Introduction to Carbapenem-Resistant Enterobacteriaceae (CRE)

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Overview

• Epidemiology of CRE

• Treatment options for CRE

• Control of CRE
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
  - Few novel molecules for other ESKAPE pathogens
  - No 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

*MAT = moving annual total.
1. Arlington Medical Resources Inc. (AMR) 2006. Total carbapenem days of therapy growth.
Total Approved Antibacterials: US

Spellberg, et. al., CID May 1 2004, Modified
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; Sjölund-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

Table 1.—Change in Parenteral Cephalosporin and Imipenem/Cilastatin Use From 1995 to 1996 Following Cephalosporin Restriction in 1996

<table>
<thead>
<tr>
<th>Antibiotics</th>
<th>Year</th>
<th>Unpaired Median Monthly Gram Use (Range)</th>
<th>Change, %</th>
<th>P</th>
<th>Paired Median Monthly Gram Use (Range)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>All cephalosporins</td>
<td>1995</td>
<td>5558 (4452 to 8858)</td>
<td>-80.1</td>
<td>&lt;.001</td>
<td>-4709 (-7168 to -3208)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td></td>
<td>1996</td>
<td>1106 (259 to 1680)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Imipenem</td>
<td>1995</td>
<td>197 (76 to 463)</td>
<td>140.6</td>
<td>&lt;.05</td>
<td>258 (-140 to 551)</td>
<td>.05</td>
</tr>
<tr>
<td></td>
<td>1996</td>
<td>474 (119 to 627)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 4.—Change in Number and Incidence of Patient-Related Imipenem-Resistant Pseudomonas aeruginosa From 1995 to 1996 Following Cephalosporin Restriction in 1996

<table>
<thead>
<tr>
<th>Site</th>
<th>Year</th>
<th>No. of PR-IRP</th>
<th>Change, %</th>
<th>Incidence by Unpaired Median PR-IRP/ADC* Ratio (Range)</th>
<th>P</th>
<th>Incidence by Paired Median Monthly PR-IRP/ADC Ratio Difference (Range)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospital-wide</td>
<td>1995</td>
<td>67</td>
<td>68.7</td>
<td>0.015 (0.003-0.026)</td>
<td>&lt;.01</td>
<td>0.010 (-0.008-0.031)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td></td>
<td>1996</td>
<td>113</td>
<td></td>
<td>0.025 (0.016-0.042)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Rahal, JAMA, 1998, 1233-37
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; Carmeli, Clin Micro Infect, 2010*
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/getsment/healthcare/learn-from-others/factsheets/resistance.html
International dissemination of Klebsiella pneumoniae carbapenemase (KPC)–producing Enterobacteriaceae.

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)
Tigecycline (Tygacil®)

- Glycylcycline (tetracycline derivative)
- Inhibits protein synthesis by binding to 30s ribosomal subunit
- Broad-spectrum:
  - Active against gram-positive organisms (including MRSA, VRE), gram-negative bacilli (except *Pseudomonas* species) and anaerobes
- IV only: 100 mg followed by 50 mg q 12 hours
  - No renal adjustment necessary
  - Limited serum concentrations
- Major side effects: nausea/vomiting (~20% of patients)
- Limitations
  - Emergence of resistance among GNR during treatment
  - Low serum concentrations – not good option for BSI

Dominguez, Infec Dis Clin Prac, 2009
FDA Drug Safety Communication: Increased risk of death with Tygacil (tigecycline) (9-1-10)

<table>
<thead>
<tr>
<th>Infection Type</th>
<th>Tygacil deaths/total patients (%)</th>
<th>Comparator Antibiotics deaths/total patients (%)</th>
<th>Risk Difference* (95% Confidence Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>cSSSI</td>
<td>12/834 (1.4%)</td>
<td>6/813 (0.7%)</td>
<td>0.7 (-0.3, 1.7)</td>
</tr>
<tr>
<td>cIAI</td>
<td>42/1382 (3.0%)</td>
<td>31/1393 (2.2%)</td>
<td>0.8 (-0.4, 2.0)</td>
</tr>
<tr>
<td>CAP</td>
<td>12/424 (2.8%)</td>
<td>11/422 (2.6%)</td>
<td>0.2 (-2.0, 2.4)</td>
</tr>
<tr>
<td>HAP</td>
<td>66/467 (14.1%)</td>
<td>57/467 (12.2%)</td>
<td>1.9 (-2.4, 6.3)</td>
</tr>
<tr>
<td>Non-VAP</td>
<td>41/336 (12.2%)</td>
<td>42/345 (12.2%)</td>
<td>0.0 (-4.9, 4.9)</td>
</tr>
<tr>
<td>VAP</td>
<td>25/131 (19.1%)</td>
<td>15/122 (12.3%)</td>
<td>6.8 (-2.1, 15.7)</td>
</tr>
<tr>
<td>RP</td>
<td>11/128 (8.6%)</td>
<td>2/43 (4.7%)</td>
<td>3.9 (-4.0, 11.9)</td>
</tr>
<tr>
<td>DFI</td>
<td>7/553 (1.3%)</td>
<td>3/508 (0.6%)</td>
<td>0.7 (-0.5, 1.8)</td>
</tr>
</tbody>
</table>

Overall Adjusted 150/3788 (4.0%) 110/3646 (3.0%) 0.6 (0.1, 1.2) **
Limited Antimicrobial Options for Treatment of Extensively Drug-Resistant Gram-Negative bacilli (XDR-GNB)

- Currently available antimicrobials are often not active against XDR-GNB
  - Acinetobacter baumannii non-susceptible to group 2 carbapenems and ampicillin/sulbactam
  - Carbapenem–resistant enterobacteriaceae (CRE)
  - *Pseudomonas aeruginosa* resistant to β-lactams, including carbapenems

- With increasing frequency, clinicians are using older agents which are retained in vitro activity

- The polymyxins are one of the most frequently used “old” agents for treatment of XDR-GNB
  - Polymyxin B
  - Polymyxin E (colistin)
New Uses for Old Antibiotics

• “Dry” industry pipeline has led to re-emergence of older drugs for treatment of multi-drug resistant pathogens

• TMP-SMX
• Minocycline
• Fosfomycin
• Rifampin
• Aminoglycosides
• Polymyxins
  – Polymyxin b
  – Polymyxin e (colistin)
Colistin

• Representative agent from polymixin class of antimicrobials

• Unique detergent like mechanisms of action
  – Electrostatic interaction with outer membrane of susceptible bacteria
  – Displacement of divalent cations from the cell membrane
  – Cell membrane integrity disrupted
  – Anti-LPS effect

• No cross-resistance with other classes
Colistin: History

- Originally introduced in 1960’s
- High toxicity rates seen
  - Abandoned for less toxic antimicrobials
- Re-introduced in 1990’s for treatment of multi drug resistant GNB
- Given as inactive prodrug colistimethate
- Spectrum of activity focuses on problematic Gram-negative organisms
  - Highly active against *P. aeruginosa*, *A. baumannii*, CRE
  - Lacks reliable activity vs *Serratia, Proteus, Providencia*
Colistin – Facts and Challenges

- Never underwent rigorous studies that are required of newer agents
  - Significant pharmacokinetic unknowns from old data
  - Recent publication has improved understanding of pharmacokinetics/dosing
- Multiple products available no conformity in dosing
  - Million units of CMS vs. mg of CMS vs. mg of colistin base activity (CBA)
    - 1 million units CMS equal to 80 mg CMS and 30 mg CBA
  - Product from different manufactures recommend different doses
- Dosing regimens based off inaccurate PK data
  - Non-specific assays
Nephrotoxicity

• Differences in rates of nephrotoxicity\(^1\)
  • Early studies reported high rates (approaching 50%)
  • More recent data reported lower rates
    • Lower doses
• Recent publications reported similar rates of dose-dependent toxicity (~ 40% of all subjects\(^2-4\))

Colistin: Clinical Experience

- Data vary greatly and interpretation is difficult
  - Significant delays in effective therapy
  - Patients with many comorbid conditions
  - Varying cocktails of antibiotics used
  - Dosing variable
  - Mono vs combination therapy
  - No randomized controlled studies (ie confounding by indication)
  - Variety of disease states treated

Petrosillo, European Soc Clin Micro Infect Dis, 14, 2008, 816-27
NIH-funded pharmacokinetic study in critically ill patients

- Recommend loading dose of 5mg/kg; cap at 300 mg
- Maintenance dose equation provided
  - Direct association between renal function and drug concentration
  - No association between weight and colistin levels
    - Applicability to overweight/obese patients unclear
- Real world application to dosing a patient
  - Assuming a organism MIC of 1 and normal renal function a patient would require ~340 mg/day
Levels of colistin necessary to treat some pathogens considered to be susceptible (MIC>1) might not be attainable without inducing high rates of nephrotoxicity (ie might require dose > 5 mg/kg/d)

Table 3. Colistin Nephrotoxicity as a Function of Dose

<table>
<thead>
<tr>
<th>Dose (mg/kg IBW)</th>
<th>Nontoxicity, no. (row %)</th>
<th>Toxicity, no. (row %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤2.0¹a</td>
<td>8 (89)</td>
<td>1 (11)</td>
</tr>
<tr>
<td>2.1–2.9</td>
<td>17 (85)</td>
<td>3 (15)</td>
</tr>
<tr>
<td>3.0–3.9</td>
<td>14 (58)</td>
<td>10 (42)</td>
</tr>
<tr>
<td>4.0–4.9</td>
<td>17 (77)</td>
<td>5 (23)</td>
</tr>
<tr>
<td>5.0–5.9</td>
<td>6 (30)</td>
<td>14 (70)</td>
</tr>
<tr>
<td>6.0–6.9</td>
<td>4 (25)</td>
<td>12 (75)</td>
</tr>
<tr>
<td>7.0–7.9</td>
<td>4 (40)</td>
<td>6 (60)</td>
</tr>
<tr>
<td>≥8.0</td>
<td>2 (40)</td>
<td>3 (60)</td>
</tr>
<tr>
<td>&lt;3.0¹a</td>
<td>25 (86)</td>
<td>4 (14)</td>
</tr>
<tr>
<td>3.0–4.9</td>
<td>31 (67)</td>
<td>15 (33)</td>
</tr>
<tr>
<td>≥5.0</td>
<td>16 (31)</td>
<td>35 (69)</td>
</tr>
</tbody>
</table>

Abbreviation: IBW, ideal body weight.

¹ P < .001 for trend.
Randomized Controlled Trial (RCT) for Treatment of Extensively Drug-Resistant (XDR) Gram-negative Bacilli
NIH 10-0065

• NIH-funded contract
• Multi-center randomized-controlled double-blind study
  – Anticipate 8 US sites; 1 international site
• Ventilator-associated pneumonia (VAP) and/or bloodstream infection due to XDR-Gram-negative bacilli
  – *Acinetobacter baumannii* non-susceptible to group 2 carbapenems and ampicillin/sulbactam
  – Carbapenem-resistant enterobacteriaceae (CRE)
  – *Pseudomonas aeruginosa* resistant to β-lactams including carbapenems
NIH 10-0065 RCT - Treatment arms

- Colistin IV + Imipenem IV vs Colistin IV + placebo IV
- 14 days of treatment (proposed change to 7-14 days)
- Colistin dosing extrapolated from Garonzik et al, 2011
  - Weight considered in dose
  - Ideal body weight (IBW) used; if patient is >130% of IBW then adjusted body weight will be used
  - Loading dose: 5 mg/kg x 1 (max 300 mg)
  - Maintenance dose
    - Clcr ≥ 50 mL/min: 1.67 mg/kg q8h (5 mg/kg/day)
    - Clcr 30 – 49 mL/min: 1.75 mg/kg q12h (3.5 mg/kg/day)
    - Clcr 10 - 29 mL/min: 1.25 mg/kg q12h (2.5 mg/kg/day)
    - Clcr < 10 or hemodialysis: 1.5 mg/kg q24h
    - CRRT: full dose
- Imipenem 500 mg or placebo IV q 6 (renally-dosed)
NIH 10-0065 RCT - Outcomes

• Primary: 28-day mortality (all-cause)

• Secondary
  – Clinical improvement
  – Microbiologic cure
  – Emergence of resistant to colistin
  – Adverse events/toxicity
  – Association between colistin serum levels and clinical, microbiologic outcomes, toxicity
  – Association between synergy and clinical, microbiologic outcomes
RCT for XDR- Gram-negative Bacilli: Challenges

- Enrollment and maintenance of subjects
  - Critically ill
  - Competing risks
  - Powers of attorney/patient surrogates

- Prior and concurrent antimicrobial exposures
  - Prior carbapenem exposure

- Timing of enrollment
  - Preliminary microbiology results
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 (MDROs).
- 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 enterococcus (VRE)
  - MDR Gram-negatives (including carbapenem-resistant enterobacteriaceae (CRE), extended-spectrum B-lactamase-producers (ESBLs), *Acinetobacter baumannii*)

Frequency of Contamination of Gowns, Gloves, and Hands of Healthcare Workers (HCWs) after Caring for Patients Colonized or Infected with Specified Bacteria

<table>
<thead>
<tr>
<th>Source of culture-positive sample</th>
<th>Patients with MDR <em>Acinetobacter baumannii</em> carriage ( (n = 199) )</th>
<th>Patients with MDR <em>Pseudomonas aeruginosa</em> carriage ( (n = 134) )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gloves</td>
<td>72 (36.2 [29.5–42.9])</td>
<td>9 (6.7 [2.5–11.0])</td>
</tr>
<tr>
<td>Gown</td>
<td>22 (11.1 [6.7–15.4])</td>
<td>6 (4.5 [1.0–8.0])</td>
</tr>
<tr>
<td>Gloves and/or gown</td>
<td>77 (38.7 [31.9–45.5])</td>
<td>11 (8.2 [3.6–12.9])</td>
</tr>
<tr>
<td>Hands*</td>
<td>9 (4.5 [1.6–7.4])</td>
<td>1 (0.7 [0–2.2])</td>
</tr>
</tbody>
</table>

*Morgan, Infect Control Hosp Epi, 2010, 716-21*
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
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?

William A. Rutala, PhD, MPH; David J. Weber, MD, MPH

## Table 1. Comparison of Room Decontamination Systems That Use UV Irradiation and Hydrogen Peroxide (HP)

<table>
<thead>
<tr>
<th></th>
<th>Sterinis</th>
<th>Steris</th>
<th>Bioquell</th>
<th>Tru-D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abbreviation</td>
<td>DMHP (dry mist HP)</td>
<td>VHP (vaporized HP)</td>
<td>HPV (HP vapor)</td>
<td>UV-C</td>
</tr>
<tr>
<td>Active agent</td>
<td>Stenusil (5% HP, &lt;50 ppm silver cations)</td>
<td>Vaprox (35% HP)</td>
<td>35% HP</td>
<td>UV-C irradiation at 254 nm</td>
</tr>
<tr>
<td>Application</td>
<td>Aerosol of active solution</td>
<td>Vapor, noncondensing</td>
<td>Vapor, condensing</td>
<td>UV irradiation, direct and reflected</td>
</tr>
<tr>
<td>Aeration (removal of active agent from enclosure)</td>
<td>Passive decomposition</td>
<td>Active catalytic conversion</td>
<td>Active catalytic conversion</td>
<td>Not necessary</td>
</tr>
<tr>
<td>Sporicidal efficacy</td>
<td>Single cycle does not inactivate <em>Bacillus atrophaeus</em> BIs; ~4-log₁₀ reduction in <em>Clostridium difficile</em> and incomplete inactivation in situ</td>
<td>Inactivation of <em>Geobacillus stearothermophilus</em> BIs</td>
<td>Inactivation of <em>G. stearothermophilus</em> BIs; &gt;6-log₁₀ reduction in <em>C. difficile</em> in vitro and complete inactivation in situ</td>
<td>1.7–4-log₁₀ reduction in <em>C. difficile</em> in situ</td>
</tr>
<tr>
<td>Evidence of clinical impact</td>
<td>None published</td>
<td>None published</td>
<td>Significant reduction in the incidence of <em>C. difficile</em></td>
<td>None published</td>
</tr>
</tbody>
</table>

*NOTE.* Adapted from Otter and Yezli.¹⁸ BIs, biological indicators; VRE, vancomycin-resistant *Enterococcus.*

¹⁸ All *C. difficile* experiments were done with *C. difficile* spores.
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
  - Reported to reduce risk for carriage and infection with MRSA and VRE

Intervention in LTAC consisted of daily CHG bathing of patients

99% reduction in CLABSI by end of intervention period
<table>
<thead>
<tr>
<th>Variable</th>
<th>Preintervention period (n = 59)</th>
<th>Intervention period (n = 29)</th>
<th>Postintervention period (n = 51)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pathogen</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CNS</td>
<td>30 (51)</td>
<td>11 (38)</td>
<td>20 (39)</td>
</tr>
<tr>
<td><em>Enterococcus</em></td>
<td>12 (20)</td>
<td>5 (17)</td>
<td>12 (24)</td>
</tr>
<tr>
<td><em>Candida</em></td>
<td>9 (15)</td>
<td>6 (21)</td>
<td>3 (6)</td>
</tr>
<tr>
<td><em>Acinetobacter</em></td>
<td>8 (13)</td>
<td>2 (7)</td>
<td>6 (12)</td>
</tr>
<tr>
<td><em>Pseudomonas</em></td>
<td>4 (7)</td>
<td>1 (3)</td>
<td>10 (12)</td>
</tr>
<tr>
<td><em>Enterobacter</em></td>
<td>4 (7)</td>
<td>0 (0)</td>
<td>2 (4)</td>
</tr>
<tr>
<td><em>Corynebacterium</em></td>
<td>3 (5)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>LF GNR</td>
<td>3 (5)</td>
<td>4 (14)</td>
<td>8 (16)</td>
</tr>
<tr>
<td>MRSA</td>
<td>0 (0)</td>
<td>1 (3)</td>
<td>7 (14)</td>
</tr>
<tr>
<td>Other</td>
<td>2 (3)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>No. of pathogens*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 pathogen</td>
<td>44 (75)</td>
<td>28 (97)</td>
<td>36 (70)</td>
</tr>
<tr>
<td>2 pathogens</td>
<td>14 (23)</td>
<td>1 (3)</td>
<td>10 (20)</td>
</tr>
<tr>
<td>3 pathogens</td>
<td>1 (2)</td>
<td>0 (0)</td>
<td>5 (10)</td>
</tr>
</tbody>
</table>

**NOTE.** Data are no. (%) of isolates. CNS, coagulase-negative *Staphylococcus*; LF GNR, lactose fermentor gram-negative rod; MRSA, methicillin-resistant *Staphylococcus aureus*. For descriptions of the 3 different study periods and their interventions, see Methods.

* Per blood culture set.
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
• Strategies for controlling MDR GNB
  – De-escalation, shorter durations of therapy, limiting group 2 carbapenem use

Recent Exposure to Antimicrobials and Carbapenem-Resistant Enterobacteriaceae: The Role of Antimicrobial Stewardship

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TABLE 2. Multivariable Models of Risk Factors for Enterobacteriaceae Isolation, Detroit Medical Center, September 1, 2008, to August 31, 2009

<table>
<thead>
<tr>
<th>Variable†</th>
<th>CRE vs uninfectedb</th>
<th>ESBL vs uninfectedb</th>
<th>Susceptible vs uninfectedb</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 (2-64.3)</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 (0.05-0.5)</td>
<td>.002</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)</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.

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

b Part of the case-case-control analysis.

c Includes methicillin-resistant Staphylococcus aureus, vancomycin-resistant Enterococcus, ESBL-producing Enterobacteriaceae, Acinetobacter baumannii, and Pseudomonas aeruginosa.
Enhanced Infection Control Processes

- Active Surveillance
- Cohorting of patients
- Dedicated staff
- Bundles
Conclusions

• MDR GNB and CRE 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

• More federal dollars geared towards treatment and control of CRE and XDR-GN

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