Multidrug-Resistant Gram-Negative Bacilli: Epidemiology and Prevention

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Faculty Disclosure

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Alex Kallen, MD, MPH
Nothing to disclose
Objectives

• Describe the epidemiology of multidrug-resistant (MDR) Gram-negative rods (GNRs) in healthcare settings

• Describe approaches designed to prevent transmission of MDR GNRs
Epidemiology
## Pathogens Reported to NHSN Jan 2006- Sept 2007

<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>E. coli</td>
<td>10% (5)</td>
<td>3%</td>
<td>21%</td>
<td>5%</td>
<td>10%</td>
</tr>
<tr>
<td>P. aeruginosa</td>
<td>8% (6)</td>
<td>3%</td>
<td>10%</td>
<td>16%</td>
<td>6%</td>
</tr>
<tr>
<td>K. pneumoniae</td>
<td>6% (7)</td>
<td>5%</td>
<td>8%</td>
<td>18%</td>
<td>3%</td>
</tr>
<tr>
<td>A. baumannii</td>
<td>3% (9)</td>
<td>2%</td>
<td>1%</td>
<td>8%</td>
<td>.6%</td>
</tr>
</tbody>
</table>

Carbapenem Resistance among Enterobacteriaceae, NHSN Device and Procedure-Associated Module, 2007-2010

In 2011, 6.5% of NHSN hospitals reported a CRE (E. coli or Klebsiella) to device or procedure module (CLABSI, CAUTI, SSI)

<table>
<thead>
<tr>
<th></th>
<th>2007/2008</th>
<th>2009/2010</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>E. coli</strong></td>
<td>1.9%</td>
<td>2.9%</td>
</tr>
<tr>
<td></td>
<td>1.9%</td>
<td>2.3%</td>
</tr>
<tr>
<td></td>
<td>1.9%</td>
<td>3.0%</td>
</tr>
<tr>
<td></td>
<td>1.9%</td>
<td>3.5%</td>
</tr>
<tr>
<td></td>
<td>1.9%</td>
<td>1.5%</td>
</tr>
<tr>
<td></td>
<td>1.9%</td>
<td>2.0%</td>
</tr>
</tbody>
</table>

| **Klebsiella** | 1.9%      | 2.9%      |
|                | 1.9%      | 2.3%      |
|                | 1.9%      | 3.0%      |
|                | 1.9%      | 3.5%      |
|                | 1.9%      | 1.5%      |
|                | 1.9%      | 2.0%      |

|                | 13.2%     | 11.7%     |
|                | 12.7%     | 12.5%     |
|                | 11.7%     | 9.9%      |
|                | 11.7%     | 11.2%     |
|                | 11.7%     | 9.5%      |
|                | 11.7%     | 8.2%      |
Percent *A. baumannii* and *P. aeruginosa* in ICUs that are multidrug-resistant, NNIS and NHSN, 2000-2008*

*Includes ICUs only (MICU, SICU, MSICU) and device-related infections only (CLABSI, CAUTI, VAP)*
Mechanisms of Carbapenem-Resistance in *Enterobacteriaceae* (CRE)

- **Before 2000:** Extended – spectrum cephalosporinase + porin loss
  - Extended-spectrum β-lactamases (ESBLs)
  - AmpC-type enzymes

- **1986-1990 in NNIS** 2.3% of *Enterobacter* NS to imipenem.
  - Did not increase over the time period unlike imipenem NS *Pseudomonas* (Gaynes and Culver. ICHE 1992 13:10-14)

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

Hesna Yigit, Anne Marie Queenan, Gregory J. Anderson, Antonio Domenech-Sanchez, James W. Biddle, Christine D. Steward, Sebastian Alberti, Karen Bush, and Fred C. Tenover

- Isolate collected during an ICU surveillance project from NC
KPC-producing CRE in the United States

Nov, 2006

CDC, unpublished data
KPC-producing CRE in the United States

CDC, unpublished data
Dissemination of CRE

~70% of Database potentially made up of ST 258

Brandon Kitchel, J. Kamile Rasheed, et al. ICAAC 2008
Worldwide Distribution of KPC

Emergence of MBLs in the United States

To date CDC has confirmed:
---14 NDM-producing Enterobacteriaceae (all but 1 had received care outside the U.S.
---3 IMP-producing Enterobacteriaceae
---3 VIM-producing Enterobacteriaceae (2/3 had received care outside the US)
---2 OXA-48 producing Enterobacteriaceae (both with healthcare exposure outside the US)

Yigit et al. 2008. AAC
MMWR. 2010. June
MMWR. 2010. Sep
Mochon et al. 2011. JCM
Limbago et al. 2011 submitted
Carbapenemase-producing CRE in the United States

CDC, unpublished data
CRE Risk Factors

- Severe illness, poor functional status, ICU admission, receipt of antibiotics
- Classes of associated antibiotics include: FQ, carbapenems, cephalosporins (particularly extended-spectrum), and vancomycin
- Admission from LTAC risk for CRE and CR *Acinetobacter*

Gasink et al. ICHE 2009; 30:1180-5
Schwaber et al AAC 2008; 52:1028-33
Marchaim et al. AJIC 2012
Antibiotics as a CRE Risk Factor

<table>
<thead>
<tr>
<th>Variable</th>
<th>CRE vs uninfected⁰</th>
<th>ESBL vs uninfected⁰</th>
<th>Susceptible vs uninfected⁰</th>
<th>CRE vs ESBL</th>
<th>CRE vs susceptible</th>
<th>CRE vs all controls combined</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>P</td>
<td>OR (95% CI)</td>
<td>P</td>
<td>OR (95% CI)</td>
<td>P</td>
</tr>
<tr>
<td>Any antibiotic exposure in previous 3 months</td>
<td>11.4 (2.6–64.3)</td>
<td>.006</td>
<td>1.7 (0.7–4.1)</td>
<td>.24</td>
<td>5.2 (1.4–19.4)</td>
<td>.015</td>
</tr>
<tr>
<td>Permanent residency in institution</td>
<td>1.04 (0.2–4.5)</td>
<td>.96</td>
<td>1.3 (0.5–3.6)</td>
<td>.56</td>
<td>0.15 (0.05–0.3)</td>
<td>.902</td>
</tr>
<tr>
<td>Isolation of resistant bacteria in previous 6 months</td>
<td>15.3 (4.2–55.6)</td>
<td>&lt;.001</td>
<td>8.25 (2.7–25.7)</td>
<td>&lt;.001</td>
<td>6.6 (1.9–23.3)</td>
<td>.003</td>
</tr>
<tr>
<td>Dependent functional status in background</td>
<td>1.4 (0.5–4.4)</td>
<td>.55</td>
<td>5.6 (2.1–14.7)</td>
<td>.001</td>
<td>2.6 (1.1–6.4)</td>
<td>.03</td>
</tr>
<tr>
<td>ICU stay in previous 3 months</td>
<td>3.9 (1.3–12.4)</td>
<td>.02</td>
<td>5.2 (2.1–13.2)</td>
<td>.001</td>
<td>3.0 (1.2–7.2)</td>
<td>.02</td>
</tr>
<tr>
<td>Recent (6 months) invasive procedure</td>
<td>4.2 (1.2–15.5)</td>
<td>.03</td>
<td>1.2 (0.4–3.4)</td>
<td>.76</td>
<td>3.2 (1.3–8)</td>
<td>.01</td>
</tr>
<tr>
<td>Charlson weighted index comorbidity ≥3</td>
<td>3.1 (0.8–11.8)</td>
<td>.1</td>
<td>1.1 (0.4–2.7)</td>
<td>.87</td>
<td>2.2 (0.94–5)</td>
<td>.07</td>
</tr>
</tbody>
</table>

Note: CI, confidence interval; CRE, carbapenem-resistant Enterobacteriaceae; ESBL, extended-spectrum β-lactamase-producing Enterobacteriaceae; ICU, intensive care unit; OR, odds ratio.

⁰ If a variable was not significant in bivariate analysis, it was not forced into the multivariable model.

¹ Part of the case-case-control analysis.

Includes methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant *Enterococcus*, ESBL-producing Enterobacteriaceae, *Acinetobacter baumannii*, and *Pseudomonas aeruginosa*.
MDR Non-Fermenter Risk factors

- **Acinetobacter**
  - Prior antibiotic use (most often carbapenems, third-generation cephalosporins)
  - Mechanical ventilation
  - Less common: ICU, severity of illness, urinary catheter, hydrotherapy, central lines

- **Pseudomonas**
  - Prior antibiotic use (most often carbapenems, FQ)
  - Mechanical ventilation
  - Hospital stay
  - Underlying comorbidities

Falagas and Kopterides. J Hosp Infect 2006;64:7-15
LTCF and MDR GNR

1990-1992 – 55 patients with ceftazidime-resistant Enterobacteriaceae admitted

31 of 35 admitted from LTCF were colonized or infected at admission

LTCF point prevalence survey = 18/39 positive
Long-Term Care

- In one study of 1,661 clinical cultures from one LTCF (Nov 2003 to Sept 2005)
  - 180 (11%) MDR GNR
  - 104 (6%) MRSA
  - 11 (1%) VRE

Duration of MDR Gram-Negative Bacilli Carriage

33 LTCF patients colonized with MDR GNB followed for 1 year with serial (q 3 to 4 week rectal swabs)

– Clearance of MDR GNB in 3/33 (9%)
– Median duration of colonization 144 days

KPC outbreak in Chicago, 2008

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

Issues in Long-Term Care

- Understaffing
- Long length of stay
- Different use of Contact Precautions
- Widespread use of antimicrobials
- Incontinence
- Lack of expertise in Infection Prevention
MDR Gram-Negative Bacilli in Dialysis

• On one outpatient hemodialysis unit evaluation 67 patients evaluated at 0, 2, and 4 months for MDR GNB (NS to 3 or more classes), MRSA and VRE

• 16% colonized with MDR GNB at baseline (5% MRSA and 13% VRE)

• Risk factors for colonization were antibiotics within 3 months, and LTCF residence

Active CRE surveillance

- **MuGSI (Multi-site Gram-Negative Surveillance Initiative) project**
  - Active, laboratory-initiated, population-based surveillance for CRE and CR Acinetobacter (CRAB) in 3 US sites (sterile sites and urine)
  - Pilot 8/11 to 12/11
    - 74 CRE, 45 CRAB
    - Urine most common source (CRE 67/74, CRAB 30/45)
    - Most with onset outside hospital (CRE 48/73, CRAB 26/45)
      - CRE 41/48, CRAB 25/26 had healthcare exposures
      - 8 were community onset without healthcare exposures
Outcomes of Invasive Carbapenem-Resistant *K. pneumoniae* (CRKP) Infections

• Case control study done by Patel et al. at Mount Sinai in NYC, where CRKP (KPC producers) are now endemic.
  – 99 patients with invasive CRKP infections (mostly bloodstream) compared to 99 patients with invasive carbapenem susceptible *K. pneumoniae* infections.

*Patel et al. Infect Control Hosp Epidemiol 2008;29:1099-1106*
Mortality

Overall Mortality

OR 3.71 (1.97-7.01)

Attributable Mortality

OR 4.5 (2.16-9.35)

MDR Acinetobacter and Mortality

- Matched multivariable analysis of MDR Acinetobacter

Table 3. Multivariable analysis of outcomes of patients with and without multidrug-resistant (MDR) Acinetobacter infections, Baltimore hospitals, 2003–2004*

<table>
<thead>
<tr>
<th>Outcome evaluated</th>
<th>MDR Acinetobacter vs. susceptible†</th>
<th>MDR Acinetobacter vs. uninfected†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Length of stay, d</td>
<td>2.5 (1.2–5.2)</td>
<td>2.5 (1.2–5.4)</td>
</tr>
<tr>
<td>Intensive care unit length of stay, d</td>
<td>2.1 (1.0–4.3)</td>
<td>4.2 (1.5–11.6)</td>
</tr>
<tr>
<td>Mortality rate (%)</td>
<td>2.6 (0.3–26.1)</td>
<td>6.6 (0.4–108.3)</td>
</tr>
</tbody>
</table>

*OR, odds ratio; CI, confidence interval.
†Models include modified Acute Physiology and Chronic Health Evaluation III score to control for severity of illness and Charlson index to control for underlying disease.

- Univariate mortality rate
  - 26% for MDR Acinetobacter
  - 18% for susceptible Acinetobacter

Trend- XDR GNB

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

Summary: CRE/MDR GNRs are Epidemiologically Important

• Associated with high mortality rates
• Often carry multiple resistance genes that limit treatment options
• KPC-producing CRE have spread widely across the US
  – Potential to become more widespread
  – Movement into community infections
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 *Klebsiella* and *E. coli*
- CDC definition (based on 2012 CLSI definitions):
  - Your lab might not be using these definitions
  - NS to one of the carbapenems (doripenem, meropenem, imipenem)
  - Resistant to all 3rd generation cephalosporins tested
  - Some Enterobacteriaceae are intrinsically resistant to imipenem (*Morganella, Providencia, Proteus*)
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
Hand Hygiene

- Proper protocols
- Available supplies (soap, towels, etc.)
- HCP education
- Adherence monitoring and feedback
- More information: www.cdc.gov/handhygiene
HCP Education

- Regular education about MDROs
  - Proper use of CP
  - Hand hygiene
Contact Precautions

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

- Minimize use of invasive devices
  - Urinary catheters
  - Central venous catheters
- HICPAC recommendations for:
  - Urinary catheters
  - Central lines
Patient and Staff Cohorting

- CRE patients in single rooms (when available)
- Cohorting (even when in single rooms)
- Staff cohorting
- Recommendation applies to both acute and long-term care settings
- 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
Laboratory Notification

- Facilities should have protocols for timely notification of appropriate staff when CRE isolated from surveillance or clinical specimens
- Facilities who send cultures to off-site laboratories should ensure that protocols are established with those labs
Antimicrobial Stewardship

- **Programs to ensure:**
  - Antimicrobials used for proper indications and duration
  - Appropriate spectrum

- **Link to Get Smart for Healthcare:**
  - [http://www.cdc.gov/getsmart/healthcare](http://www.cdc.gov/getsmart/healthcare)
Antimicrobial Stewardship and MDR GNRs

- Antimicrobial stewardship program in Surgical/Trauma ICU
  - Specific protocol for therapeutic antibiotics
  - Surgical antibiotic prophylaxis protocols
  - Quarterly rotation and limitation of dual antibiotic classes

Dortch et al Surgical Infections 2011; 12:15-25
Antimicrobial Stewardship and MDR GNRs

- Proportion of MDR GNR pathogens decreased (37% to 9%)
- Rate of infections caused by MDR GNRs decreased yearly by 0.78/1,000 patient days
- Yearly decrease was for:
  - MDR *Pseudomonas* (-0.14/1,000 pd),
  - MDR *Acinetobacter* (-0.49/1,000 pd),
  - MDR Enterobacteriaceae (-0.14/1,000 pd)

Dortch et al Surgical Infections 2011; 12:15-25
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
  - 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
  - Screening of epidemiologically linked patients
    - Roommates
    - Patients who shared primary HCP
Active Surveillance Cultures

- Controversial

- 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); fewer than 5/16 had a positive clinical culture for CRKP. (Weiner-Well et al. J Hosp Infect 2010;74:344-9)
  - A study of surveillance cultures at a US hospital found that they identified a third of all positive CRKP patients. Placing these patients in CP resulted in about 1400 days from unprotected exposure. (Calfee et al. ICHE 2008;29:966-8.)
Active Surveillance Cultures

- One study from Israel used surveillance cultures - (ICU) admission and weekly; (non-ICU) patients with epi-links to CRE patients
  - Found a 4.7-fold reduction in in CRKP infection incidence

- Kochar et al. used rectal surveillance cultures as part of a multifaceted intervention in an ICU
  - Found decrease in number of new patients per 1,000 patient days per quarter that were positive for CRKP

Ben-David et al. ICHE 2010; 31:620-6
Kochar et al. ICHE 2009; 30:447-52
Active Surveillance Cultures

- **Potential considerations:**
  - Focus on patients admitted to certain high-risk settings (e.g., ICU) or specific populations (e.g., from LTCF/LTAC)
  - Generally done at admission but can also be done periodically during admission

- Patients identified as positive on these surveillance cultures should be treated as colonized

- Applicable to both acute and long-term care settings.
Chlorhexidine Bathing

- Reviews basics of this process
  - Limited evidence for CRE
    - Used effectively by Munoz-Price in outbreak in LTAC as part of a package of interventions
  - Applied to all patients regardless of CRE colonization status

- In long-term care:
  - Might be used on targeted high-risk residents (e.g., residents that are totally dependent upon healthcare personnel for activities of daily living, are ventilator-dependent, are incontinent of stool, or have wounds whose drainage is difficult to control)
  - Might be less frequent depending on the facility’s usual bathing protocol.

Munoz-Price et al. ICHE 2010;31:341-7
Chlorhexidine bathing and *Acinetobacter*

- In one study of patients in Trauma ICU:
  - Daily CHG baths (2% impregnated wipes)
  - Significant decrease in...
    - CRBSI
    - Less colonization with MRSA and with *Acinetobacter*
- Not a substitute for good baseline infection control

Evans HL, et al., Arch Surg 2010;145:240-246
Acinetobacter:
Environmental Measures

• Due to length of time *Acinetobacter* can survive in the environment, special attention needed for environmental disinfection
  – High levels of environmental contamination may be present
• Clean and disinfect surfaces in close proximity to patient and high-touch surfaces more frequently than minimal-touch surfaces
  – Special attention to potentially contaminated water sources/devices
• Dedicate non-critical equipment to use on individual patients
Cases MDR-Ab, Hospital A

October 2006-July 2007 (N=13)

Cluster identified
Terminal clean/active surveillance
CDC team arrives

Intensive Care Unit (ICU)
Telemetry Unit (Tele)

Cases MDR-Ab, Hospital A

October 2006-July 2007 (N=13)

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Cases MDR-Ab, Hospital A

October 2006-July 2007 (N=13)

Cluster identified
Terminal clean/active surveillance
CDC team arrives

Intensive Care Unit (ICU)
Telemetry Unit (Tele)
**Acinetobacter baumannii Investigation: Environmental sources**

- Case-patient isolates indistinguishable (ST10)
- 2 of 50 samples positive *A. baumannii*
  - Portable x-ray machine: outbreak strain (ST10) recovered from two machines
  - Portable ultrasound machine for PICC catheter insertion: related strain (ST12) recovered
- All isolates multi-drug resistant
Regional CRE Prevention
Inter-Facility Transmission of MDROs (Including CRE)

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.

Regional Approach to MDRO Prevention is Essential

- **Rationale for regional approach**
  - What happens in one facility will impact surrounding facilities
  - Individual facilities can reduce MDRO prevalence only to a certain point

- **Successful regional coordination by public health**
  - VRE control in Siouxland region
  - CRE containment in Israel

Israel Experience

- KPCs likely originally from US identified in Israel beginning in late 2005 (Navon-Venezia et al. AAC 2009)
- By early 2006, increase in cases
- Isolates compared with those and were identical to isolates from NY, NJ, and AZ
- 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
Schwaber et al. CID 2011; 848-855
Thanks for Your Attention

AKallen@cdc.gov

For more information please contact Centers for Disease Control and Prevention

1600 Clifton Road NE, Atlanta, GA 30333
Telephone, 1-800-CDC-INFO (232-4636)/TTY: 1-888-232-6348
E-mail: cdcinfo@cdc.gov  Web: www.cdc.gov