Carbapenem-Resistant Enterobacteriaceae (CRE): Epidemiology and Prevention

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Objectives

- Provide overview of healthcare-associated infections and antimicrobial resistance in healthcare settings
- Describe the epidemiology of carbapenem-resistant Enterobacteriaceae (CRE)
- Describe best practices in the management and control of CRE in healthcare settings
- Define the role of public health in CRE prevention
BACKGROUND
Healthcare-Associated Infections (HAIs)

- Definition
  - Infections acquired during course of receiving treatment for other conditions within a healthcare setting
  - Onset of infection can occur during stay in healthcare setting or after discharge

- Healthcare settings
  - Hospitals: acute care facilities, critical access facilities
  - Long term care facilities (LTCF)
  - Outpatient settings: dialysis centers, ambulatory surgical centers, specialty clinics, physicians’ offices
Annual HAI Burden
What is Known: Acute Care Settings

- 1.7 million infections (5% of all admissions)
  - Most (1.3 million) were outside of ICUs

- 1 in 20 patients

- $28–33 billion in excess costs

- Estimated 100,000 associated deaths

Key HAI Concepts

- **Mode of transmission**
  - Contact (direct, indirect)
  - Droplet
  - Airborne

- **Colonization vs. infection**
Site-Specific or Procedure-Associated HAIs

- **Bloodstream infections**
  - Central-line associated bloodstream infections (CLABSI)

- **Pneumonia**
  - Ventilator-associated pneumonia (VAP)

- **Urinary tract infections**
  - Catheter-associated urinary tract infections (CAUTI)

- **Surgical site infections**
Causative Agents of HAIs

- Variety of pathogens (bacteria, virus, fungi)
- Common pathogens
  - *Staphylococcus aureus*
  - Enterococcus
  - *Clostridium difficile*
  - *Klebsiella pneumoniae*
  - *Escherichia coli*
  - *Pseudomonas aeruginosa*
  - *Acinetobacter spp.*
  - Norovirus
  - Influenza
  - Bloodborne pathogens (hepatitis B, hepatitis C, HIV)
Enterobacteriaceae

- Bacterial pathogens commonly associated with community and healthcare-associated infections

- *E. coli* is the most common cause of outpatient urinary tract infections

- *E. coli* and *Klebsiella* species
  - Important causes of healthcare associated infections
  - Account for >15% of all healthcare-associated infections (HAIs) reported to National Healthcare Safety Network in 2007
# HAI Pathogens

**NHSN Data, Jan 2006- Sept 2007 (n=33,848)**

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Overall percentage (rank)</th>
<th>CLABSI</th>
<th>CAUTI</th>
<th>VAP</th>
<th>SSI</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>E. coli</em></td>
<td>10% (5)</td>
<td>3%</td>
<td>21%</td>
<td>5%</td>
<td>10%</td>
</tr>
<tr>
<td><em>P. aeruginosa</em></td>
<td>8% (6)</td>
<td>3%</td>
<td>10%</td>
<td>16%</td>
<td>6%</td>
</tr>
<tr>
<td><em>K. pneumoniae</em></td>
<td>6% (7)</td>
<td>5%</td>
<td>8%</td>
<td>18%</td>
<td>3%</td>
</tr>
<tr>
<td><em>A. baumannii</em></td>
<td>3% (9)</td>
<td>2%</td>
<td>1%</td>
<td>8%</td>
<td>.6%</td>
</tr>
</tbody>
</table>

National Healthcare Safety Network (NHSN)
EMERGENCE OF MULTIDRUG-RESISTANT ORGANISMS
Multidrug-Resistant Organisms (MDROs): Epidemiologically Important Pathogens

- Infectious organisms resistant to one or more classes of antimicrobial agents

- Common characteristics:
  - Newly discovered or reemerging pathogen
  - Propensity for transmission
  - Antimicrobial resistance/limited treatment options
  - Serious clinical disease, increased morbidity and mortality

2006 HICPAC MDRO Guideline
Gram-Negative Bacilli: Highly Resistant Pathogens in Healthcare

- **Enterobacteriaceae**
  - *Klebsiella pneumoniae*
  - *Escherichia coli*
  - *Citrobacter freundii*
  - *Enterobacter species*
  - *Serratia species*
  - *Salmonella species*

- **Non-fermenters**
  - *Pseudomonas aeruginosa*
  - *Acinetobactor baumannii*
Why is Antimicrobial Resistance Increasing?

- Susceptible hosts
- Inattention to basic infection control measures
- Selective pressure from antibiotic use
- Overuse/inappropriate use of antibiotics
- Unrecognized colonization
- Unrecognized reservoirs (e.g., environmental)
- Movement of patients and staff between institutions
β-lactam antibiotics (derivatives of penicillin) have long been the mainstay of treatment for infections caused by Enterobacteriaceae.

- However, resistance to β-lactams emerged several years ago and has continued to rise.
  - Extended spectrum β-lactamases (ESBLs)
  - Plasmid-mediated AmpC-type enzymes
Carbapenems: The Last Line of Defense

- **Most potent β-lactam class of agents**
  - Doripenem, Ertapenem, Imipenem, Meropenem

- Remained effective against most Enterobacteriaceae

- However, resistance to carbapenems began to emerge
CARBAPENEM-RESISTANT ENTEROBACTERIACEAE (CRE)
Emerging Threat in Healthcare

Carbapenem-Resistant Enterobacteriaceae
A Potential Threat
CRE Infections

- **Types of infections**
  - Central line-associated bloodstream infection (CLABSI)
  - Catheter-associated urinary tract infection (CAUTI)
  - Ventilator-associated pneumonia (VAP)

- **Medical or surgical intensive care units**

- **Resistance to \( \geq 1 \) antimicrobial in \( \geq 3 \) classes**

**Table 1.** Prevalence of Multidrug Resistance among Isolates Reported to the National Nosocomial Infection Surveillance (NNIS) system and the National Healthcare Safety Network (NHSN), 2000–2008

<table>
<thead>
<tr>
<th>Organism(s)</th>
<th>2000</th>
<th>2001</th>
<th>2002</th>
<th>2003</th>
<th>2004</th>
<th>2006</th>
<th>2007</th>
<th>2008</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>A. baumannii</em></td>
<td>195/303 (64)</td>
<td>205/327 (63)</td>
<td>182/277 (66)</td>
<td>229/326 (70)</td>
<td>168/248 (68)</td>
<td>132/208 (63)</td>
<td>251/362 (69)</td>
<td>312/420 (74)</td>
</tr>
<tr>
<td><em>P. aeruginosa</em></td>
<td>217/1,174 (18)</td>
<td>210/1,096 (19)</td>
<td>204/1,029 (20)</td>
<td>204/966 (21)</td>
<td>146/700 (21)</td>
<td>102/574 (18)</td>
<td>156/707 (22)</td>
<td>182/1,080 (17)</td>
</tr>
<tr>
<td><em>E. coli</em> and</td>
<td>69/1,003 (7)</td>
<td>87/1,018 (9)</td>
<td>89/968 (9)</td>
<td>103/893 (12)</td>
<td>119/792 (15)</td>
<td>80/630 (13)</td>
<td>122/852 (14)</td>
<td>214/1,677 (13)</td>
</tr>
</tbody>
</table>

Kallen et al. *Infect Control Hosp Epidemiol* 2010;31(S1):S51.
Carbapenem-Resistant Enterobacteriaceae: Public Health Importance

- Resistance via mobile genetic elements
- High mortality
- Limited or no treatment options
# Mechanisms of Carbapenem Resistance

<table>
<thead>
<tr>
<th></th>
<th>Serine carbapenemases</th>
<th>Metallo-(\beta)-lactamases (MBL)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Examples</strong></td>
<td><em>K. pneumoniae</em> carbapenemase (KPC)</td>
<td>Active against imipenem (IMP)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>New Delhi MBL (NDM)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Verona integron-encoded MBL (VIM)</td>
</tr>
<tr>
<td><strong>Prevalence</strong></td>
<td>Most common carbapenemase in the United States</td>
<td>Rare among <em>Enterobacteriaceae</em> in the United States. Common in other parts of the world.</td>
</tr>
</tbody>
</table>
**Klebsiella Pneumoniae Carbapenemase**

- **Class A carbapenemase**
  - Confers resistance to all β-lactams, including extended-spectrum cephalosporins and carbapenems

- **Occurs in Enterobacteriaceae**
  - Most commonly in *K. pneumoniae* and *E. coli*

- **KPC-producing *K. pneumoniae***
  - First reported from North Carolina in 1990s
  - <1% of all *K. pneumoniae* reported in 2000
  - 11% of all *K. pneumoniae* associated with CLABSI in 2006-2007
Carbapenem resistance in *K. pneumoniae*
NHSN Jan 2006-Sept 2007

<table>
<thead>
<tr>
<th></th>
<th>CLABSI</th>
<th>CAUTI</th>
<th>VAP</th>
<th>Pooled</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbapenem-resistant <em>K. Pneumoniae</em></td>
<td>11%</td>
<td>10%</td>
<td>4%</td>
<td>8%</td>
</tr>
</tbody>
</table>

Hidron, A et al Infect Control Hospital Epidemiol. 2008;29:996
# Antimicrobial Susceptibility Profile: KPC-Producing *K. pneumoniae*

<table>
<thead>
<tr>
<th>Antimicrobial</th>
<th>Interpretation</th>
<th>Antimicrobial</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amikacin</td>
<td>I</td>
<td>Chloramphenicol</td>
<td>R</td>
</tr>
<tr>
<td>Amox/clav</td>
<td>R</td>
<td>Ciprofloxacin</td>
<td>R</td>
</tr>
<tr>
<td>Ampicillin</td>
<td>R</td>
<td>Ertapenem</td>
<td>R</td>
</tr>
<tr>
<td>Aztreonam</td>
<td>R</td>
<td>Gentamicin</td>
<td>R</td>
</tr>
<tr>
<td>Cefazolin</td>
<td>R</td>
<td>Imipenem</td>
<td>R</td>
</tr>
<tr>
<td>Cefpodoxime</td>
<td>R</td>
<td>Meropenem</td>
<td>R</td>
</tr>
<tr>
<td>Cefotaxime</td>
<td>R</td>
<td>Pipercillin/Tazo</td>
<td>R</td>
</tr>
<tr>
<td>Cetotetan</td>
<td>R</td>
<td>Tobramycin</td>
<td>R</td>
</tr>
<tr>
<td>Cefoxitin</td>
<td>R</td>
<td>Trimeth/Sulfa</td>
<td>R</td>
</tr>
<tr>
<td>Ceftazidime</td>
<td>R</td>
<td>Polymyxin B</td>
<td>MIC &gt;4mg/ml</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>R</td>
<td>Colistin</td>
<td>MIC &gt;4mg/ml</td>
</tr>
<tr>
<td>Cefepime</td>
<td>R</td>
<td>Tigecycline</td>
<td>S</td>
</tr>
</tbody>
</table>
What Else is There for Treatment?

- **Treatment Options**
  - Polymyxin E / Colistin
  - Tigecycline

- Both retain *in vitro* susceptibility against many KPC-producing organisms

- Treatment experience has not been encouraging

- Drug toxicities are concerns
EPIDEMIOLOGY OF CRE
Risk Factors for and Outcomes of Carbapenem-Resistant *K. pneumoniae* (CRKP) Infections

- Case control studies done by Patel et al. at Mount Sinai in NYC, where CRKP are now endemic

- 99 patients with invasive CRKP infections compared to 99 patients with invasive carbapenem-susceptible *K. pneumoniae* (CSKP) infections

Patient-Specific Risk Factors

* $p < 0.001$

### Pre-infection Length of Stay

<table>
<thead>
<tr>
<th>Pre-infection LOS (days)</th>
<th>CRKP (n=99)</th>
<th>CSKP (n=99)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>25.1</td>
<td>6.44</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>Median</td>
<td>21</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>0-129</td>
<td>0-59</td>
<td></td>
</tr>
</tbody>
</table>

Healthcare-Associated Factors


* p <0.001
## Prior Antibiotics

<table>
<thead>
<tr>
<th></th>
<th>CRKP (n=99)</th>
<th>CSKP (n=99)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cephalosporins</td>
<td>63</td>
<td>31</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>Fluoroquinolones</td>
<td>36</td>
<td>23</td>
<td>p=0.05</td>
</tr>
<tr>
<td>B-lactam/ inhibitor</td>
<td>54</td>
<td>33</td>
<td>p=0.005</td>
</tr>
<tr>
<td>Aminoglycosides</td>
<td>14</td>
<td>3</td>
<td>p=0.01</td>
</tr>
<tr>
<td>Carbapenems</td>
<td>54*</td>
<td>6</td>
<td>p&lt;0.001</td>
</tr>
</tbody>
</table>

- *26 (48%) on carbapenems at time of isolation of CRKP
- *37 (69%) either on carbapenems or completed a course of carbapenems within 2 weeks prior to CRKP isolation

Geographical Distribution of KPC-Producers, November 2006

Widespread
Sporadic Isolate(s)
Geographical Distribution of KPC-Producers, March 2011
CRE PREVENTION
A Call to Action

Carbapenem-Resistant Enterobacteriaceae
A Potential Threat

Mitchell J. Schwaber, MD, MSc
Yehuda Carmeli, MD, MPH

After more than 7 decades of antibiotic use, a recurrent pattern of antimicrobial resistance spread is evident among certain bacterial pathogens. In this pattern, resistance occurs first among the most severely affected patients, due to the activities of the hospital. Among these are carbapenemases, primarily the serine β-lactamase KPC and the metallo-β-lactamase VIM. The genes coding for these enzymes are carried by plasmids that often carry other resistance factors as well, resulting in extensively drug-resistant (XDR) bacteria. Moreover, plasmids carrying resistance genes also may carry virulence factors, thus leading to severe infections. Since plasmids are readily transferred, these resistance genes can easily spread within and between health care facilities. In the Achei, 2008;300:2911

“An effective intervention at containing the spread of CRE should ideally be implemented before CRE have entered a region, or at the very least, immediately after its recognition. Policy makers and public health authorities must ensure the early recognition and coordinated control of CRE.”

JAMA December 2008;300:2911
A Call To Action- Answered

- CDC agrees that the time to act to control CRE is now
- Recommendations approved by the Healthcare Infection Control Practices Advisory Committee and published in 2009 MMWR
Guidance for Control of Infections with Carbapenem-Resistant or Carbapenemase-Producing *Enterobacteriaceae* in Acute Care Facilities

Infection with carbapenem-resistant *Enterobacteriaceae* (CRE) or carbapenemase-producing *Enterobacteriaceae* is emerging as an important challenge in health-care settings (1). Currently, carbapenem-resistant *Klebsiella pneumoniae* (CRKP) is the species of CRE most commonly encountered in the United States. CRKP is resistant to almost all available antimicrobial agents, and infections with CRKP have been associated with high rates of morbidity and mortality, particularly among persons with prolonged hospitalization and those who are critically ill and exposed to invasive devices (e.g., ventilators or central venous catheters). This report provides updated recommendations from CDC and the Healthcare Infection Control Practices Advisory Committee (HICPAC) for the control of CRE or carbapenemase-producing *Enterobacteriaceae* in acute care (inpatient) facilities. For all acute care facilities, CDC and HICPAC recommend an aggressive infection control strategy, including managing all patients with CRE using contact precautions and implementing Clinical and Laboratory Standards Institute (CLSI) guidelines for detection of carbapenemase production. In areas where CRE are not endemic, acute care facilities should 1) review microbiology records for the preceding 6--12 months to determine whether CRE have been recovered at the facility, 2) if the review finds previously unrecognized CRE, perform a point prevalence culture survey in high-risk units to look for other cases of CRE, and 3) perform active surveillance cultures of patients with epidemiologic links to persons from whom CRE have been recovered. In areas where CRE are endemic, an increased likelihood exists for importation of CRE, and facilities should consider additional strategies to reduce rates of CRE (2). Acute care facilities should review these recommendations and implement appropriate strategies to limit the spread of these pathogens.
Infection Control Recommendations Regardless of CRE Prevalence

- Implement Contact Precautions for patients colonized or infected with CRE

- Place all patients colonized or infected with CRE in single-patient rooms when possible

- Ensure a mechanism is in place for microbiology staff to alert infection prevention staff immediately whenever CRE is identified in the laboratory
Surveillance Recommendations in Areas Where CRE Are Not Endemic

- Review preceding 6-12 months of microbiology records

- **No CRE identified**
  - Continue monitoring for clinical infections

- **Unrecognized CRE identified**
  - Perform point prevalence survey in high-risk units
Surveillance Recommendations in Areas Where CRE Are Not Endemic

If CRE detected in clinical infections or if point prevalence survey reveals unrecognized colonization

Conduct active surveillance testing of patients with epidemiological links to patient with CRE infection

Continue active surveillance periodically until no new cases of CRE infection or colonization are identified

If no CRE transmission is identified after repeated active surveillance, consider periodic point prevalence
Surveillance Recommendations in Areas Where CRE Are Endemic

- Implement Tier 2 recommendations of the 2006 “Guidelines for Management of MDROs in Healthcare Settings”
  - Presumptive Contact Precautions for patients admitted from settings/facilities with high CRE prevalence
  - Conduct serial (e.g., weekly) unit-specific point prevalence culture surveys of CRE to assess efficacy of intensified interventions
  - Monitor cleaning performance to ensure consistent environmental cleaning and disinfection of surfaces frequently touched
Active surveillance cultures will increase the workload of hospital microbiology labs that are already stretched.

However, unrecognized transmission has been widespread in some instances.

Facilities can stop doing active surveillance if they consistently show their infection control measures control CRE transmission.
The Iceberg Effect

Infected

Colonized
Carbapenem-Resistant *Enterobacteriaceae*: Not Just in Acute Care Hospitals

- Number of reports of CRE cases from as early as 2004 from long-term acute care hospitals (LTACH) and long-term care facilities (LTCF)

- Similar pattern had been recognized with ESBLs (e.g., movement from acute care into LTCF)
Experience from Outbreak Investigations

- In November of 2008, DHQP was invited to help investigate an outbreak of four patients from one long-term care facility who had recently had CRKP recovered from urine cultures.

- CRE colonization among other patients on same floor as the initial cases: 20/41 = 49%
CRKP Outbreaks: Lessons Learned

- Healthcare epidemiology/infection control staff might not be aware that CRE are present in their facilities.

- The etiology of outbreaks of CRE are multi-factorial, but are due in part to:
  - Non-compliance with infection control
  - Unrecognized carriers serving as reservoirs for transmission
Where Are We Now?
The Bad News

- CRE, especially CRKP, are being encountered more commonly in healthcare settings
- Infections caused by these pathogens are associated with high mortality
- They are readily transmitted in healthcare settings
- New treatment options are non-existent
- These are also commonly encountered pathogens in community infections
Where Are We Now?
The Good News

- Simple infection control interventions have been very successful in controlling the transmission of CRE
  - Hand hygiene
  - Contact Precautions
  - Identification of unrecognized carriers
The Healthcare System — More than Just Hospitals

- Acute Care Facility
- Outpatient/Ambulatory Facility
- Long Term Care Facility
- Home Care
# Inter-facility Infection Control Transfer Form

This form must be filled out for transfer to accepting facility with information communicated prior to or with transfer. Please attach copies of latest culture reports with susceptibilities if available.

## Sending Healthcare Facility:

<table>
<thead>
<tr>
<th>Patient/Resident Last Name</th>
<th>First Name</th>
<th>Date of Birth</th>
<th>Medical Record Number</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Name/Address of Sending Facility</th>
<th>Sending Unit</th>
<th>Sending Facility phone</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Sending Facility Contacts</th>
<th>NAME</th>
<th>PHONE</th>
<th>E-mail</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case Manager/Admin/SW</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infection Prevention</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Is the patient currently in isolation?**  □ NO  □ YES

**Type of Isolation (check all that apply)**  □ Contact  □ Droplet  □ Airborne  □ Other:

## Does patient currently have an infection, colonization OR a history of positive culture of a multidrug-resistant organism (MDRO) or other organism of epidemiological significance?

<table>
<thead>
<tr>
<th>Methicillin-resistant Staphylococcus aureus (MRSA)</th>
<th>Colonization or history Check if YES</th>
<th>Active infection on Treatment Check if YES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vancomycin-resistant Enterococcus (VRE)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clostridium difficile</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acinetobacter, multidrug-resistant*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>E. coli, Klebsiella, Proteus etc. w/Extended Spectrum B-Lactamase (ESBL)*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carbenepenemase resistant Enterobacteriaceae (CRE)*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other:</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Resources

- **CDC MDRO guidelines**

- **MMWR: Guidance for control of CRE**
  - [http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5810a4.htm](http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5810a4.htm)

- **Interfacility transfer forms**
  - [http://www.cdc.gov/HAI/toolkits/InterfacilityTransferCommunicationForm11-2010.pdf](http://www.cdc.gov/HAI/toolkits/InterfacilityTransferCommunicationForm11-2010.pdf)

- **CDC CRE took kit**
  - Coming summer 2011…
Thank You

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