Antimicrobial Resistance Surveillance in Hospital and Community-Issues for Human Population Medicine

Kurt B. Stevenson MD MPH
Division of Infectious Diseases

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Disclosures

- No financial disclosures or conflicts of interest relative to this presentation.
“Nearly all experts agree that (by the year 2000) bacterial and viral diseases will have been wiped out. Probably arteriosclerotic heart disease will also have been eliminated.”
Rene Dubos-1941

- “...the readiness with which microorganisms selectively change their enzymatic constitution in response to change in the environment may ...be of importance in determining the pathology of infectious diseases.”
Critical impact of antimicrobial resistance

“If we do not act to address the problem of AR, we may lose quick and reliable treatment of infections that have been a manageable problem in the United States since the 1940s. Drug choices for the treatment of common infections will become increasingly limited and expensive — and, in some cases, nonexistent.”

-A Public Health Action Plan to Combat Antimicrobial Resistance

CDC
Antimicrobials present unique management challenges

- 200-300 million antibiotics are prescribed annually
  - 45% for outpatient use

- 25-40% of hospitalized patients receive antibiotics
  - 10-70% are unnecessary or sub-optimal
  - 5% of hospitalized patients who receive antibiotics experience an adverse reaction

- Antibiotics are unlike any other drugs, in that use of the agent in one patient can compromise its efficacy in another (“Societal Drugs”)

Slide courtesy of Sara Cosgrove, MD  Johns Hopkins University
Transferable penicillinase first observed in a gonococcus

Cefotaxime approved by FDA

Cefotaxime resistance observed

First penicillin-resistant Enterococcus reported

Vancomycin-resistant Enterococcus (VRE) observed

First outbreak of Klebsiella pneumoniae resistant to third-generation cephalosporins

S. aureus with intermediate resistance to vancomycin (VISA) reported

Community-acquired MRSA reported

Linezolid-resistant S. aureus and VRE observed

Linezolid, first antibiotic in the oxazolidinone class, approved by FDA

S. aureus with complete resistance to vancomycin (VRSA) observed

*Science* 2008;321:356-361
Selection for antimicrobial-resistant Strains

Resistant Strains
- Rare

Antimicrobial Exposure

Resistant Strains
- Dominant

Campaign to Prevent Antimicrobial Resistance in Healthcare Settings
ESKAPE pathogens

- *Enterococcus faecium* (VRE)
- *Staphylococcus aureus* (MRSA)
- *Klebsiella pneumonia* (ESBL-producing)
- *Acinetobacter baumannii*
- *Pseudomonas aeruginosa*
- *Enterobacter* species

Rice LB. *J Infect Dis* 2008;197:1079-81
Emerging antimicrobial resistance of importance in human medicine

- Methicillin-Resistant *Staphylococcus aureus* (MRSA)
- Multi-drug resistant gram-negative bacilli
  - “SPACE” organisms (Serratia, Pseudomonas, Acinetobacter, Citrobacter, Enterobacter)
  - Ciprofloxacin resistance
  - AmpC/inducible beta-lactamases
  - Extended spectrum beta-lactamases (ESBLs)
  - Carbapenem-resistance
- Now with colistin resistance
Emerging antimicrobial resistance of importance in human medicine

- Epidemic strains of *C. difficile*
- Vancomycin-resistant *Enterococcus ssp.* (VRE)
- Vancomycin-intermediate *Staphylococcus aureus* (VISA)
- Vancomycin-resistant *Staphylococcus aureus* (VRSA)
Definitions of antimicrobial resistance
MDRO=multidrug resistant organisms

- Resistant to more than one class of antimicrobial agent (IOM, 1998)
  - Although this definition suggests resistance to only one class, most of the pathogens discussed are resistant to multiple classes
  - May use more explicit definitions

- Epidemiologically important
  - Known to be transmitted in the healthcare environment
  - Modifiable risk factors
  - Effective infection control interventions
Definitions of antimicrobial resistance
MDRO=multidrug resistant organisms

- Facility specific parameters
  - First isolate, newly introduced
  - Increasing in frequency
- Limited treatment options
- Associated with poor patient outcomes
Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: an international expert proposal for interim standard definitions for acquired resistance


¹) European Centre for Disease Prevention and Control, Stockholm, Sweden, 2) Office of Infectious Diseases, Department of Health and Human Services, Centers for Disease Control and Prevention, Atlanta, GA, USA, 3) Division of Epidemiology, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel, 4) Alfa Institute of Biomedical Sciences (AIBS), Athens, Greece, 5) Department of Medicine, Tufts University School of Medicine, Boston, MA, USA, 6) Department of Clinical Microbiology, Karolinska University Hospital, Stockholm, Sweden, 7) Infection Control Programme, University of Geneva Hospitals, Geneva, Switzerland, 8) Department of Pathology and Laboratory Medicine, University of California Los Angeles Medical Center, Los Angeles, CA, USA, 9) Department of Clinical Microbiology, Central Hospital, Växjö, 10) Department of Bacteriology, Swedish Institute for Infectious Disease Control, Solna, Sweden, 11) The University of Queensland Centre for Clinical Research, Royal Brisbane and Women’s Hospital, Brisbane, Qld, Australia, 12) Warren Alpert Medical School of Brown University, Providence, RI, 13) Department of Medicine, Brigham and Women’s Hospital, Boston, MA, USA and 14) Department of Microbiology, National School of Public Health, Athens, Greece

Clin Microbiol Infect 2012:18:268-281
Abbreviations

- MDR=multidrug-resistant
- XDR=extensively drug-resistant
- PDR=pandrug-resistant
**TABLE 6. Definitions for multidrug-resistant (MDR), extensively drug-resistant (XDR) and pandrug-resistant (PDR) bacteria**

<table>
<thead>
<tr>
<th>Bacterium</th>
<th>MDR</th>
<th>XDR</th>
<th>PDR</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Staphylococcus aureus</em></td>
<td>The isolate is non-susceptible to at least 1 agent in ≥3 antimicrobial categories listed in Table 1*</td>
<td>The isolate is non-susceptible to at least 1 agent in all but 2 or fewer antimicrobial categories in Table 1.</td>
<td>Non-susceptibility to all agents in all antimicrobial categories for each bacterium in Tables 1–5</td>
</tr>
<tr>
<td><em>Enterococcus spp.</em></td>
<td>The isolate is non-susceptible to at least 1 agent in ≥3 antimicrobial categories listed in Table 2</td>
<td>The isolate is non-susceptible to at least 1 agent in all but 2 or fewer antimicrobial categories in Table 2.</td>
<td></td>
</tr>
<tr>
<td><em>Enterobacteriaceae</em></td>
<td>The isolate is non-susceptible to at least 1 agent in ≥3 antimicrobial categories listed in Table 3</td>
<td>The isolate is non-susceptible to at least 1 agent in all but 2 or fewer antimicrobial categories in Table 3.</td>
<td></td>
</tr>
<tr>
<td><em>Pseudomonas aeruginosa</em></td>
<td>The isolate is non-susceptible to at least 1 agent in ≥3 antimicrobial categories listed in Table 4</td>
<td>The isolate is non-susceptible to at least 1 agent in all but 2 or fewer antimicrobial categories in Table 4.</td>
<td></td>
</tr>
<tr>
<td><em>Acinetobacter spp.</em></td>
<td>The isolate is non-susceptible to at least 1 agent in ≥3 antimicrobial categories listed in Table 5</td>
<td>The isolate is non-susceptible to at least 1 agent in all but 2 or fewer antimicrobial categories in Table 5.</td>
<td></td>
</tr>
</tbody>
</table>

*All isolates are defined as MDR because resistance to oxacillin or cefoxitin predicts non-susceptibility to all categories of β-lactam antimicrobials listed in this document, with the exception of the anti-MRSA cephalosporins (i.e. all categories of penicillins, cephalosporins, β-lactamase inhibitors and carbapenems currently approved up until 25 January 2011).*

Multi-Drug Resistant Organisms (MDRO)

Genotyping
- PFGE
- Sequence-based typing
- MLST

Epidemiologic and risk factor data

Social network analysis

Geographic links
Methicillin-resistant S. aureus (MRSA)

- A group of anti-penicillinase antibiotics were developed in the 1960s to treat penicillin-resistant staph (mecillin, nafcillin, oxacillin)
- MRSA contains meca gene which encodes for a modified penicillin-binding protein with reduced binding of mecinillin, oxacillin, or nafcillin
- Also resistant to cephalosporins
- meca gene is housed within the staphyloccocal chromosomal cassette (SCC) which also houses multiple resistance genes
MRSA

- Historically, MRSA has been isolated almost exclusively in healthcare settings, suggesting that transmission has occurred primarily in this environment.
- Typically, nosocomial MRSA have multi-drug resistance patterns.
- Risk factors for healthcare-associated MRSA acquisition include hospitalization, antimicrobial exposure, device utilization, hemodialysis, nursing home, open wounds.
- Healthcare-associated MRSA results in infections at many different clinical sites.
Community-associated MRSA

- Increasing reports of MRSA occurring in patients with little or no direct contact with the healthcare system
- Interpretation of these reports are complicated by lack of consistent definitions
- Phenotypic definition: lack of multi-drug resistance profile
- Genotypic definition: presence of type IV SCCmec gene cassette
- Typically younger patients and most often associated with skin and soft tissue infections
MRSA

Hospital-acquired

- Large SCCmec A (types I, II, III)
- Multi-drug resistance
- Multiple risk factors for contact with the healthcare system
- Infections at many sites (blood, lung, skin, etc)
- USA 100, 200, 500, 600, 800 PFGE types (2003)

Community-acquired

- Small SCCmecA (Type IV)
- Typically resistant only to beta-lactam drugs
- No risk factors for contact with healthcare system
- Younger patients
- Skin and soft tissue infections
- Toxin-producing strains
- USA 300, 400 PFGE types
Multi-Drug Resistant Organisms (MRSA) Epidemiologic and risk factor data

HA-MRSA
CA-MRSA

Genotyping
PFGE
RepPCR
Spa Typing
MLST
SCCmecA

Social network analysis

Geographic links
MRSA Surveillance Study
Funded by CDC Prevention Epicenter Program

Objectives:
- To compare clinical characteristics and molecular genotypes of MRSA isolates
- Use a network of a tertiary medical center and 7 referring community hospitals
- To characterize transmission of CA- and HA-MRSA between these facilities.

Ohio State Health Network Infection Control Collaborative

7 Outreach hospitals
27 to 121 miles from OSU Wexner Medical Center (OSUWMC)
1. Each hospital collects data and PHI on +MRSA cases and sends to:

2. IW de-identifies the data, sends a code back to the hospital for each case.

3. Each hospital sends +MRSA micro samples with assigned de-identified code to:

4. OSU lab sends micro samples using assigned de-identified code for PFGE testing to:

5. ODH sends PFGE results back to OSU lab.

6. OSU lab sends PCR and PFGE results using assigned de-identified code to IW.

7. IW stores all data in:

8. Data Analysis

OSU Epicenter reports back de-identified data to OHSNICC and publishes results.

Potential for MLST and spa typing.

OSUWMC Clinical Micro Lab (REP-PCR, Storage of Specimens)

ODH Lab

OSUWMC IW (Honest Broker)

Web-Based Data Entry Portal

OSUWMC Clinical Micro Lab

OSU Epicenter

MRSA Database

OSHNICC

MRSA Project Process Flow
Web portal - Outreach Hospital
Study Design

- Retrospective analysis of OSUMC banked isolates (projected ~450 isolates) **Study period 1/1/07-10/31/08**
  - Endemic clonal distribution/molecular typing
  - Geographic distribution
  - Epidemiologic and Risk factors
  - Social Networking analysis-social relatedness of cases

- Concurrent analysis of OSHNICC hospitals (~1300 isolates) **Study period 11/01/08 to 6/30/10**
  - All cases at outreach hospitals
  - All cases at OSUMC from outreach hospital catchment areas
  - Sampling of other OSUMC cases
  - Collect all of the same data elements
Methicillin-Resistant Staphylococcus aureus Sequence Type 239-III, Ohio, USA, 2007–2009

Shu-Hua Wang, Yosef Khan, Lisa Hines, José R. Mediavilla, Liangfen Zhang, Liang Chen, Armando Hoet, Tammy Bannerman, Preeti Pancholi, D. Ashley Robinson, Barry N. Kreiswirth, and Kurt B. Stevenson, for the Prevention Epicenter Program of the Centers for Disease Control and Prevention

Emerging Infectious Diseases • www.cdc.gov/eid • Vol. 18, No. 10, October 2012

Emerg Infect Dis 2012;18:1557-1565
Results

- Among 1286 MRSA isolates collected as part of the MRSA surveillance project there were 78 (6%) isolates that were sequence typed as ST-239
- ST-239 has a history of successful dissemination in many regions but had not been noted to play a predominant role in the US
ST 239

- Demonstrated epidemic/outbreak potential-caused a 2 year ICU outbreak in London
- Healthcare-associated with pulmonary and central venous catheter associated bloodstream infections in Korea and China
- Highly drug resistant beyond methicillin
  - Resistant to clindamycin, TMP-SMX, moxifloxacin, gentamicin.
Table. Characteristics of 1,286 patients with MRSA ST239-III and non-MRSA ST239-III infections, Ohio, USA, 2007-2009*  

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>ST239, n = 78</th>
<th>USA100, n = 481</th>
<th>USA300, n = 574</th>
<th>All other, n = 153</th>
<th>p value</th>
<th>p value</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Outreach hospital isolates</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient demographics</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean age, y (range)</td>
<td>58 (19-90)</td>
<td>61 (18-99)</td>
<td>0.06</td>
<td>43 (18-92)</td>
<td>&lt;0.0001</td>
<td>49 (18-94)</td>
<td>0.001</td>
</tr>
<tr>
<td>Male sex</td>
<td>46 (59)</td>
<td>259 (54)</td>
<td>0.39</td>
<td>311 (54)</td>
<td>0.42</td>
<td>80 (52)</td>
<td>0.33</td>
</tr>
<tr>
<td>White race</td>
<td>66 (83)</td>
<td>383 (82)</td>
<td>0.65</td>
<td>441 (77)</td>
<td>0.61</td>
<td>128 (82)</td>
<td>0.77</td>
</tr>
<tr>
<td>Medical history</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>33 (42)</td>
<td>149 (31)</td>
<td>0.047</td>
<td>116 (20)</td>
<td>&lt;0.0001</td>
<td>35 (23)</td>
<td>0.002</td>
</tr>
<tr>
<td>Chronic lung disease</td>
<td>26 (33)</td>
<td>117 (24)</td>
<td>0.09</td>
<td>74 (13)</td>
<td>&lt;0.0001</td>
<td>17 (11)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Renal failure</td>
<td>19 (24)</td>
<td>93 (19)</td>
<td>0.39</td>
<td>37 (6)</td>
<td>&lt;0.0001</td>
<td>17 (11)</td>
<td>0.008</td>
</tr>
<tr>
<td>Malignancy</td>
<td>13 (17)</td>
<td>97 (20)</td>
<td>0.47</td>
<td>48 (8)</td>
<td>0.02</td>
<td>30 (20)</td>
<td>0.58</td>
</tr>
<tr>
<td>Health care–associated risk factors, past 12 mo</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospitalization</td>
<td>58 (74)</td>
<td>296 (62)</td>
<td>0.03</td>
<td>148 (26)</td>
<td>&lt;0.0001</td>
<td>58 (38)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Use of invasive device</td>
<td>35 (45)</td>
<td>168 (35)</td>
<td>0.09</td>
<td>66 (12)</td>
<td>&lt;0.0001</td>
<td>35 (23)</td>
<td>0.006</td>
</tr>
<tr>
<td>Surgery</td>
<td>35 (45)</td>
<td>179 (37)</td>
<td>0.19</td>
<td>79 (14)</td>
<td>&lt;0.0001</td>
<td>33 (22)</td>
<td>0.0002</td>
</tr>
<tr>
<td>History of MRSA infection</td>
<td>26 (33)</td>
<td>77 (16)</td>
<td>0.0003</td>
<td>62 (14)</td>
<td>&lt;0.0001</td>
<td>29 (19)</td>
<td>0.15</td>
</tr>
<tr>
<td>Stay in long-term care facility</td>
<td>22 (28)</td>
<td>155 (32)</td>
<td>0.47</td>
<td>34 (6)</td>
<td>&lt;0.0001</td>
<td>14 (9)</td>
<td>0.0002</td>
</tr>
<tr>
<td>Hemodialysis</td>
<td>15 (19)</td>
<td>47 (10)</td>
<td>0.068</td>
<td>18 (3)</td>
<td>&lt;0.0001</td>
<td>10 (7)</td>
<td>0.015</td>
</tr>
<tr>
<td>Other</td>
<td>10 (13)</td>
<td>29 (6)</td>
<td>0.03</td>
<td>40 (7)</td>
<td>0.06</td>
<td>7 (5)</td>
<td>0.02</td>
</tr>
<tr>
<td>Invasive devices ≤7 d before infection</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Central venous catheter</td>
<td>25 (32)</td>
<td>156 (32)</td>
<td>0.94</td>
<td>61 (11)</td>
<td>&lt;0.0001</td>
<td>32 (21)</td>
<td>0.06</td>
</tr>
<tr>
<td>Foley catheter</td>
<td>17 (22)</td>
<td>99 (21)</td>
<td>0.8</td>
<td>55 (10)</td>
<td>0.001</td>
<td>17 (11)</td>
<td>0.03</td>
</tr>
<tr>
<td>Hemodialysis</td>
<td>13 (17)</td>
<td>49 (10)</td>
<td>0.02</td>
<td>19 (3)</td>
<td>&lt;0.0001</td>
<td>8 (5)</td>
<td>0.008</td>
</tr>
<tr>
<td>Mechanical ventilation</td>
<td>14 (18)</td>
<td>85 (18)</td>
<td>0.95</td>
<td>35 (6)</td>
<td>0.0002</td>
<td>11 (7)</td>
<td>0.012</td>
</tr>
<tr>
<td>Drainage tubes</td>
<td>8 (10)</td>
<td>50 (10)</td>
<td>0.97</td>
<td>10 (2)</td>
<td>&lt;0.0001</td>
<td>5 (3)</td>
<td>0.02</td>
</tr>
<tr>
<td>Total parenteral nutrition</td>
<td>8 (10)</td>
<td>22 (5)</td>
<td>0.04</td>
<td>4 (1)</td>
<td>&lt;0.0001</td>
<td>0</td>
<td>0.0001</td>
</tr>
<tr>
<td>Other</td>
<td>20 (26)</td>
<td>71 (15)</td>
<td>0.016</td>
<td>39 (7)</td>
<td>&lt;0.0001</td>
<td>15 (10)</td>
<td>0.0015</td>
</tr>
<tr>
<td>Classification of MRSA infection</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Health care–associated</td>
<td>32 (41)</td>
<td>197 (41)</td>
<td>0.97</td>
<td>63 (11)</td>
<td>&lt;0.0001</td>
<td>37 (24)</td>
<td>0.01</td>
</tr>
<tr>
<td>Health care–associated community onset</td>
<td>42 (54)</td>
<td>214 (44)</td>
<td>0.12</td>
<td>113 (20)</td>
<td>&lt;0.0001</td>
<td>49 (32)</td>
<td>0.0012</td>
</tr>
<tr>
<td>Community-associated</td>
<td>4 (5)</td>
<td>70 (15)</td>
<td>0.02</td>
<td>386 (69)</td>
<td>0.0003</td>
<td>67 (44)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Outcome</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cure</td>
<td>23 (29)</td>
<td>149 (31)</td>
<td>0.81</td>
<td>94 (16)</td>
<td>0.005</td>
<td>38 (25)</td>
<td>0.49</td>
</tr>
<tr>
<td>Failure</td>
<td>3 (4)</td>
<td>7 (1.5)</td>
<td>0.14</td>
<td>12 (2)</td>
<td>0.33</td>
<td>5 (3)</td>
<td>0.81</td>
</tr>
<tr>
<td>Relapse</td>
<td>4 (5)</td>
<td>7 (1.5)</td>
<td>0.03</td>
<td>2 (1)</td>
<td>0.0001</td>
<td>1 (1)</td>
<td>0.022</td>
</tr>
<tr>
<td>Recurrent</td>
<td>11 (14)</td>
<td>45 (9)</td>
<td>0.2</td>
<td>56 (6)</td>
<td>0.012</td>
<td>3 (2)</td>
<td>0.0002</td>
</tr>
<tr>
<td>Indeterminate</td>
<td>20 (26)</td>
<td>192 (40)</td>
<td>0.015</td>
<td>408 (71)</td>
<td>0.001</td>
<td>97 (63)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Death</td>
<td>17 (22)</td>
<td>81 (17)</td>
<td>0.02</td>
<td>22 (4)</td>
<td>&lt;0.0001</td>
<td>9 (6)</td>
<td>0.0033</td>
</tr>
<tr>
<td>No. patients admitted</td>
<td>74</td>
<td>429</td>
<td>0.005</td>
<td>310</td>
<td>0.0003</td>
<td>111</td>
<td>0.003</td>
</tr>
<tr>
<td>Admitting service</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intensive care unit</td>
<td>14 (19)</td>
<td>58 (14)</td>
<td>0.2</td>
<td>29 (9)</td>
<td>0.019</td>
<td>9 (8)</td>
<td>0.047</td>
</tr>
<tr>
<td>Medicine service</td>
<td>31 (42)</td>
<td>238 (55)</td>
<td>0.03</td>
<td>203 (66)</td>
<td>0.0002</td>
<td>75 (68)</td>
<td>0.0007</td>
</tr>
<tr>
<td>Surgery service</td>
<td>20 (27)</td>
<td>117 (27)</td>
<td>0.05</td>
<td>59 (10)</td>
<td>0.12</td>
<td>20 (18)</td>
<td>0.126</td>
</tr>
<tr>
<td>Other specialty care unit</td>
<td>9 (12)</td>
<td>16 (4)</td>
<td>0.002</td>
<td>19 (6)</td>
<td>0.073</td>
<td>7 (6)</td>
<td>0.16</td>
</tr>
<tr>
<td>Destination after discharge</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Home</td>
<td>20 (27)</td>
<td>146 (34)</td>
<td>0.24</td>
<td>209 (67)</td>
<td>&lt;0.0001</td>
<td>60 (54)</td>
<td>0.0003</td>
</tr>
<tr>
<td>Another facility, long-term care center, or rehabilitation center</td>
<td>35 (47)</td>
<td>204 (46)</td>
<td>0.97</td>
<td>79 (24)</td>
<td>&lt;0.0001</td>
<td>40 (36)</td>
<td>0.12</td>
</tr>
<tr>
<td>Median duration of hospitalization, d (range)</td>
<td>16 (1-143)</td>
<td>11 (0-136)</td>
<td>0.07</td>
<td>6 (0-169)</td>
<td>&lt;0.0001</td>
<td>9 (1-124)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Emerg Infect Dis 2012;18:1557-1565
Figure 3. Single-nucleotide polymorphism (SNP) haplotype map showing position of methicillin-resistant Staphylococcus aureus sequence type 239-III (MRSA ST239-III) isolates, Ohio, USA, 2007–2009, within the global population structure of the MRSA ST239-III clonal group. Circles indicate distinct haplotypes, as defined by using a panel of 43 SNPs (9). Sizes of circles indicate relative frequency of different haplotypes. Arrows indicate haplotype 5 (H5), which includes the Brazilian clone, and haplotype 9 (H9), which includes the 22 MRSA ST239-III isolates from Ohio. Relationships between haplotypes were determined by using maximum-parsimony analysis (9).
**Pseudomonas aeruginosa**

- Gram-negative, non-fermenting bacillus
- Common environmental pathogen, especially in water
- Reservoirs for infection can develop, even in intensive care units
- One of the most serious causes of ventilator-associated pneumonia (VAP)
Clinical Infections

- Bacteremia in neutropenic patients; more common in the 1980’s, decreasing in past decade

- Cystic fibrosis
  - *Science* 2000;288:1251

- Healthcare-associated infections (VAP, bacteremia)
  - *Am Surg* 1999;65:706
  - *Arch Int Med* 1985;145:1621

- Community-acquired infections (hot tub folliculitis)
  - *J Clin Microbiol* 1986;23:655
Imipenem-resistant *Pseudomonas aeruginosa*

- University of Pennsylvania
- 1991 to 2000, significant increase in imipenem resistance (p<0.001)
- Only independent risk factor for acquisition was prior fluoroquinolone use
- Resistant infections resulted in longer hospital stay (15.5 vs 9 days, p=0.02) and increased costs ($81,330 vs $48,381)
- Increased mortality rate (31.1 vs 16.7%)

Extended spectrum β-lactamases

- *K. pneumoniae, E. coli*
- Also reported with Salmonella, Proteus, Enterobacter, Citrobacter, Serratia, and Pseudomonas
- Plasmid-mediated enzymes able to hydrolyze most penicillins and cephalosporins
- Mutated from native β-lactamases, particularly TEM-1, TEM-2, and SHV-1; heterogeneous group of enzymes also derived from other β-lactamases—now CTX-M

*Clin Infect Dis* 2006;42:S153
ESBLs

- Phenotype: resistance to 3\textsuperscript{rd} generation cephalosporins and monobactams
- Their proliferation is a global concern and results in serious limitations in treatment options
- Usually carbapenems are the best and only treatment option
Table 3. Risk factors associated with infection or colonization with extended-spectrum β-lactamase–producing pathogens.

<table>
<thead>
<tr>
<th>Risk Factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prolonged hospital stay</td>
</tr>
<tr>
<td>Prolonged intensive care unit or neonatal intensive care unit stay</td>
</tr>
<tr>
<td>Residency in long-term care facility</td>
</tr>
<tr>
<td>Exposure to third-generation cephalosporins</td>
</tr>
<tr>
<td>Exposure to trimethoprim-sulfamethoxazole</td>
</tr>
<tr>
<td>Exposure to ciprofloxacin</td>
</tr>
<tr>
<td>Total antibiotic use</td>
</tr>
<tr>
<td>Delayed appropriate therapy</td>
</tr>
<tr>
<td>Indwelling catheter</td>
</tr>
<tr>
<td>Gastrostomy or tracheostomy</td>
</tr>
<tr>
<td>Severity of illness</td>
</tr>
<tr>
<td>Decubitus ulcer</td>
</tr>
<tr>
<td>Total dependence on health care workers</td>
</tr>
<tr>
<td>Endotracheal or nasogastric tube</td>
</tr>
</tbody>
</table>

**NOTE.** Data are from [30–37].
Table 2. SENTRY Antimicrobial Surveillance Program: regional prevalence of *Escherichia coli* and *Klebsiella* species that produce extended-spectrum β-lactamase (ESBL).

<table>
<thead>
<tr>
<th>Study, location, year(s)</th>
<th>Organism (no. of isolates tested)</th>
<th>Prevalence by ESBL status, %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Presumptive(^a)</td>
</tr>
<tr>
<td>Jones et al. [26], United States, 1997–2000</td>
<td><em>Klebsiella</em> species (2768)</td>
<td>6–7</td>
</tr>
<tr>
<td>Gales et al. [27], Latin America</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1997–1999(^c)</td>
<td><em>E. coli</em> (801)</td>
<td>4–6</td>
</tr>
<tr>
<td></td>
<td><em>Klebsiella</em> species (166)</td>
<td>29–32</td>
</tr>
<tr>
<td>2000(^c)</td>
<td><em>E. coli</em> (320)</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td><em>Klebsiella</em> species (61)</td>
<td>44–46</td>
</tr>
<tr>
<td>Bell et al. [28], Asia/Pacific and South Africa, 1998–1999</td>
<td><em>Escherichia coli</em> (1377)</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td><em>Klebsiella pneumoniae</em> (678)</td>
<td>25</td>
</tr>
<tr>
<td>Winokur et al. [29], Europe, 1997–1999</td>
<td><em>E. coli</em> (3822)</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td><em>K. pneumoniae</em> (946)</td>
<td>23</td>
</tr>
</tbody>
</table>

\(^a\) According to NCCLS 2002 criteria: MIC, ≥2 μg/mL for aztreonam, ceftriaxone, or ceftazidime.

\(^b\) Confirmation was made by reduction (>4-fold) in substrate MIC with the addition of clavulanic acid.

\(^c\) Urinary tract infection isolates.
Carbapenemases

- Carbapenemases are enzymes which can inactivate a wide range of antibiotics including the carbapenem class, thus rendering the bacteria highly resistant to most treatment modalities.

- Two current classes noted:
  - KPC: class A
  - NDM-1: class B
Outbreak of *Klebsiella pneumoniae* Producing a New Carbapenem-Hydrolyzing Class A β-Lactamase, KPC-3, in a New York Medical Center


*Antibiotic Resistance Monitoring and Reference Laboratory, Specialist and Reference Microbiology Division—Colindale, Health Protection Agency, London, United Kingdom; Departments of Microbiology & Pathology, Tisch Hospital, NYU Medical Center, and New York City Department of Health, Public Health Laboratory, New York, New York; and Human and Animal Infectious Disease Research, Merck Research Laboratories, Rahway, New Jersey*

From April 2000 to April 2001, 24 patients in intensive care units at Tisch Hospital, New York, N.Y., were infected or colonized by carbapenem-resistant *Klebsiella pneumoniae*. Pulsed-field gel electrophoresis identified a predominant outbreak strain, but other resistant strains were also recovered. Three representatives of the outbreak strain from separate patients were studied in detail. All were resistant or had reduced susceptibility to imipenem, meropenem, ceftazidime, piperacillin-tazobactam, and gentamicin but remained fully susceptible to tetracycline. PCR amplified a *bla*KPC allele encoding a novel variant, KPC-3, with a His(272)→Tyr substi-
KPC

- 96 isolates from 10 Brooklyn hospitals
- All resistant to carbapenems and most other antibiotics
- About 50% susceptible to aminoglycosides and 90% to polymixin B; all susceptible to tigecycline.
- Therapeutic options: colistin, tigecycline

JAC 2005;56:128
NDM-1 strain

- New Delhi metallo-beta-lactamase-1
- *Klebsiella pneumoniae* and *Escherichia coli*.
- NDM-1 has been reported in >37 states within the United States, including Ohio
Emergence of a new antibiotic resistance mechanism in India, Pakistan, and the UK: a molecular, biological, and epidemiological study


Lancet Infect Dis 2010;10:597-602
Figure 1: Numbers of carbapenemase-producing Enterobacteriaceae referred from UK laboratories to the UK Health Protection Agency’s national reference laboratory from 2003 to 2009. The predominant gene is *bla*<sub>NDM-1</sub>, which was first identified in 2008. The other group includes diverse producers of KPC, OXA-48, IMP, and VIM enzymes.

*Lancet Infect Dis* 2010;10:597-602
*Figure 5: Distribution of NDM-1-producing Enterobacteriaceae strains in Bangladesh, Indian, Pakistan, and the UK*

*Lancet Infect Dis 2010;10:597-602*
Acinetobacter baumannii

- *Acinetobacter baumannii* (Ab) is a ubiquitous encapsulated, aerobic, nonfermentative gram-negative coccobacillus.
- It is capable of causing both community and healthcare-associated infections involving pulmonary system, urinary tract, bloodstream, and surgical wounds.
- These organisms have a high propensity to accumulate mechanisms of drug-resistance; large HAI outbreaks with pan resistant strains have been reported.

Acinetobacter baumannii (Ab)

- Major risk factors include invasive procedures such as using mechanical ventilation, central venous or urinary catheters, and exposure to broad spectrum antimicrobials.
- The organisms exist in the environment in both wet and dry conditions and can survive for months on clothing, bedrails, ventilators, and other surfaces.

J Clin Microbiol 1996;34:2881-2887
Principles and Practices of Infectious Diseases 2000:2339-2344
MDR Ab outbreaks across geographic distances

- Citywide clonal outbreak of MDR-Ab; involved 15 hospitals in Brooklyn (based on ribotyping)
- Interhospital transfer of MDR-Ab among 4 hospitals in Johannesburg, South Africa (based on PFGE)

Arch Intern Med 2002;162:1515-1520
Am J Infect Control 2004;32:278-281
Colistin

- Mixture of cyclic polypeptides (polymixin A and B); polycationic with both hydrophilic and lipophilic moieties
- Disrupts cell membrane
- Active against gram negative bacteria esp *Pseudomonas* and *Acinetobacter*
- Previous concerns for neurotoxicity and nephrotoxicity
- Resistance currently has been generally rare
Colistin resistance

- 265 isolates of Acinetobacter from 2 Korean hospitals

- Categorized into 3 subgroups:
  - Subgroup I (142 isolates [53.6%])
  - Subgroup II (54 [20.4%])
  - Subgroup III (18 [6.8%])

- Forty-eight isolates (18.1%) and 74 isolates (27.9%) were resistant to polymyxin B and colistin, respectively.

*J Antimicrob Chemother.* 2007 Aug 29
Emerging antimicrobial resistance of importance in human medicine

- Methicillin-Resistant *Staphylococcus aureus* (MRSA)
- Multi-drug resistant gram-negative bacilli
  - “SPACE” organisms (Serratia, Pseudomonas, Acinetobacter, Citrobacter, Enterobacter)
  - Ciprofloxacin resistance
  - AmpC/inducible beta-lactamases
  - Extended spectrum beta-lactamases (ESBLs)
  - Carbapenem-resistance
- Now with colistin resistance
Emerging antimicrobial resistance of importance in human medicine

- Epidemic strains of *C. difficile*
- Vancomycin-resistant *Enterococcus ssp.* (VRE)
- Vancomycin-intermediate *Staphylococcus aureus* (VISA)
- Vancomycin-resistant *Staphylococcus aureus* (VRSA)