Epidemiology and Prevention of Carbapenem-Resistant Enterobacteriaceae

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Centers for Disease Control and Prevention

The findings and conclusions in this report are those of the author and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

Objectives

- Describe the epidemiology of carbapenem-resistant Enterobacteriaceae (CRE) in the United States
- Review measures necessary to halt transmission
- Recognize the importance of a regional approach to CRE control

Enterobacteriaceae

- Normal human gut flora & environmental organisms
- More than 70 species
- Range of human infections: UTI, wound infections, pneumonia, bacteremia
- Important cause of healthcare- and community-associated infections
  - Some of the most common organisms encountered in clinical laboratories
### Pathogens Reported to NHSN 2009-2010

<table>
<thead>
<tr>
<th>Overall percentage</th>
<th>CLABSI</th>
<th>CAUTI</th>
<th>VAP</th>
<th>SSI</th>
</tr>
</thead>
<tbody>
<tr>
<td>E. coli</td>
<td>12% (2)</td>
<td>4%</td>
<td>11%</td>
<td>17%</td>
</tr>
<tr>
<td>K. pneumoniae</td>
<td>8% (4)</td>
<td>8%</td>
<td>11%</td>
<td>10%</td>
</tr>
<tr>
<td>P. aeruginosa</td>
<td>8% (5)</td>
<td>4%</td>
<td>9%</td>
<td>9%</td>
</tr>
<tr>
<td>Enterobacter spp.</td>
<td>5% (8)</td>
<td>5%</td>
<td>4%</td>
<td>9%</td>
</tr>
</tbody>
</table>

These three groups of organisms make up about 25% of organisms reported to NHSN Device and Procedure module


### Enterobacteriaceae

- Resistance to β-lactams has been a concern for decades
  - β-lactamases
  - Extended-spectrum β-lactamases
- Carbapenems
  - Imipenem, meropenem, doripenem, ertapenem
- Resistance before 2000, combination of mechanisms
  - 1986-1990 in NNIS 2.3% of Enterobacter NS to imipenem

### Novel Carbapenem-Hydrolyzing β-Lactamase, KPC-1, from a Carbapenem-Resistant Strain of Klebsiella pneumoniae

- Isolate collected in 1996 during an ICU surveillance project from NC
- Class A β-lactamase
Carbapenemase-producing CRE in the United States

KPC-producing CRE in the United States

Carbapenemases

<table>
<thead>
<tr>
<th>Enzyme</th>
<th>Classification</th>
<th>Activity</th>
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<tbody>
<tr>
<td>KPC</td>
<td>Class A</td>
<td>Hydrolyzes all β-lactam agents</td>
</tr>
<tr>
<td>NDM-1</td>
<td>Class B: metallo-β-lactamase (MBL)</td>
<td>Hydrolyzes all β-lactam agents except aztreonam</td>
</tr>
<tr>
<td>IMP</td>
<td>Class D</td>
<td>Hydrolyzes carbapenems but not active against 3rd generation cephalosporins</td>
</tr>
<tr>
<td>VIM</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OXA</td>
<td>Class D</td>
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Carbapenemase-producing CRE in the United States

Change in CRE incidence, 2001-2011

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<thead>
<tr>
<th>Organism</th>
<th>2001 Isolates</th>
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<th>2011 Isolates</th>
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<tbody>
<tr>
<td>Klebsiella pneumoniae and oxytoca</td>
<td>654</td>
<td>253 (38.7)</td>
<td>1,002</td>
<td>1,312 (70.6)</td>
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<tr>
<td>E. coli</td>
<td>1,424</td>
<td>421 (29.6)</td>
<td>2,348</td>
<td>2,412 (64.8)</td>
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<tr>
<td>Enterobacter aerogenes and cloacae</td>
<td>553</td>
<td>288 (52.1)</td>
<td>728 (99.7)</td>
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<tr>
<td>Total</td>
<td>2,631</td>
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<tr>
<th>Organism</th>
<th>2001</th>
<th>2011</th>
<th>National Nosocomial Infection Surveillance system, Number (%) of isolates</th>
<th>National Healthcare Safety Network, Number (%) of isolates</th>
</tr>
</thead>
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<tr>
<td></td>
<td>2001</td>
<td>2011</td>
<td>Non-susceptible</td>
<td>Non-susceptible</td>
</tr>
<tr>
<td>Klebsiella pneumoniae and oxytoca</td>
<td>654</td>
<td>1,902</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(38.7)</td>
<td>(70.0)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>4 (1.6)</td>
<td>136 (10.4)</td>
</tr>
<tr>
<td>E. coli</td>
<td>1,424</td>
<td>3,626</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(29.6)</td>
<td>(64.8)</td>
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<td></td>
<td></td>
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<td>24 (1.0)</td>
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<tr>
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<td>553</td>
<td>1,045</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(52.1)</td>
<td>(69.7)</td>
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<td></td>
<td></td>
<td></td>
<td>4 (1.4)</td>
<td>26 (3.6)</td>
</tr>
<tr>
<td>Total</td>
<td>2,631</td>
<td>6,573</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>12 (1.2)</td>
<td>186 (4.2)</td>
</tr>
</tbody>
</table>

### Active CRE surveillance

- **MuGSI (Multi-site Gram-Negative Surveillance Initiative) project**
  - Active, laboratory-initiated, population-based surveillance for CRE and CR Acinetobacter (CRAB) in 6 US sites (sterile sites and urine)
  - Pilot 8/11 to 12/11 (3 sites)
  - 72 CRE (64 patients) - most (59) from one site (OR had 3)
  - Urine most common source (88%)
  - CR K. pneumoniae most common (68%)
  - Most with onset outside hospital (66%)
    - 41/47 (87%) had healthcare exposures (72% hospitalization)
    - 6 were community onset without healthcare exposures

Kallen et al. ID Week 2012, San Diego

### Why are CRE Clinically and Epidemiologically Important?
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- Cause infections associated with high mortality rates

Mortality

P<0.001

<table>
<thead>
<tr>
<th>Percent of Subjects</th>
<th>Overall Mortality</th>
<th>Attributable Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CRKP</td>
<td>CSKP</td>
</tr>
<tr>
<td>Overall Mortality</td>
<td>48</td>
<td>20</td>
</tr>
<tr>
<td>Attributable Mortality</td>
<td>38</td>
<td>12</td>
</tr>
<tr>
<td>OR 3.71 (1.97-7.01)</td>
<td>p&lt;0.001</td>
<td>OR 4.3 (2.16-9.35)</td>
</tr>
</tbody>
</table>


Why are CRE Clinically and Epidemiologically Important?

- Cause infections associated with high mortality rates
- Resistance is highly transmissible
  - Between organisms - plasmids
  - Between patients
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  - Pan-resistant strains identified
  - Could be decades before new agents are available to treat

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Pan-Resistant Enterobacteriaceae

- Report from New York City of 2 "Panresistant" K. pneumoniae
  - 1 patient died
  - 1 had continuing asymptomatic bacteruria


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- Potential for spread into the community
  - E. coli common cause of community infection
MDR GNRs in the Community

ESBLs
- 40 patients with CTX-M E. coli from urine in a facility in Texas
  - 30/40 were isolated from outpatients, 7 (18%) had no documented contact with the healthcare system in previous 6 months and no comorbidities
- Swedish travelers – 100 travelers outside of Northern Europe
  - 24 came back with ESBL in stool (mostly NDM)
  - 7/8 to India, 10/31 to Asia
  - Development of gastroenteritis a risk factor
  - 5/21 persistently colonized

Lewis JS, et al. Poster Presentation, 49th ICAAC 2009, San Francisco
Tangden T et al. AAC 2010: 3564-3568

MDR GNRs in the Community

NDM
- Identified in K. pneumoniae in river in Hanoi, Viet Nam
- Cause of community-onset infections in India
  - In one survey, isolates from 2 sites often from community acquired UTIs
- Gene for NDM detected in 2/50 drinking water samples and 51/171 water seepage samples from New Delhi

Isozumi R et al. EID 2012: 1383-4
Kumarasamy K Lancet ID 2010;
Walsh TR Lancet ID 2011:355-362

Why are CRE Clinically and Epidemiologically Important?

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- Resistance is highly transmissible
  - Between organisms – plasmids
  - Between patients
- Treatment options are limited
  - Pan-resistant strains identified
  - Could be decades before new agents are available to treat
- Potential for spread into the community
  - E. coli common cause of community infection
  - In most areas in the United States this organism appears to infrequently identified
Facilities Reporting at least One CRE (CAUTI or CLABSI) to NHSN, First Half of 2012

<table>
<thead>
<tr>
<th>Facility characteristic</th>
<th>Number of facilities with CRE from CAUTI or CLABSI (2012)</th>
<th>Total facilities performing CAUTI or CLABSI surveillance (2012)</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All acute care hospitals</td>
<td>181</td>
<td>3,918</td>
<td>4.6</td>
</tr>
<tr>
<td>Short stay acute hospital</td>
<td>145</td>
<td>3,216</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>
</tbody>
</table>

ROLE OF LONG-TERM CARE

- Of 40 KPC patients, only 4 definitively acquired KPC in acute care hospital
- Most (60%) linked to 1 LTACH

Prevalence of CRE Carriage at admission to 4 acute care hospitals:

-丁 (1.5%)
- VSNF (27.3%)
- LCTF (33.3%)
- LTCF overall (8.3%)

0% from those admitted to the community

Prevention

http://www.cdc.gov/hai/organisms/cre/cre-toolkit/

Surveillance and Definitions

- Facilities/Regions should have an awareness of the prevalence of CRE in their Facility/Region
  - Could concentrate on K. pneumoniae
  - Could concentrate on those NS to a carbapenem OR add R to a third-generation cephalosporin to the definition to increase specificity for KPC
    - Ceftazidime/cefotaxime, ceftazidime
- No easy way right now to check for carbapenemases
**Interventions**

- **Core**
  - Hand hygiene
  - Contact Precautions*
  - HCP education
  - Minimizing device use
  - Patient and Staff cohorting
  - Laboratory notification*
  - Antimicrobial stewardship
  - CRE Screening*

- **Supplemental**
  - Active surveillance cultures
  - Chlorhexidine bathing

* Included in 2009 document

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**Contact Precautions**

- CP for patients colonized or infected with CRE
- Systems in place to identify patients at readmission
- Education of HCP about use and rationale behind CP
- Adherence monitoring
- Consideration of pre-emptive CP in patients transferred from high-risk settings

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**Contact Precautions in Long-Term Care**

- CP could be modified in these settings:
  - CP should be used for residents with CRE who are at higher risk for transmission
    - Dependent upon HCP for their activities of daily living
    - Ventilator-dependent
    - Incontinent of stool
    - Wounds with drainage that is difficult to control
  - For other residents the requirement for Contact Precautions might be relaxed
  - Standard Precautions should still be observed
Duration of KPC Carriage

- KPC Patients swabbed 5 to 6 times (at discharge, 2 weeks, 1, 2, 3 mos post-discharge)
- Overall resolution of carriage (2 consecutive negatives)
  - 62/125 (52%)
  - 39% of recently identified patient
  - 79% of remotely identified patients (> 4 mos prior)


Risk Factors for Persistent Carriage


Risk Factors for CRE at Readmission

- Case-control study of 66 patients with CRE
  - Compared those positive at readmission with those that were negative

Schechner V et al. ICHE 2011;32:497-503
### Number of Screens to Determine CRE Clearance

- One negative (N=97) – 65 (67%) cleared
- Two negative (N=67) – 57 (85%) cleared
- Three negative (N=50) – 45 (90%) cleared


### Patient and Staff Cohorting

- CRE patients in single rooms (when available)
- Cohorting (even when in single rooms)
- Staff cohorting
- Preference for single rooms should be given to patients at highest risk for transmission such as patients with incontinence, medical devices, or wounds with uncontrolled drainage

### CRE Screening

- Studies suggest that only a minority of patients colonized with CRE will have positive clinical cultures
  - CRKP Point prevalence study in Israel (5.4% prevalence rate); 5/16 had a positive clinical culture for CRKP.
  - A study of surveillance cultures at a US hospital found that they identified a third of all positive CRKP patients. Not having these patients in CP resulted in about 1400 days of unprotected exposure.

_Calfee et al. JCHE 2008;29:966-8_
CRE Screening
- Used to identify unrecognized CRE colonization among contacts of CRE patients
- Stool, rectal, peri-rectal
- Link to laboratory protocol [http://www.cdc.gov/ncidod/dhqp/pdf/ar/Klebsiella_or_E.coli.pdf](http://www.cdc.gov/ncidod/dhqp/pdf/ar/Klebsiella_or_E.coli.pdf)
- Applicable to both acute and long-term care settings
- Description of types
  - Screening of epidemiologically linked patients
    - Roommates
    - Patients who shared primary HCP
  - Point prevalence survey
  - Rapid assessment of CRE Prevalence on particular wards/units
  - Might be useful if lab review identifies one or more previously unrecognized CRE patient on a particular unit

Active Surveillance Cultures
- Screening patients (generally at admission) for CRE
- Controversial
- Potential considerations:
  - Focus on patients admitted to certain high-risk settings (e.g., ICU) or specific populations (e.g., from LTCF/LTAC)
  - Patients hospitalized outside the US

Chlorhexidine Bathing
- Limited evidence for CRE
  - Used effectively in outbreak in LTAC as part of a package of interventions
  - Applied to all patients regardless of CRE colonization status
  - Has shown decrease transmission of MRSA and VRE
- Some studies suggest CHG bathing may not be done "well"

Munoz-Price et al. ICHE 2010;31:341-7
REGIONAL APPROACH TO CRE PREVENTION

Inter-Facility Transmission of MDROs (Including CRE)

Israel Experience
- KPCs likely originally from US identified in Israel beginning in late 2005
- By early 2006, increase in cases
- Initiated National effort to control CRE
  - Mandatory reporting of patients with CRE
  - Mandatory isolation (CP) of CRE patients
  - Staff and patient cohorting
  - Task Force developed with authority to collect data and intervene

Figure 3. Patient flow among regional health care facilities. Outbreaks of infection with multidrug-resistant organisms have been found to follow the flow of colonized patients across institutions.

Summary

- Carbapenem-resistance among Enterobacteriaceae appears to be increasing
  - Appears to be driven primarily by the emergence of carbapenemases
- Heterogeneously distributed within and across regions
- Has the potential to spread widely
  - Healthcare and community settings
- Most areas in a position to act to slow emergence
- A regional approach to MDRO prevention is required
  - Public health well-positioned to facilitate and support regional prevention efforts

Thanks for your attention.

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