Carbapenem-Resistant Enterobacteriaceae (CRE): Regional Prevention of an Urgent Global Threat

OHSU Medicine Grand Rounds
Christopher D. Pfeiffer, MD, MHS
Oct 22, 2013
I do not have any relationship(s) to disclose.
A 63 y.o. Indian female is transferred from a hospital in India for treatment of end-stage lung disease per her son’s request. She arrives intubated/sedated. Sparse transfer documents.

2 days later, new fever (103°F). BP drops. No immediately obvious etiology.

- What antibiotics would you start?

12 hours later, blood cultures + GNB
CDC: 'Nightmare bacteria' spreading

By William Hudson, CNN
updated 11:02 AM EST, Thu March 7, 2013

CDC warns about drug-resistant bug CRE
Learning Objectives / Outline

1. Understand: what are CRE? Which CRE are most important?


3. Learn about the regional CRE Prevention efforts including the DROP–CRE Network and the Oregon CRE Toolkit.
Important Multidrug–Resistant Gram Negative Bacilli (MDR–GNB)

- *Pseudomonas aeruginosa*
- *Acinetobacter baumannii*
- **MDR–Enterobacteriaceae***
  - Extended spectrum cephalosporinase (e.g., AmpC)
  - Extended-spectrum β-lactamases (ESBLs)
  - CRE

*Common Enterobacteriaceae include* *E. coli, Klebsiella* spp., and *Enterobacter* spp.
What are CRE?
Carbapenem-resistant Enterobacteriaceae...

Are non-susceptible (i.e., intermediate or resistant) to ANY carbapenem (e.g., doripenem, ertapenem, imipenem, or meropenem) AND resistant to ANY of the following 3rd generation cephalosporins tested: cefotaxime, ceftriaxone, or ceftazidime

—OR—

Possess/contain a gene sequence specific for carbapenemase (PCR)

—OR—

Are positive for carbapenemase production by a phenotypic test (e.g., Modified Hodge Test)
CRE Resistance Mechanisms

1. **Carbapenemase**
   - Enzymes produced by bacteria which *directly* inactivate carbapenem antibiotics

2. **Non-Carbapenemase**
   - Multiple resistance mechanisms combine to confer carbapenem resistance
<table>
<thead>
<tr>
<th>Tier</th>
<th>Description</th>
<th>Recommended Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Carbapenemase–producing CRE (CP–CRE)</td>
<td>Most aggressive control measures</td>
</tr>
<tr>
<td>2</td>
<td>CRE with acquired resistance NOT due to carbapenemase production</td>
<td>Intensified control measures including contact precautions</td>
</tr>
<tr>
<td>3</td>
<td>CRE with intrinsic (natural) imipenem resistance</td>
<td>No special control measures needed</td>
</tr>
</tbody>
</table>

*see Oregon CRE Toolkit 2013*
# Tier 1 CRE: Carbapenemase-producing CRE

- **#1 Organism:** *Klebsiella* spp.
- **Carbapenemases to know:**
  - *Klebsiella pneumoniae* carbapenemase (KPC)
  - New Delhi metallo-β-lactamase (NDM)
  - Oxacillinase-48 (OXA-48)
  - Verona integron encoded metallo-β-lactamase (VIM)
  - Imipenemase metallo-β-lactamase (IMP)

- **Epidemiology:** rapid **worldwide** dissemination
  - plasmid-mediated spread
Tier 2 CRE: Acquired resistance NOT due to a carbapenemase

- #1 Organism: *Enterobacter* spp.
- Resistance mechanism to know: AmpC and/or ESBL
  
  **Plus**
  
  Decreased cell wall permeability (e.g., porin mutation)

- Epidemiology
  - Incidence stable ~20 years
Proteus spp., Providencia spp., and Morganella spp. may test imipenem-nonsusceptible (MICs 2–4 µg/mL) using 2012 updated susceptibility testing breakpoints.

- **Example: PVAMC Antibiogram for Morganella morganii**
  
  2009 100% imi-S
  2010 100% imi-S
  2011 20% imi-S
  2012 34% imi-S

- However, non-susceptibility to any other carbapenem is unusual and concerning.
## CLSI Breakpoint Changes: *Enterobacteriaceae* to carbapenems

<table>
<thead>
<tr>
<th></th>
<th>Breakpoints Predating 2010 Update (µg/mL) (through Jan. 2010; M100–S19)</th>
<th>2012 Breakpoints (µg/mL) (revised Jun. 2010 and Jan. 2012; M100–S22)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>S</td>
<td>I</td>
</tr>
<tr>
<td><strong>Doripenem</strong></td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td><strong>Ertapenem</strong></td>
<td>≤2</td>
<td>4</td>
</tr>
<tr>
<td><strong>Imipenem</strong></td>
<td>≤4</td>
<td>8</td>
</tr>
<tr>
<td><strong>Meropenem</strong></td>
<td>≤4</td>
<td>8</td>
</tr>
</tbody>
</table>

CLSI = Clinical and Laboratory Standards Institute
CRE:
Epidemiology, detection, clinical impact, and treatment
## CRE Epidemiology, 2013

<table>
<thead>
<tr>
<th>Name</th>
<th>1&lt;sup&gt;st&lt;/sup&gt; Report Worldwide</th>
<th>1&lt;sup&gt;st&lt;/sup&gt; Report US</th>
<th>Current US Epidemiology</th>
</tr>
</thead>
<tbody>
<tr>
<td>KPC</td>
<td>2001 North Carolina</td>
<td>2001 CDC surveillance (NC)</td>
<td><strong>Widespread:</strong> ~11% of <em>Klebsiella</em> spp. reported to NHSN were carbapenem–R</td>
</tr>
<tr>
<td>NDM</td>
<td>2009 Sweden (from India)</td>
<td>2010 Returned travelers, India</td>
<td><strong>Uncommon:</strong> 49 cases reported to CDC (July 1)</td>
</tr>
<tr>
<td>OXA–48</td>
<td>2004 Turkey</td>
<td>2012 SMART surveillance, unknown location</td>
<td>Rare</td>
</tr>
<tr>
<td>IMP</td>
<td>1994 Japan</td>
<td>2011 CA (3 cases/NICU, source unknown)</td>
<td>Rare</td>
</tr>
<tr>
<td>VIM</td>
<td>2002/2003 Greece, Korea, Taiwan</td>
<td>2010 Returned traveler, Greece</td>
<td>Rare</td>
</tr>
</tbody>
</table>
Carbapenemase–producing CRE in the United States circa 2009

CDC, unpublished data
Carbapenemase–producing CRE in the United States, 2013

CDC, unpublished data

CDC, unpublished data

Slide from Alex Kallen, MD, MPH

KPC
KPC, NDM
KPC, NDM, OXA
KPC, NDM, VIM
KPC, NDM, VIM, IMP
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No. of facilities with carbapenem-resistant Enterobacteriaceae from CAUTI or CLABSI</th>
<th>Total no. of facilities performing CAUTI or CLABSI surveillance (N = 3,918)</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Facility type</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All acute-care hospitals</td>
<td>181</td>
<td>3,918</td>
<td>4.6</td>
</tr>
<tr>
<td>Short-stay acute-care hospital</td>
<td>145</td>
<td>3,716</td>
<td>3.9</td>
</tr>
<tr>
<td>Long-term acute-care hospital</td>
<td>36</td>
<td>202</td>
<td>17.8</td>
</tr>
<tr>
<td>Hospital size (no. of beds)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;100</td>
<td>48</td>
<td>1,609</td>
<td>3.0</td>
</tr>
<tr>
<td>100–299</td>
<td>46</td>
<td>1,480</td>
<td>3.1</td>
</tr>
<tr>
<td>300–499</td>
<td>41</td>
<td>541</td>
<td>7.6</td>
</tr>
<tr>
<td>≥500</td>
<td>45</td>
<td>258</td>
<td>17.4</td>
</tr>
<tr>
<td>Medical school affiliation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>102</td>
<td>1,079</td>
<td>9.5</td>
</tr>
<tr>
<td>No</td>
<td>53</td>
<td>2,839</td>
<td>1.9</td>
</tr>
</tbody>
</table>

From facilities reporting CRE to NHSN, Jan–June 2012
CAUTI=catheter-associated UTI; CLABSI=central-line-associated bloodstream infection
180 matched pairs of LTCF and community patients admitted to Chicago 4 hospitals had KPC surveillance via rectal swabs. Patients matched by age, admission date, and admitting service. LTCF patients had higher rates of dementia, incontinence, trachs, decubitus ulcers, etc.
Israel’s CRE Outbreak

- 2005: CRE thought to be imported to Israel
- 2006: Multiple CRE outbreaks occurred in hospitals
- March 2007: the Ministry of Health issued guidelines for country-wide CRE control
- Intervention included:
  - mandatory CRE reporting to public health;
  - mandatory isolation of hospitalized CRE carriers; and
  - creation of a multi-disciplinary task force which paid site visits and supervised adherence to the guidelines

Incidence of clinical CRE cases

- Pre-intervention (retrospective data)
- Intervention period (prospective data)

Launch of intervention
Next potential frontier

- ESBLs (on *E. coli*) are in the community.
- Is CRE next?

1. Antimicrobial susceptibility testing
   ◦ Neither specific nor sensitive for carbapenemases

2. Nucleic acid amplification test (NAAT; e.g., PCR)
   ◦ Current gold standard for *known* carbapenemases

3. Phenotypic detection of carbapenemases
   ◦ Variable performance (next slide)
**Phenotypic Carbapenemase Detection**

**Modified Hodge Test (MHT)**
- Carbapenemase diffused into media if present (18 hours, hard to interpret).
- Good for detection of KPC on *Klebsiella* spp. and *E. coli*.
- Performance is otherwise unreliable
  - >50% of *Enterobacter* spp. CRE in Oregon are MHT+ (all PCR negative).

**CarbaNP (**NEW**)**
- Test measures in vitro hydrolysis of imipenem (2 hours, cheap, easy).
- Highly sensitive and specific for ALL carbapenemases in several reports.
CRE: Clinical Impact

- 30–50% mortality of invasive infection across multiple studies (with exceptions)

- Limited treatment options
  - Colistin
  - Tigecycline (black box warning)
  - Aminoglycoside
  - Fosfomycin (UTIs)

- Some CRE are “pan-resistant”

Patel et al. ICHE 2008;29:1099–1106
New systemic antibacterial agents approved by the US Food and Drug Administration per 5-year period, through 2012.

http://www.idsociety.org/Index.aspx, accessed 10/20/13
## Agents in Clinical Trials

<table>
<thead>
<tr>
<th>Product</th>
<th>Class (Mechanism of Action)</th>
<th>Novel Mechanism of Action?</th>
<th>Status</th>
<th>Enterobacteriaceae</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ceftolozane/taxobactam (CXA-201; CXA-101/tazobactam)</td>
<td>Antipseudomonal cephalosporin/BLI combination (cell wall synthesis inhibitor)</td>
<td>No</td>
<td>Phase 3 (cUTI, cIAI)</td>
<td>Yes</td>
</tr>
<tr>
<td>Ceftazidime-avibactam (ceftazidime/NXL104)</td>
<td>Antipseudomonal cephalosporin/BLI combination (cell wall synthesis inhibitor)</td>
<td>No</td>
<td>Phase 3 (cIAI)</td>
<td>Yes</td>
</tr>
<tr>
<td>Ceftaroline-avibactam (CPT-avibactam; ceftaroline/NXL104)</td>
<td>Anti-MRSA cephalosporin/BLI combination (cell wall synthesis inhibitor)</td>
<td>No</td>
<td>Phase 2 (cUTI, cIAI)</td>
<td>Yes</td>
</tr>
<tr>
<td>Imipenem/MK-7655</td>
<td>Carbapenem/BLI combination (cell wall synthesis inhibitor)</td>
<td>No</td>
<td>Phase 2 (cUTI, cIAI)</td>
<td>Yes</td>
</tr>
<tr>
<td>Plazomicin (ACHN-490)</td>
<td>Aminoglycoside (protein synthesis inhibitor)</td>
<td>No</td>
<td>Phase 2 (cUTI)</td>
<td>Yes</td>
</tr>
<tr>
<td>Eravalcine (TP-434)</td>
<td>Fluorocycline (protein synthesis inhibitor targeting the ribosome)</td>
<td>No</td>
<td>Phase 2 (cIAI)</td>
<td>Yes</td>
</tr>
<tr>
<td>Brilacidin (PMX-30063)</td>
<td>Peptide defense protein mimetic (cell membrane disruption)</td>
<td>Yes?</td>
<td>Phase 2 (ABSSSI)</td>
<td>Yes</td>
</tr>
</tbody>
</table>

**sCBP:** serine carbapenemase (e.g., KPC, OXA-48)  
**mCBP:** metallo-β-lactamase (e.g., NDM, IMP, VIM)

CARBAPENEM-RESISTANT ENTEROBACTERIACEAE

THREAT LEVEL
URGENT
This bacteria is an immediate public health threat that requires urgent and aggressive action.

9,000 DRUG-RESISTANT INFECTIONS PER YEAR
600 DEATHS

7,900 CARBAPENEM-RESISTANT KLEBSIELLA SPP.
1,400 CARBAPENEM-RESISTANT E. COLI

CRE HAVE BECOME RESISTANT TO ALL OR NEARLY ALL AVAILABLE ANTIBIOTICS

http://www.cdc.gov/drugresistance/threat-report-2013/
Accessed October 5, 2013
"GREAT NEWS - MORE DOOM AND GLOOM"
Drug–Resistant Organism Prevention and Coordinated Regional Epidemiology (DROP–CRE) Network

Statewide network to detect, control, and prevent multidrug-resistant organisms (MDROs)

Initiated September 2012
Working Group

- Zintars Beldavs, MS  | OHA
- Genevieve Buser, MD, MSHP  | OHA
- Maureen Cassidy, MT, MPH  | OHA
- Ann Thomas, MD, MPH  | OHA
- JJ Furuno, PhD  | OSU College of Pharmacy
- Christopher Pfeiffer, MD, MHS  | PVAMC, OHSU
- John Townes, MD  | OHSU
Advisory Committee

- Dianna Appelgate, MS, MPH, CIC at Sacred Heart, Springfield
- Avanthi Doppalapudi, MD at Providence, Medford
- Ronald Dworkin, MD at Providence, Portland
- Kendra Gohl, RN, BSN, CIC at Columbia, Astoria
- Alex Kallen, MD, MPH at CDC
- Margret Oethinger, MD, PhD at Providence, Portland
- Robert Pelz, MD, PhD at PeaceHealth, Springfield
- Kathy Phipps, RN, BSN, CPUR at Acumentra, Portland
- Mary Post, RN, MS, CNS, CIC at OPSC, Portland
- Pat Preston, MS at Consultant, McMinnville
- Sheryl Ritz, RN, BSN at Vibra, Portland
- Susan Sharpe, PhD, DABMM, FAAM at Kaiser, Portland
- Sarah Slaughter, MD at Providence, Portland
- Cathy Stone, MT, CIC at Good Sam, Corvallis
Initial Goals

- Develop a CRE surveillance and response plan
- Assess statewide needs and capabilities for MDRO/CRE response
- Coordinate statewide MDRO/CRE education
- Develop and disseminate an Oregon-specific CRE Toolkit
Methods

1. CRE surveillance case definition established
2. CRE database created
3. Real-time outbreak assistance initiated
4. Self-administered surveys performed statewide:
   ◦ Microbiology lab directors
   ◦ Infection preventionists (IPs) in acute care hospitals
   ◦ IPs in long term care facilities (LTCFs)
5. Working group members lectured statewide
6. Oregon CRE Toolkit published
Oregon CRE Surveillance

- Mandated December, 2011.
  - Laboratories and clinicians required to report.

- Laboratories submit certain isolates to OSPHL.
  - *E. coli*, *Klebsiella* spp., and *Enterobacter* spp. which meet the Oregon CRE case definition.
  - OSPHL performs MHT and KPC/NDM PCR and informs submitting lab of results in 2–3 business days.
## CRE Reported (Dec 2011–Oct 2013)

<table>
<thead>
<tr>
<th>Organism</th>
<th>Number reported</th>
<th>Modified Hodge Test Positive No. (%)</th>
<th>PCR positive for KPC No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Enterobacter aerogenes</strong></td>
<td>12</td>
<td>6 (50)</td>
<td>0</td>
</tr>
<tr>
<td><strong>Enterobacter cloacae</strong></td>
<td>69</td>
<td>50 (73)</td>
<td>0</td>
</tr>
<tr>
<td><strong>Enterobacter spp.</strong></td>
<td>4</td>
<td>1 (25)</td>
<td>0</td>
</tr>
<tr>
<td><strong>Escherichia coli</strong></td>
<td>10</td>
<td>3 (30)</td>
<td>0</td>
</tr>
<tr>
<td><strong>Klebsiella pneumoniae</strong></td>
<td>11</td>
<td>5 (46)</td>
<td>3 (27)</td>
</tr>
<tr>
<td><strong>Proteus mirabilis</strong></td>
<td>1</td>
<td>n/a</td>
<td>0</td>
</tr>
<tr>
<td><strong>Citrobacter spp</strong></td>
<td>4</td>
<td>3 (75)</td>
<td>0</td>
</tr>
<tr>
<td><strong>Serratia marcescens</strong></td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>113</td>
<td>68 (60)</td>
<td>3 (3)</td>
</tr>
</tbody>
</table>
Microbiology Laboratory Survey

37/48 (77%) laboratories responded

- 25 (68%) used the CLSI breakpoints predating the 2010 update
  - Of those, only 2 (8%) also performed the Modified Hodge Test

- None performed carbapenemase PCR testing.

Pfeiffer CD et al. ICAAC 2013. Slide presentation K-1534
Reporting Practices

"Flag" CR-GNB*

"Flag" ESBLs**

*CR-GNB = carbapenem-resistant GNB
**ESBLs = extended spectrum β-lactamases

Pfeiffer CD et al. ICAAC 2013. Slide presentation K-1534
### Notification Practices when MDR-Enterobacteriaceae are encountered*

<table>
<thead>
<tr>
<th>Action</th>
<th>% of Laboratories</th>
</tr>
</thead>
<tbody>
<tr>
<td>Notify infection control</td>
<td>44%</td>
</tr>
<tr>
<td>Notify nursing station</td>
<td>44%</td>
</tr>
<tr>
<td>Generate an automated report on medical record</td>
<td>42%</td>
</tr>
<tr>
<td>Notify ordering physician</td>
<td>33%</td>
</tr>
<tr>
<td>No further action</td>
<td>14%</td>
</tr>
</tbody>
</table>

Note: Similar responses reported for *Pseudomonas aeruginosa* and *Acinetobacter baumannii*

---

Pfeiffer CD et al. ICAAC 2013. Slide presentation K-1534
Acute Care Survey

- 45/62 (73%) programs responded

Facility Definitions of MDR–Enterobacteriaceae

- Resistant to at least 3 classes of antimicrobials: 25%
- Resistant to at least 2 classes of antimicrobials: 41%
- Susceptible to only 2 classes of antimicrobials: 28%
- Other: 6%
Figure 2  MDROs indicating placement in contact precautions

- MDR-Pseudomonas spp.
- ESBL
- MDR-Acinetobacter spp.
- CRE
- VRE
- MRSA
- C. diff

Percent Yes Response

Poissant T et al. IDWeek 2013. Poster# 1605
Only 58% of respondents agreed that their facility is made aware of patients’ MDRO status upon admission.

82% believed that the receiving facility was made aware of patients’ MDRO status on discharge.

Poissant T et al. IDWeek 2013. Poster# 1605
59/140 (42%) responded

Average daily census: 48

Types of care provided
- Long-term custodial care (97%)
- Skilled nursing/short-term rehabilitation (87%)
- Manage ventilated residents (none)
Average number of staff hours per week dedicated to infection prevention and control

- <2 hours: 2 (3%)
- 2-3 hours: 13 (22%)
- 4-5 hours: 22 (37%)
- 5-9 hours: 9 (15%)
- >10 hours: 6 (10%)
- Other (e.g. "depends", "not sure", "variable"): 7 (12%)
Are you aware of a class of multi-drug resistant gram negative rods termed "Carbapenem-resistant Enterobacteriaceae (CRE)? (n=59)

53% Yes
47% No
The Oregon CRE Toolkit

- Published June, 2013
- Contains specific recommendations for Oregon facilities.
Oregon CRE Toolkit

1. OHA CRE Definition and CRE Reference Guide
2. Prevention and Control in Acute Care
3. Prevention and Control in Long Term Care
4. Prevention and Control in Ambulatory Care
5. Recommendations for Microbiology Laboratories
6. References
7. Appendices (response diagrams, laboratory protocols, patient/staff FAQs, environmental cleaning monitoring tool, inter-facility transfer form)
General Measures for CRE Prevention in Acute Care

- Educate clinical staff
- Ensure reporting of CRE (per correct definition)
- Ensure Infection Prevention & Control is rapidly notified when CRE is detected
- Review lab records for previously unrecognized CRE
- Consider active surveillance cultures for CRE colonization in select patients on admission
Think “NICE” when CRE are encountered:

N - Notify the county health department, pertinent clinician groups, and the antibiotic stewardship program to presence of CRE in the facility. Additionally, for carbapenemase-producing (CP-CRE), notify hospital administration.

I - Intervene on all cases with core infection prevention and control strategies: hand hygiene, contact precautions, private rooms, and optimized environmental cleaning. Reduce unnecessary antibiotics and use of invasive devices. Additionally, for CP-CRE, screen patient contacts and cohort staff and patients.

C - Communicate CRE infection or colonization status to the receiving facility upon patient transfer.

E - Educate patients, staff, and visitors about CRE.
CRE Education/Resources

- Oregon CRE website (and Toolkit)

- Oregon CD Summary (April 23, 2013)
  - “Drop everything, the CRE are coming!”

- CDC CRE website (and Toolkit)
Future Directions

- Continue CRE surveillance and education
  - Tweak definition?
  - Point prevalence survey?
  - Active CRE surveillance for high risk admissions?

- Improve Communication
  - Create regional MDRO collaboratives

- Apply lessons learned to focus on other MDROs
Summary

- CRE are an urgent global threat.
- CRE cases are currently uncommon in Oregon.
- Weaknesses in CRE prevention practices and knowledge of front-line personnel have been identified and are targeted for improvement.
- Oregon has implemented a regional, collaborative approach towards CRE prevention.
Current Working Group
Zintars Beldavs, MS
Gen Buser, MD, MSHP
Maureen Cassidy, MT, MPH
Ann Thomas, MD, MPH
JJ Furuno, PhD
John Townes, MD
Andy Leitz, MD

Regional Collaborators
DROP–CRE Advisory Committee
Margaret Cunningham, MPH
Tasha Poissant, MPH
Robert Arao, MPH
Melissa Parkerton, MA

National Collaborators
Alex Kallen, MD, MPH (CDC)
Nimalie Stone, MD (CDC)
Keith Kaye, MD, MPH (Detroit Medical Center)

PVAMC and the OHSU ID Division
Brian Wong, MD
Tom Ward, MD
Graeme Forrest, MBBS
And others

And of course, Janice Jou, MD, MHS

THANK YOU!