Objectives:
- Define multidrug resistant organisms (MDRO’s).
- Identify mechanisms of resistance.
- Identify the MDRO epidemiology.
- Describe MDRO surveillance programs.
- State appropriate antimicrobial therapy to treat MDRO’s.
MDRO’s

- Multidrug-Resistant Organisms
- MRSA
- MRSA/MSSA
- MDR Acinetobacter spp.
  - Resistant to at least 1 agent in at least 3 antimicrobial classes
  - Piperacillin, Piperacillin/tazobactam
  - Aminoglycoside
  - Carbapenems
  - Fluoroquinolones
  - Ceftazidime, Cefepime
  - Ampicillin/Sulbactam (sulbactam)
- Vancomycin resistant Enterococci spp (VRE)
- Capnili Klebsiella spp
- Resistant to carbapenem, cephalosporin, OR cephalosporin
- Carbapenem resistant Enterobacteriaceae spp (CRE)
- E. coli, Klebsiella species, Klebsiella pneumoniae, or Enterobacter spp
  - Resistant to carbapenem OR
  - Production of a carbapenemase
  - PCR, metallo-β-lactamase test, modified-hodge test, Carba-NP

MDR, XDR, PDR

Multidrug-resistant, extensively drug-resistant and pan-drug-resistant bacteria: an international expert proposal for interim standard definitions for acquired resistance

<table>
<thead>
<tr>
<th>Isolate resistance</th>
<th>MDR</th>
<th>XDR</th>
<th>PDR</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRSA</td>
<td></td>
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<td>MDR Acinetobacter</td>
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<td></td>
</tr>
<tr>
<td>Carbapenem resistant Enterobacteriaceae</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Piperacillin, Piperacillin/tazobactam
Aminoglycoside
Carbapenems
Ceftazidime, Cefepime
Ampicillin/Sulbactam
Vancomycin resistant Enterococci spp
CephR
Klebsiella spp
Resistant to ceftazidime, ceftriaxone, OR cefepime
Carbapenem resistant Enterobacteriacea spp
Resistant to carbapenem OR
Production of a carbapenemase
PCR, metallo-β-lactamase test, modified-hodge test, Carba-NP

MDRO/CDI CDC module April 2015
MDR, XDR, PDR

Cefazolin, or cephalosporin, or carbapenem
Carbapenems
Fluoroquinolones
Ceftazidime, Cefepime
Ampicillin/Sulbactam
Vancomycin resistant Enterococci spp
CephR
Klebsiella spp
Resistant to ceftazidime, ceftriaxone, OR cefepime
Carbapenem resistant Enterobacteriacea spp
Resistant to carbapenem OR
Production of a carbapenemase
PCR, metallo-β-lactamase test, modified-hodge test, Carba-NP

Beta-Lactam Antibiotics

Penicillins:
- Anti-staphylococcal penicillins
- Methicillin
- Nafcillin
- Cloxacillin
- Erythromycin
- Tetracycline
- Gentamicin

Cephalosporins:
- 1st generation
- 2nd generation
- 3rd generation
- 4th generation
- 5th generation

Monobactams:
- Aztreonam

Carbapenems:
- Imipenem
- Meropenem
- Ertapenem
- Doripenem

Beta-Lactam Ring

Beta-Lactam Ring

Thiazolidine Ring
**Precursor formation:**
- N-acetylglucosamine
- N-acetylmuramic acid + pentapeptide

**Transglycosylation:**
- Transglycosylases (PBP)
- Forms long polymer backbone

**Transpeptidation:**
- Transpeptidases (PBP)
- Links via pentapeptide

---

**Beta-Lactam Antibiotics**
- **Mechanism of Action**
  - Binds to penicillin binding protein (PBP)
  - Transpeptidase
  - Prevents peptidoglycan cross linking

**β-Lactamases**
- Hydrolyzes beta-lactam ring
  - Penicillin
  - Cephalosporin
  - Carbapenem
Penicillinase-Resistant Penicillins

- **Penicillin Core**

- **Nafcillin**
- **Methicillin**
- **Oxacillin**
- **Cloxacillin**
- **Dicloxacillin**

- **Methicillin**
  - Resistant to hydrolysis by Staphylococcal penicillinase

- **Penicillinase-Resistant**
  - bulky side chains
SCCmec

SCC: Staphylococcal cassette

- codes for PBP2a
- intrinsic resistance to beta-lactams
Beta-Lactam MOA/Resistance

Infect Control Hosp Epidemiol 2005;26:166-174

TABLE 3
Multivariate Analysis of the Impact of Colonizer Characteristics on Morbidity, Length of Hospital Stay, NDx, and Hospital Charges

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Measure of Effect (OR)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality*</td>
<td>OR = 0.77 (0.53-1.10)</td>
<td>0.45</td>
</tr>
<tr>
<td>Length of hospital stay after</td>
<td>HR = 1.26 (1.05-1.50)</td>
<td>0.016</td>
</tr>
<tr>
<td>Staphylococcus aureus bacteremia</td>
<td>MI = 1.38 (1.06-1.75)</td>
<td>0.017</td>
</tr>
<tr>
<td>Streptococcus pneumonia bacteremia</td>
<td>MI = 0.79 (0.61-1.02)</td>
<td>0.067</td>
</tr>
</tbody>
</table>

*Adjusted for age, sex, race, social history, and comorbidities.

Infect Control Hosp Epidemiol 2005;26:166-174
β-Lactamases

- Serine
  - TEM-1
  - CTX-M
  - KPC
  - AmpC
  - OXA
  - PBP, VIM, NDM

- Nontalos (B)
  - Ph, CBF
  - RES, AIA, SME, CDI

- Early gen CPH
  - Carbapenem, oxazolam, ticarcillin, aztreonam, meropenem, imipenem, doripenem

- Enteral: Amox/clav, Cefotaxime, Ceftriaxone

- TEM (IRT): Amp/sul, Amox/clav

- ESBL
  - CTX-M
  - KPC
  - NDM
  - VIM
  - IMP

- Carbapenem

Infection Control and Hospital Epidemiology, Vol. 24, No. 9 (September 2003), pp. 690-698
Table 1. Number and percentage of facilities reporting carbapenem-resistant Enterobacteriaceae (CRE) in 2014, by selected characteristics: United States, National Healthcare Safety Network, 2014

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No. of Facilities (n=191)</th>
<th>Total no. of facilities reporting CRE (n=3,191)</th>
<th>Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Facility type</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute care hospitals</td>
<td>87</td>
<td>1,730</td>
<td>54.6</td>
</tr>
<tr>
<td>Long-term care hospital</td>
<td>33</td>
<td>931</td>
<td>29.2</td>
</tr>
<tr>
<td>Hospital size of facility</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;100 beds</td>
<td>108</td>
<td>2,695</td>
<td>85.0</td>
</tr>
<tr>
<td>100-200 beds</td>
<td>51</td>
<td>625</td>
<td>19.6</td>
</tr>
<tr>
<td>&gt;200 beds</td>
<td>12</td>
<td>87</td>
<td>2.7</td>
</tr>
<tr>
<td>Medical referral affiliation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>75</td>
<td>1,750</td>
<td>55.1</td>
</tr>
<tr>
<td>No</td>
<td>116</td>
<td>1,437</td>
<td>44.9</td>
</tr>
</tbody>
</table>

*Percentages may not sum to 100% due to rounding.
**Table 1.** Numbers of *Escherichia coli* isolates, percentage reported to be tested against carbapenems, and percentage reported as carbapenem-resistant *E. coli*.

<table>
<thead>
<tr>
<th>Type of infection</th>
<th>No. of isolates</th>
<th>% reported tested against carbapenems</th>
<th>% reported as CPE</th>
<th>No. of isolates</th>
<th>% reported tested against carbapenems</th>
<th>% reported as CPE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enteric fever</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
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<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

**TGN (1999)**

<table>
<thead>
<tr>
<th>Type of infection</th>
<th>No. of isolates</th>
<th>% reported tested against carbapenems</th>
<th>% reported as CPE</th>
<th>No. of isolates</th>
<th>% reported tested against carbapenems</th>
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</table>

**TGN (2004)**

<table>
<thead>
<tr>
<th>Type of infection</th>
<th>No. of isolates</th>
<th>% reported tested against carbapenems</th>
<th>% reported as CPE</th>
<th>No. of isolates</th>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
**Klebsiella pneumoniae resistant to carbapenems**

<table>
<thead>
<tr>
<th>Region of the Americas</th>
<th>Overall reported percentage resistant properties (%)</th>
<th>Reported range of resistant properties (by all resistant isolates/� all reports)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Latin American countries</td>
<td>0-4</td>
<td>0-4</td>
</tr>
<tr>
<td>Caribbean Region</td>
<td>0-11</td>
<td>0-11</td>
</tr>
<tr>
<td>Eastern Mediterranean Region</td>
<td>0-54</td>
<td>0-54</td>
</tr>
<tr>
<td>Europe</td>
<td>0-21</td>
<td>0-21</td>
</tr>
<tr>
<td>South-East Asia Region</td>
<td>0-48</td>
<td>0-48</td>
</tr>
<tr>
<td>Western Pacific Region</td>
<td>0-32</td>
<td>0-32</td>
</tr>
</tbody>
</table>

**OXA-48-Producing K. pneumoniae**

- Oxacillinase, plasmid mediated
- Turkey 2001, North Africa, Gulf region, India
- Penicillins, carbapenems (especially imipenem)
- Does not hydrolyze cephalosporins
- Co production of ESBL

*Semin Respir Crit Care Med 2015;36:74–84.*
Metallo-β-lactamases

- New Delhi metallo-β-lactamase (NDM)
  - India 2006
  - Pakistan
  - Hydrolyzes penicillins, cephalosporins, carbapenems
  - Does not hydrolyze aztreonam
  - K. pneumoniae, E. coli
- VIM, IMP

Semin Respir Crit Care Med 2015;36:74–84.
Treatment of MDRO’s

- **MRSA**
  - Glycopeptides
    - Vancomycin
  - Lipopeptide
    - Daptomycin
  - Lipoglycopeptide
    - Telavancin
  - Oxazolidinone
    - Linezolid
    - Tedizolid
  - Lincosamide
    - Clindamycin
  - Tetracyclines
    - Tigecycline, doxycycline, minocycline

- **VRE**
  - Linezolid
  - Tedizolid
  - Daptomycin
  - Quinupristin/dalfopristin (E. faecium only)
  - Tigecycline
  - Fosfomycin
  - Telavancin

Treatment of MDRO’s

- **ESBL producing Enterobacteriaceae**
  - Beta-lactam antibiotics
    - Carbapenems
  - Non-Beta-lactam antibiotics
    - Aminoglycosides
    - Fluoroquinolones
    - Tetracyclines
    - Trimethoprim/sulfamethoxazole
    - Nitrofurantoin
    - Fosfomycin

- **Carbapenemase Producing Enterobacteriaceae**
  - Tigecycline
  - Colistin
  - Gentamicin
  - VRE
  - Tigecycline
  - Fosfomycin
  - Telavancin

Prevention

- Infection prevention and control program:
  - Multidisciplinary program
  - Ensures implementation of recommended practices
Guidelines/Surveillance

- SHEA (2003)
  - Guidelines for prevention of nosocomial transmission of MDR Staphylococcus aureus and Enterococcus sp
- HICPAC/CDC (2006)
  - Guidelines for the management of MDRO in healthcare settings
- SHEA/HICPAC (2008)
  - MDRO metrics
- NHSN (2012)
  - Multi Site Gram negative bacilli surveillance initiative (MuGSI)
    - CRE, MDR Acinetobacter
    - CO, GA, MD, MN, NY, OR, TN
  - Population: 14,810,092
  - Replaced previous NNIS

National Healthcare Safety Network (NHSN)

Core Reporting for MDRO

- CDC recommendations
  - Addresses MDRO and CDI
    - MDRO:
      - MRSA/MSSA
      - VRE
      - CephR-Klebsiella
      - CRE
      - MDR Acinetobacter
    - Does not include surveillance specimens
- Laboratory-Identified (LabID) event reporting
- Infection Surveillance Reporting
### MRSA Bacteremia: Laboratory Science Reports, Best Blockbuster Incidents

#### 2013 Reporting and Indication

<table>
<thead>
<tr>
<th>State</th>
<th>MRSA Bacteremia</th>
<th>MRSA Infection</th>
<th>Lab Test</th>
<th>MRSA Bacteremia %</th>
<th>MRSA Infection %</th>
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<tbody>
<tr>
<td>Arizona</td>
<td>122</td>
<td>132</td>
<td>Yes</td>
<td>93</td>
<td>91.9</td>
</tr>
<tr>
<td>Alaska</td>
<td>32</td>
<td>29</td>
<td>No</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arizona</td>
<td>47</td>
<td>43</td>
<td>Yes</td>
<td>94</td>
<td>91.9</td>
</tr>
<tr>
<td>California</td>
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<td>152</td>
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<td>Louisiana</td>
<td>8</td>
<td>8</td>
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#### 2013 State MRSA Bacteremia %

- **Arizona**: 93%
- **California**: 93%
- **Colorado**: 93%
- **Kentucky**: 93%
- **Louisiana**: 93%

### MRSA Bacteremia: Laboratory Science Reports, Best Blockbuster Incidents

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#### 2013 State MRSA Bacteremia %

- **Arizona**: 93%
- **California**: 93%
- **Colorado**: 93%
- **Kentucky**: 93%
- **Louisiana**: 93%
Prevention

- Improvement in hand hygiene
- Use of contact precautions
- Active surveillance of cultures (ASC)
- Staff education
- Enhanced environmental cleaning
- Better sharing of information between healthcare regarding MDRO status

AJIC 2010;39;5:368-378
### AMR in Food-Producing Animals and Food Chain

1. Major gaps exist in surveillance and data sharing.
2. Integrated surveillance systems would enable data comparison from food-producing animals, food products, and humans.
3. Surveillance is hampered by lack of implemented global standards.
4. SIHO is pursuing a multidisciplinary approach by collaborating with the Food and Agriculture Organization (FAO), the World Organization for Animal Health (OIE) and other stakeholders.

Adapted from: World Health Organization, Global Network of One Health (2016).

### Table

<table>
<thead>
<tr>
<th>Measure</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>IC Program Development</td>
<td>Establish IC program development.</td>
</tr>
<tr>
<td>ABX Management Team</td>
<td>APAC, Infectious Disease physician.</td>
</tr>
<tr>
<td>Senior Microbiologist</td>
<td>Attend ward rounds.</td>
</tr>
<tr>
<td>Monitor Adherence</td>
<td>Monitor adherence to IC program.</td>
</tr>
<tr>
<td>Antibiotic Policy</td>
<td>Empower staff; inform of MRSA rate.</td>
</tr>
<tr>
<td>Hand Hygiene</td>
<td>Implement hand hygiene program.</td>
</tr>
<tr>
<td>Audits, Reporting, CDI Rates</td>
<td>Audit, feedback ABX use, CDI rates.</td>
</tr>
<tr>
<td>Appropriate ABX Use</td>
<td>Promote appropriate ABX use.</td>
</tr>
<tr>
<td>Hand Hygiene Campaign</td>
<td>Increase IC presence in ICU to promote compliance.</td>
</tr>
<tr>
<td>Patient Education</td>
<td>Educate staff regarding nosocomial infections.</td>
</tr>
<tr>
<td>Narrow Spectrum Antibiotics</td>
<td>Discourage 2nd/3rd generation CPH.</td>
</tr>
<tr>
<td>ABX Restriction</td>
<td>Restrict ABX to ID physicians.</td>
</tr>
<tr>
<td>Multidisciplinary Rounds</td>
<td>Prospective monitoring for individualized therapeutic recommendations.</td>
</tr>
<tr>
<td>Environmental Audits</td>
<td>Environmental cultures, contact isolation, rectal VRE samples.</td>
</tr>
</tbody>
</table>

Adapted from: AJIC 2010;39;5:368-378.