notification System Author
- Health Care Worker Background Check System
- Healthy Homes and Lead Poisoning Surveillance System
- Hospital ByPass/State Disaster Reporting System
- I-CARE/Immunization Registry (click here to select the KeyMaster’s e-mail: ___________)
- I-CARESFTP (MoveIT) HEL/ File Transfer
- INEDSS (Disease Surveillance) System/Extensively Drug-Resistant Organisms (XDO)

Please check the appropriate box(es) below to request access to restricted applications.
User Sign-In

State of Illinois
Web Authentication Portal

Security (show explanation)
- This is a public or shared computer
- This is a private computer

- I want to change my password after logging on

**Warning! Unauthorized access is prohibited**
Further access is limited to authorized users only. By accessing or using this system you are consenting to monitoring and recording, which may be disclosed for administrative, disciplinary, civil, or criminal actions, penalties, or prosecution. Users should have no expectation of privacy when accessing or using this system or any of its components.

Domain: General Public (Not employed by the State of Illinois)
User name: john.smith
Password: ************

Log On

Don’t have an Illinois.gov ID? Sign up

© 2007 State of Illinois. All rights reserved.
XDRO Report

XDRO culture information

* Organism name (genus/species)
  * Please Select Organism:

* Specimen source
  * Please Select Specimen:

* XDRO criteria (select all that apply)
  Reporting rule
  - Molecular test (e.g. PCR) specific for carbapenemase
  - Phenotypic test (e.g. Modified Hodge) specific for carbapenemase production
  - For E. coli and Klebsiella spp. only: Resistant to ALL 3rd gen cephalosporins tested and non-susceptible (intermediate or resistant) to one carbapenem. Ignore ertapenem.

* Date (culture acquisition)
  mm / dd / yyyy

* Mechanism of resistance
  * Please Select Mechanism:
    - (molecular test required)

Facility information

* Facility name
  Sample Hospital

* Culture obtained

Patient demographics

* First name

* Gender
  - Male
  - Female

* Race
  * Please Select One:

* Street address

* City
  * Chicago

* County
  * Cook

* State
  * Illinois

* Zip code
Xdro Report

Xdro Culture Information

* Organism Name
  (Genus/species)
  Please Select Organism:

* Specimen Source
  Please Select Specimen:

* XDRO Criteria (Select All That Apply)
  Reporting Rule
  Molecular Test (e.g., PCR) Specific for Carbapenemase
  Phenotypic Test (e.g., Modified Hodge) Specific for Carbapenemase Production
  For E. Coli and Klebsiella spp. only:
  Resistant to all 3rd gen cephalosporins tested and non-susceptible (intermediate or resistant) to one carbapenem. Ignore ertapenem.

* Date (Culture Acquisition)
  Mm / dd / yyyy

* Mechanism of Resistance
  Please Select Mechanism:

Facility Information

* Facility Name
  Sample Hospital

* Patient MRN

* Date of Admission/Encounter Date
  Mm / dd / yyyy

□ Culture obtained as outpatient
XDRO Report

XDRO culture information

* Organism name (genus/species)
  Please Select Organism:
  - Citrobacter freundii
  - Citrobacter kosen
  - Citrobacter spp.
  - Enterobacter aerogenes
  - Enterobacter cloacae
  - Enterobacter spp.
  - Escherichia coli
  - Klebsiella oxytoca
  - Klebsiella pneumoniae
  - Klebsiella spp.
  - Morganella morganii
  - Pantoea agglomerans
  - Proteus mirabilis
  - Proteus spp.
  - Providencia stuartii
  - Providencia spp.
  - Salmonella spp.
  - Serratia marcescens
  - Serratia spp.

* XDRO criteria (select all that apply)
  Reporting rule
  □ Molecular test (e.g. PCR) specific for carbapenemase
  □ Phenotypic test (e.g. Modified Hodge) specific for carbapenemase production
  □ For E. coli and Klebsiella spp. only:

* Date (culture acquisition)
  mm / dd / yyyy

* Mechanism of resistance
  Please Select Mechanism:

* Patient MRN

* Date of admission/Encounter Date
  mm / dd / yyyy

* First name

* Last name

Maiden name (if applicable)
XDRO culture information

* Organism name (genus/species)
  Klebsiella pneumoniae

* XDRO criteria (select all that apply)
  Reporting rule
  □ Molecular test (e.g. PCR) specific for carbapenemase
  □ Phenotypic test (e.g. Modified Hodge) specific for carbapenemase production
  □ For E. coli and Klebsiella spp. only: Resistant to ALL 3rd gen cephalosporins tested and non-susceptible (intermediate or resistant) to one carbapenem. Ignore ertapenem.

* Date (culture acquisition)
  mm / dd / yyyy

* Mechanism of resistance
  Please Select Mechanism:

Facility information

Facility name
Sample Hospital

* Patient MRN

* Date of admission/Encounter Date
  mm / dd / yyyy

□ Culture obtained as outpatient

Patient demographics

* First name

* Last name

Maiden name (if applicable)
**XDRO culture information**

* Organism name (genus/species)
  - Klebsiella pneumoniae

* XDRO criteria
  - Molecular test (e.g. PCR) specific for carbapenemase
  - Phenotypic test (e.g. Modified Hodge) specific for carbapenemase production
  - For E. coli and Klebsiella spp. only: Resistant to ALL 3rd gen cephalosporins tested and non-susceptible (intermediate or resistant) to one carbapenem. Ignore ertapenem.

* Specimen source
  - Please Select Specimen:

* Date (culture acquisition)
  - mm / dd / yyyy

**Facility information**

* Facility name
  - Sample Hospital

* Patient MRN

* Date of admission/Encounter Date
  - mm / dd / yyyy

- Culture obtained as outpatient

**Patient demographics**

* First name

* Last name

Maiden name (if applicable)
**XDRO Report**

**XDRO culture information**

* Organism name (genus/species)  
Klebsiella pneumoniae

* XDRO criteria
  - Molecular test (e.g. PCR) specific for carbapenemase
  - Phenotypic test (e.g. Modified Hodge) specific for carbapenemase production
  - For E. coli and Klebsiella spp. only:
    Resistant to ALL 3rd gen cephalosporins tested and non-susceptible (intermediate or resistant) to one carbapenem. Ignore ertapenem.

* Date (culture acquisition)

  mm  /  dd  /  yyyy

* Mechanism of resistance
  - KPC (Klebsiella pneumoniae carbapenemase)
  - NDM-1 (New Delhi Metallo-ß-lactamase)
  - OXA
  - Other
  - Unknown

**Facility information**

Facility name
Sample Hospital

* Patient MRN

* D

  mm  /  dd  /  yyyy

- Culture obtained as outpatient

**Patient demographics**

* First name

* Last name

Maiden name (if applicable)
<table>
<thead>
<tr>
<th>Action</th>
<th>Facility Name</th>
<th>DPHSiteCode</th>
<th>Street</th>
<th>City State Zip</th>
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<tbody>
<tr>
<td>ADD</td>
<td>Veterans Rehabilitation Cent..</td>
<td>6075</td>
<td>2449 West Washington</td>
<td>Chicago, Illinois 60612</td>
</tr>
<tr>
<td>ADD</td>
<td>Vet Administration West Side..</td>
<td>6074</td>
<td>820 South Damen Avenue</td>
<td>Chicago, Illinois 60612</td>
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<tr>
<td>ADD</td>
<td>University Of Illinois Hospi..</td>
<td>6072</td>
<td>1740 West Taylor</td>
<td>4 West O.b. - 4th Floor ..</td>
</tr>
<tr>
<td>ADD</td>
<td>U Of I College Of Medicine</td>
<td>6070</td>
<td>1819 West Polk Street</td>
<td>Chicago, Illinois 60612</td>
</tr>
<tr>
<td>ADD</td>
<td>Rush University Medical Cent..</td>
<td>6053</td>
<td>1753 West Congress Parkway</td>
<td>Chicago, Illinois 60612</td>
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<tr>
<td>ADD</td>
<td>John H. Stroger, Jr. Hospita..</td>
<td>6020</td>
<td>1835 West Harrison Street</td>
<td>Chicago, Illinois 60612</td>
</tr>
<tr>
<td>ADD</td>
<td>Illinois State Psychiatric I..</td>
<td>6033</td>
<td>1601 West Taylor Street</td>
<td>Chicago, Illinois 60612</td>
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<tr>
<td>ADD</td>
<td>Ill Research And Education H..</td>
<td>6031</td>
<td>1819 West Polk Street</td>
<td>Chicago, Illinois 60612</td>
</tr>
<tr>
<td>ADD</td>
<td>City Morgue</td>
<td>6018</td>
<td>1828 West Polk Street</td>
<td>Chicago, Illinois 60612</td>
</tr>
</tbody>
</table>
Search Instruction

a. Available fields
   Last name (required), first name (optional), DOB (required).

b. Search algorithm
   i. If you enter all 3 fields, then attempt to match (exact; case insensitive) on all 3 fields.
   ii. If no match returns on 3 fields, then attempt to match (exact; case insensitive) on last name and DOB (ignore first name completely).

c. Results display
   i. In general, You will see the search results for exactly how you entered the information.
   If there are no exact matches for last name and dob, you will see a NULL result.
XDRO Report - Rush-presb-st Lukes Medical Center

Patient information
Patient name: J, J  
MRN: 
Date of birth: 10/10/1999  
SSN (last 4): 
Admission date: 10/10/2012  
Race: Black/African American  
Address: 2200, Chicago, IL 60612

XDRO culture information
Organism: Other Enterobacteriaceae  
Culture date: 10/10/2012  
XDRO criterion:  
Specimen source: Blood  
Mechanism of resistance: 
Comments:

Submitted by Vicky G, 10/10/2013, Rush-presb-st Lukes Medical Center
<table>
<thead>
<tr>
<th>RID</th>
<th>Name</th>
<th>Date of Birth</th>
<th>MRN</th>
<th>Organism</th>
<th>Culture Date</th>
<th>Status</th>
<th>Username</th>
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</thead>
<tbody>
<tr>
<td>585</td>
<td>Q, Q</td>
<td>12/12/2010</td>
<td>1212</td>
<td>Citrobacter spp.</td>
<td>03/01/2014</td>
<td>Pending</td>
<td>devxtest</td>
</tr>
<tr>
<td>835</td>
<td>Duck, Daffy</td>
<td>11/13/1973</td>
<td>1234</td>
<td>Klebsiella pneumoniae</td>
<td>02/14/2014</td>
<td>Submitted</td>
<td>reidig</td>
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<tr>
<td>1017</td>
<td>T, Test</td>
<td>01/01/1955</td>
<td>1234536</td>
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<td>Submitted</td>
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<tr>
<td>846</td>
<td>S, B</td>
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<td>32152</td>
<td>Citrobacter spp.</td>
<td>12/12/2013</td>
<td>Submitted</td>
<td>devxtest</td>
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<tr>
<td>777</td>
<td>E, Ds</td>
<td>11/11/1982</td>
<td>1110</td>
<td>Enterobacter aerogenes</td>
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<td>devxtest</td>
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<td>861</td>
<td>, Test Criteria</td>
<td></td>
<td></td>
<td>Escherichia coli</td>
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<td>Pending</td>
<td>devxtest</td>
</tr>
<tr>
<td>872</td>
<td>D, Testzip</td>
<td>11/12/1950</td>
<td>2321321</td>
<td>Enterobacter aerogenes</td>
<td>11/11/2013</td>
<td>Submitted</td>
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<tr>
<td>899</td>
<td>T, Test</td>
<td>01/23/1980</td>
<td>3232132</td>
<td>Citrobacter spp.</td>
<td>11/11/2013</td>
<td>Submitted</td>
<td>devxtest</td>
</tr>
</tbody>
</table>
XDRO Report - Sample Hospital

Patient information
Patient name: Duck, Daffy  
MRN: 1234  
Admission date: 03/13/2014  
Date of birth: 11/13/1973  
SSN (last 4):  
Race:  
Address: 122 S. Michigan, Chicago, IL 60603

XDRO culture information
Organism: Klebsiella pneumoniae  
Culture date: 02/14/2014  
XDRO criterion: Molecular test  
Specimen source:  
Mechanism of resistance: KPC  
Comments:
Submitted by ROBYNN LEIDIG, 03/14/2014, Sample Hospital
XDRO Report - Sample Hospital

Patient information
Patient name: Duck, Daffy  MRN: 1234  Admission date: 03/13/2014
Date of birth: 11/13/1973  SSN (last 4):  Race:
Address: 122 S. Michigan, Chicago, IL 60603

XDRO culture information
Organism: Klebsiella pneumoniae  Culture date: 02/14/2014
XDRO criterion: Molecular test  Specimen source:
Mechanism of resistance: KPC
Comments:
Submitted by ROBYNN LEIDIG, 03/14/2014, Sample Hospital

Reason for deleting the above record: De-colonization or infection resolved
Please Select Reason: [Dropdown]
Comment: 

Querying the XDRO registry
Planned: Automated CRE Alerts

Your facility

1. Send patient info (encrypted)

2. Receive CRE alert if match

XDRO registry

All Illinois facilities

Automated alerts will be piloted at limited hospitals in 2014; anticipate wider availability in 2015
Take home points

1. Stand alone reference labs
   - Report labs on behalf of facilities
   - If the facility is not listed, let us know by email: DPH.XDROregistry@Illinois.gov
   - Encourage facilities to register and report on their own

2. Hospital-based labs
   - Submit under your hospital name
   - Coordinate submission with the infection prevention dept.

3. Hospital-based reference labs
   - Ideally, the IP will submit “local” isolates
   - The laboratory would submit on behalf of other facilities
Question and answer forum
# Upcoming Webinar

<table>
<thead>
<tr>
<th>Target Audience</th>
<th>Topics</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Long Term Care</td>
<td>Antibiotic Use in Nursing Homes</td>
<td>June 26</td>
</tr>
</tbody>
</table>

CRE webinar recordings and slides will be available at [https://www.xdro.org/cre-campaign/index.html](https://www.xdro.org/cre-campaign/index.html)
Survey and Continuing Education

• Fill out webinar evaluation on SurveyMonkey at: https://www.surveymonkey.com/s/cre-labs

• Instructions on applying for CEUs will appear at the end of the SurveyMonkey

• Surveys and CEU applications must be completed by Monday, June 16!

Contact: Robynn.Leidig@illinois.gov or Angela.Tang@illinois.gov