Infections due to Multi-Drug Resistant (MDR) Gram-Negative Pathogens

Prof. Keith Kaye, Wayne State University

Broadcast live from the 2012 APIC conference (www.apic.org)

**Overview**

- MDR Gram-negative bacilli (GNB) of interest
- Role of long-term care and the community in the spread of MDR GNB
- Methods to control the spread of MDR GNBs
- Challenges and opportunities for future management and control

**Bad Bugs, No Drugs: No ESKAPE**

- Enterococcus faecium (E), Staphylococcus aureus (S), Klebsiella pneumoniae (K), Acinetobacter baumannii (A), Pseudomonas aeruginosa (P), and Enterobacter spp. (E)

- The late-stage clinical development pipeline remains unacceptably lean
  - Some important molecules for problematic pathogens such as MRSA are lacking.
  - Few novel molecules for other ESKAPE pathogens
  - New drugs for infection due to multidrug-resistant Gram-negative bacilli (eg, A. baumannii and P. aeruginosa)
  - None represent more than an incremental advance over currently available therapies

**Commonly Used Antibacterials for Serious Infections Are Being Challenged**

- Days of carbapenem therapy increased 17.4% in a 12-month period ending June 2006

**Total Approved Antibacterials: US**

**MDR GNB Pathogens of Interest**
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Extended-spectrum β-lactamases (ESBLs): The Forgotten (and Underrated) MDR GNB
- Most commonly identified in enterobacteriaceae
- Plasmid-mediated
- Impart decreased susceptibility to β-lactam antimicrobials
  - Often co-resistance to aminoglycosides, fluoroquinolones
- Carbapenems are drugs of choice for invasive infections due to ESBL-producers

CTX-M: ESBL Epidemic
- Common ESBL worldwide, often produced by Escherichia coli
- Often causes UTI
- Now reported in US
  - Healthcare associated
  - Some community
- Community-based ESBL infection raise concern for continued increases in carbapenem use

Urban, Diag Micro Infect Dis, 2010; Sjöland-Karlsson, EID, 2011

The CTX-M Detroit Experience
- From 2006-2011, total number of ESBL-producing E. coli increased from
  - 1.9% of all E. coli tested to 13.8% of all E. coli tested
- From 2/11-7/11 at Detroit Medical Center, 575 cases of ESBL-producing E. coli were identified
  - 82% urine
  - 8% wound
  - 5% blood
- 491 (85%) were CTX-M producers
- Compared to uninfected controls, unique predictors of CTX-M producing E. coli included
  - Prior UTI
  - Nursing home status/impaired functional status
  - Cephalosporin exposure

Hayakawa et al, 2012

Unintended Consequences of Carbapenem Use

Carbapenem Resistance
- Emerging problem in Pseudomonas aeruginosa, Acinetobacter baumannii, Enterobacteriaceae (CRE)
- Risk factors include ICU stay, prolonged exposures to healthcare, indwelling devices, antibiotic exposures
  - Long-term acute care centers (LTACs)
- Severely limits treatment options
  - Increased use of older, toxic agents such as colistin

Klebsiella pneumoniae Carbapenemases (KPCs)
- Plasmid-mediated carbapenemase
- KPC-producing strains of Klebsiella pneumonia and other enterobacteriaceae
  - KPC-2, KPC-3
- Endemicity in many locales in the US
  - Hyperendemicity in NYC
  - 24% of K. pneumoniae infections were due to KPCs in 2 hospitals
- Country-wide outbreak ongoing in Israel, Greece, Columbia and others

Bratu, AAC, 2005; Quale, CID, 2004; Leavitt, AAC, 2007; Carmell, Clin Micro Infect, 2010

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KPCs (cont)

- Might appear susceptible to imipenem or meropenem, but with borderline MICs per 2009 CLSI breakpoints
  - Usually ertapenem resistant
  - Modified Hodge test

- Usually only susceptible to colistin, tigecycline and select aminoglycosides

- Easily spread in hospitals (often requires cohorting of staff and patients to control)

KPCs in the United States

http://www.cdc.gov/getsmart/healthcare/learn-from-others/factsheets/resistance.html

International dissemination of Klebsiella pneumoniae carbapenemase (KPC)–producing Enterobacteriaceae.

http://www.cdc.gov/getsmart/healthcare/learn-from-others/factsheets/resistance.html

Outbreak of Colistin-Resistant, Carbapenem-Resistant Klebsiella pneumoniae in Metropolitan Detroit, Michigan

Involved 1 LTAC, 2 hospitals

Marchaim, Antimicrob Agents Chemother. 2011, 593-9

New Delhi metallo-beta-lactamase-1 (NDM-1)

- Carbapenemase mediating broad spectrum resistance
  - Usually found in Klebsiella pneumonia, E. coli
  - Initially identified in India, Pakistan, Bangladesh
  - Recovered in Australia, France, Japan, Kenya, North America, Singapore, Taiwan, and the United Kingdom, Australia, Canada
  - Recovered in the US (Massachusetts, Illinois and California)

Acinetobacter baumannii

- Traditionally ICU organism

- Now being seen in general hospital population and nursing homes

- Antimicrobial resistance is a major concern

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Susceptibility trends of Acinetobacter baumannii at Detroit Medical Center (DMC), 2003-2008*

<table>
<thead>
<tr>
<th>Year</th>
<th>No. of isolates</th>
<th>Imi</th>
<th>A/S</th>
<th>Cefaz</th>
<th>Cipro</th>
<th>Temp/Strax</th>
<th>Amik</th>
<th>Tobra</th>
</tr>
</thead>
<tbody>
<tr>
<td>2003</td>
<td>596</td>
<td>19%</td>
<td>99%</td>
<td>31%</td>
<td>34%</td>
<td>33%</td>
<td>90%</td>
<td>4%</td>
</tr>
<tr>
<td>2004</td>
<td>592</td>
<td>97%</td>
<td>99%</td>
<td>43%</td>
<td>33%</td>
<td>31%</td>
<td>77%</td>
<td>36%</td>
</tr>
<tr>
<td>2005</td>
<td>896</td>
<td>99%</td>
<td>87%</td>
<td>28%</td>
<td>28%</td>
<td>21%</td>
<td>81%</td>
<td>29%</td>
</tr>
<tr>
<td>2006</td>
<td>751</td>
<td>99%</td>
<td>62%</td>
<td>29%</td>
<td>23%</td>
<td>21%</td>
<td>92%</td>
<td>56%</td>
</tr>
<tr>
<td>2007</td>
<td>117%</td>
<td>65%</td>
<td>37%</td>
<td>16%</td>
<td>14%</td>
<td>17%</td>
<td>82%</td>
<td>46%</td>
</tr>
<tr>
<td>2008</td>
<td>1230</td>
<td>42%</td>
<td>45%</td>
<td>15%</td>
<td>15%</td>
<td>18%</td>
<td>33%</td>
<td>46%</td>
</tr>
</tbody>
</table>

Reddy, AAC, 2009

MDR GNB in Long Term Care
- Quinolone resistance increasingly common in hospitals, long-term care and in some community settings
- B-lactam resistance established in hospitals, many long-term care settings
- Risk factors in long-term care for resistant Gram-negative bacilli
  - Indwelling devices
  - Poor functional status
  - Pressure ulcers/wounds
  - Antimicrobial/quinolone exposure
  - Prior hospitalization

Evolution of Nursing Home Care
- Long stay vs short + long stay
- Low level care vs increasing acuity (long-term acute care [LTAC])
- Wider range of residents:
  - Post-operative care
  - Rehabilitation
  - Prolonged antibiotics
  - Long-term ventilation
  - Long-term care

Role of Long-term Care Facilities and MDR-GNB

Admission from LTAC increased risk for MDR-GNR > 3-fold
Marchaim et al, AJIC, 2012

MDR A. baumannii in Older Adults and Long-term care

Admission from LTAC increased risk for MDR-GNR > 3-fold
Marchaim et al, AJIC, 2012

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Strategies to Control the Spread of MDR GNB

• Contact precautions/hand hygiene
• Environment and source control
• Antibiotic stewardship
• Enhanced infection control measures
• Bundles

Barrier Precautions: Do They Work to Limit the Spread of Multi-Drug Resistant Organisms?

• In outbreak settings, gowns/gloves effective in preventing spread of multidrug-resistant organisms (MDROSs)
• In terms of prevention of endemic spread, data are mostly observational
• Success with many different types of MDROs
  – Clostridium difficile
  – Methicillin-resistant S. aureus (MRSA)
  – Vancomycin-resistant enterococci (VRE)
  – MDR Gram-negatives (including carbapenem-resistant enterobacteriaceae (CRE), extended-spectrum β-lactamase-producers (ESBLs), Acinetobacter baumannii)


Role of the Environment

• Environmental sources of contamination/infection
  – Increasingly recognized as sources of infection
• Particularly important with pathogens such as Clostridium difficile, Norovirus, Acinetobacter spp.
• Bleach preparations are more effective for some pathogens (still need cleaning)
• Latest technology being tested: UV light, hydrogen peroxide vapor

Morgan, Infect Control Hosp Epi, 2010, 716-21
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Environmental cleaning
- Adequacy of cleaning of patients’ rooms suboptimal
- Improve monitoring and feedback of efficacy of cleaning
  - Direct observation and culturing not efficient, time-consuming and expensive
- Other options: ATP bioluminescence and fluorescent dyes
  - Monitor process, efficacy of cleaning

Supplements to Routine Environmental Cleaning
- Disinfection units that decontaminate environmental surfaces
- Must remove debris and dirt in order for these units to be effective
- Two most common methods
  - UV light
  - Hydrogen peroxide (HP)

Are Room Decontamination Units Needed to Prevent Transmission of Environmental Pathogens?

<table>
<thead>
<tr>
<th>Method</th>
<th>Statue</th>
<th>Efficacy</th>
<th>Application</th>
<th>Disinfection units that decontaminate environmental surfaces</th>
<th>Must remove debris and dirt in order for these units to be effective</th>
<th>Two most common methods</th>
</tr>
</thead>
<tbody>
<tr>
<td>UV light</td>
<td>Yes</td>
<td>99%</td>
<td>Active &amp; passive</td>
<td>Effective in eliminating vegetative bacteria</td>
<td>Sporicidal (HP &gt; UV light)</td>
<td>UV light</td>
</tr>
<tr>
<td>Hydrogen peroxide (HP)</td>
<td>Yes</td>
<td>99%</td>
<td>Active &amp; passive</td>
<td>Effective in eliminating vegetative bacteria</td>
<td>Sporicidal (HP &gt; UV light)</td>
<td>HP</td>
</tr>
</tbody>
</table>

Room Decontamination Systems: Pros and Cons

- Advantages
  - Effective in eliminating vegetative bacteria
  - Sporicidal (HP > UV light)

- Disadvantages
  - Capital cost
  - Room turnover
  - Does not obviate cleaning

Chlorhexidine Gluconate (CHG)
- Broad-spectrum antimicrobial disinfectant
- Preferred agent for skin preparation prior to insertion of vascular catheter and prior to surgery
- Studied for “source control”, decrease in degree of contamination of patients by problem hospital pathogens

Prevention of Bloodstream Infections by Use of Daily Chlorhexidine Baths for Patients at a Long-Term Acute Care Hospital

- Intervention in LTAC consisted of daily CHG bathing of patients
- 99% reduction in CLABSI by end of intervention period

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Observational study, pre/post implementation of CHG cloth bathing in trauma ICU
Main outcomes: VAP, CLABSI and colonization with MDROs

Antimicrobial Stewardship - Goals
- Optimize appropriate use of antimicrobials
  – The right agent, dose, timing, duration, route
- Optimize clinical outcomes
  – Reduce emergence of resistance
  – Limit drug-related adverse events
  – Minimize risk of unintentional consequences
- Help reduce antimicrobial resistance
  – The combination of effective antimicrobial stewardship and infection control has been shown to limit the emergence and transmission of antimicrobial-resistant bacteria

Enhanced Infection Control Processes
- Active Surveillance
  – Use of "screening" cultures to identify patients colonized with pathogens (usually MDR) of interest
  – Goal is to prevent spread in the hospital by identifying patients who are colonized and intervening to prevent spread
  – Most experience is with Gram positive pathogens
  – Limited use for some pathogens (due to low sensitivity)
- Cohorting of patients
- Dedicated staff

Bundles
- A bundle is a structured way of improving the processes of care and patient outcomes: a small, straightforward set of evidence-based practices (e.g. 3-5) that, when performed collectively and reliably, have been proven to improve patient outcomes.

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An APIC Guide to the Elimination of Multidrug-resistant Acinetobacter baumannii
Transmission in Healthcare Settings (2010)

- Extensive summary of strategies
- Stresses important of surveillance, understanding local epidemiology and adherence to infection control practices
- Active surveillance/screening cultures of limited value – 55% sensitivity

Table 3. Rate of pandrug-resistant Acinetobacter baumannii infection and colonization among intervention intensive care units.

<table>
<thead>
<tr>
<th>Unit</th>
<th>No. of cases per 1000 patient-days</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Period 1</td>
</tr>
<tr>
<td>Medical intensive care</td>
<td>1.4</td>
</tr>
<tr>
<td>Surgical intensive</td>
<td>1.2</td>
</tr>
<tr>
<td>Coronary care</td>
<td>1.0</td>
</tr>
</tbody>
</table>

NOTE. Period 1 was the baseline period (1 January 2005 through 31 December 2005). Period 2 was the intervention period (1 January 2006 through 31 December 2006). Period 3 was the follow-up period (1 January 2007 through 31 December 2007).

- Pandrug-resistant Acinetobacter baumannii

Conclusions

- MDR GNB are growing in prevalence in multiple geographic locales
- Occur in a variety of healthcare associated settings – Even in the community
- Antimicrobial stewardship is here to stay
- Problem is compounded by dry pharmaceutical pipeline
- Novel methods to control spread of MDROs are attractive but not clearly effective/cost-effective
Conclusions (2)

• Technologic advances regarding environmental hygiene are helpful

• Technology and protocols alone will not prevent infections – need compliance with basic process components

• No single process is completely effective in limiting the spread of MDR GNB
  – Bundled interventions have been successful

• Regional approaches to controlling the spread of antimicrobial resistance are needed
  – Increased CDC and public health involvement