Recognizing the Significance of
Pseudomonas aeruginosa Resistance

Where do we stand today?
Epidemiology and Burden of Antimicrobial-Resistant *P. aeruginosa* Infections

Keith S. Kaye, MD, MPH
Professor of Medicine
Division of Infectious Diseases
Department of Internal Medicine
University of Michigan Medical School
Ann Arbor, Michigan
The Burden of HAIs in the US

• On any given day, approximately one in 25 US patients has at least one infection contracted during the course of their hospital care
  – >700,000 HAIs annually

• ~75,000 patients with HAI die during hospitalization
  – More than half of all HAIs occur outside of the intensive care unit

HAIs, healthcare-associated infections.
# HAIs in US Acute Care Hospitals

<table>
<thead>
<tr>
<th>Major Site of Infection</th>
<th>Estimated No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumonia</td>
<td>157,500</td>
</tr>
<tr>
<td>Gastrointestinal illness</td>
<td>123,100</td>
</tr>
<tr>
<td>Urinary tract infections</td>
<td>93,300</td>
</tr>
<tr>
<td>Primary bloodstream infections</td>
<td>71,900</td>
</tr>
<tr>
<td>Surgical site infections from any inpatient surgery</td>
<td>157,500</td>
</tr>
<tr>
<td>Other types of infections</td>
<td>118,500</td>
</tr>
<tr>
<td><strong>Estimated total number of HAIs</strong></td>
<td><strong>721,800</strong></td>
</tr>
</tbody>
</table>

ANTIBIOTIC RESISTANCE THREATS
in the United States, 2013
CDC Recognized Bacterial Threats

• **Urgent Threats**
  – *Clostridium difficile*
  – Carbapenem-resistant Enterobacteriaceae
  – Drug-resistant *Neisseria gonorrhoeae*

• **Serious Threats**
  – MDR *P. aeruginosa* and *Acinetobacter*
  – ESBL-producing Enterobacteriaceae
  – MRSA and VRE
  – Various drug-resistant species (*Campylobacter, S. pneumoniae, Salmonella, tuberculosis, Shigella*)

### HAIs Attributed to Antibiotic-Resistant Threat Bacteria*


CAUTI, catheter-associated urinary tract infection; SSI, surgical site infection; CLABSII, central line-associated bloodstream infection.


<table>
<thead>
<tr>
<th>Pathogen</th>
<th>CAUTI No. tested (% Resistant)</th>
<th>SSI No. tested (% Resistant)</th>
<th>CLABSII No. tested (% Resistant)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methicillin-resistant <em>Staphylococcus aureus</em> (MRSA)</td>
<td>629 (49)</td>
<td>3212 (44)</td>
<td>2556 (47.3)</td>
</tr>
<tr>
<td>Vancomycin-resistant enterococci (VRE)</td>
<td>4690 (21.7)</td>
<td>3427 (18)</td>
<td>3079 (44.6)</td>
</tr>
<tr>
<td>ESBL Enterobacteriaceae</td>
<td>11,146 (16.0)</td>
<td>4184 (12.6)</td>
<td>2804 (21.1)</td>
</tr>
<tr>
<td>Carbapenem-resistant Enterobacteriaceae</td>
<td>10,530 (2.8)</td>
<td>4441 (1.3)</td>
<td>3199 (4.9)</td>
</tr>
<tr>
<td>MDR <em>Pseudomonas aeruginosa</em></td>
<td>3392 (13.9)</td>
<td>1061 (6.5)</td>
<td>810 (15.7)</td>
</tr>
<tr>
<td>MDR <em>Acinetobacter baumannii</em></td>
<td>171 (63)</td>
<td>63 (47.6)</td>
<td>369 (36.6)</td>
</tr>
</tbody>
</table>

MDR *P. aeruginosa*: Serious Threat

*Pseudomonas aeruginosa* is a common cause of healthcare-associated infections including pneumonia, bloodstream infections, urinary tract infections, and surgical site infections.

**Resistance of Concern**

- Some strains of *Pseudomonas aeruginosa* have been found to be resistant to nearly all or all antibiotics including aminoglycosides, cephalosporins, fluoroquinolones, and carbapenems.
- Approximately 8% of all healthcare-associated infections reported to CDC’s National Healthcare Safety Network are caused by *Pseudomonas aeruginosa*.
- About 13% of severe healthcare-associated infections caused by *Pseudomonas aeruginosa* are multidrug resistant, meaning several classes of antibiotics no longer cure infections.

**Public Health Threat**

- An estimated 51,000 healthcare-associated *Pseudomonas aeruginosa* infections occur in the United States each year. More than 6,000 (or 13%) of these are multidrug-resistant, with roughly 400 deaths per year attributed to these infections.

<table>
<thead>
<tr>
<th>Percentage of <em>P. aeruginosa</em> HAIs that are multidrug-resistant</th>
<th>Estimated number of infections</th>
<th>Estimated number of deaths attributed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multi-drug resistant P. aeruginosa</td>
<td>13%</td>
<td>6700</td>
</tr>
</tbody>
</table>

**P. aeruginosa** is a Common Cause of HAIs

**P. aeruginosa** accounts for 7.5% of all HAIs in US hospitals (fifth-leading cause among all bacteria)*

**P. aeruginosa** is a major cause of various types of HAIs

<table>
<thead>
<tr>
<th>Infection Type</th>
<th>Rank Among All HAI Pathogens</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLABSI</td>
<td>10</td>
</tr>
<tr>
<td>CAUTI</td>
<td>2</td>
</tr>
<tr>
<td>VAP</td>
<td>2</td>
</tr>
<tr>
<td>SSI</td>
<td>5</td>
</tr>
</tbody>
</table>

*Data compiled by CDC National Healthcare Safety Network from 2039 hospitals and 69,475 reported HAIs from 2009-2010.

CAUTI, catheter-associated urinary tract infections; SSI, surgical site infection; CLABSI, central line-associated bloodstream infection; VAP, ventilator-associated pneumonia.

**P. aeruginosa** Frequently Exhibits Resistance and Multidrug-Resistance

According to the CDC NHSN, approximately 23% of HAIs caused by *P. aeruginosa* are resistant to carbapenems.

**NHSN Data for 2009–2010**

<table>
<thead>
<tr>
<th><em>P. aeruginosa</em> phenotype</th>
<th>Type of HAI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CLABSI</td>
</tr>
<tr>
<td>Carbapenem-resistant</td>
<td>26.1%</td>
</tr>
<tr>
<td>Multidrug-resistant*</td>
<td>15.4%</td>
</tr>
</tbody>
</table>

*Pathogen must test as I or R to at least 1 drug in 3 of the 5 following classes: extended-spectrum cephalosporins, respiratory fluoroquinolones, aminoglycosides, carbapenems, and piperacillin or piperacillin/tazobactam.

**P. aeruginosa Utilizes a Multitude of Resistance Mechanisms**

- Intrinsically resistant to many antimicrobials
- Acquire resistance determinants commonly via mutations or via horizontal gene transfer

# P. aeruginosa

## Mechanisms of Acquired Resistance

<table>
<thead>
<tr>
<th>Antimicrobial class</th>
<th>Mechanism of resistance</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>β-lactams</strong></td>
<td>• β-lactamases (endogenous and acquired)</td>
</tr>
<tr>
<td></td>
<td>• Efflux pumps</td>
</tr>
<tr>
<td></td>
<td>• Changes in outer membrane permeability</td>
</tr>
<tr>
<td>Fluoroquinolones</td>
<td>• Target site mutations</td>
</tr>
<tr>
<td></td>
<td>• Efflux pumps</td>
</tr>
<tr>
<td>Aminoglycosides</td>
<td>• Aminoglycoside-modifying enzymes</td>
</tr>
<tr>
<td></td>
<td>• Efflux pumps</td>
</tr>
<tr>
<td></td>
<td>• 16s RNA methylases</td>
</tr>
<tr>
<td>Polymyxins</td>
<td>• Changes in lipopolysaccharide</td>
</tr>
</tbody>
</table>

Antimicrobial-Resistant *P. aeruginosa* is Associated with Adverse Outcomes

- MDR *P. aeruginosa* (compared to matched uninfected controls) associated with:
  - 4.4-fold increase in mortality
  - 2-fold increase in duration of hospitalization

- Imipenem-resistant *P. aeruginosa* (compared to imipenem-susceptible *P. aeruginosa*) associated with:
  - OR for mortality 5.43 in bloodstream infection
  - Longer duration of hospitalization by 7 days
  - Increased hospital charges of $85,299

The Impact of MDR *P. aeruginosa* on Mortality

Summary

- *P. aeruginosa* is a leading cause of various types of HAIs in the US, including CLABSI, CAUTI, VAP, and SSI.

- MDR *P. aeruginosa* is recognized by the CDC as a serious threat.

- Antimicrobial-resistant *P. aeruginosa* infections result in poorer clinical outcomes and higher economic costs compared to susceptible infections.
Recognizing the Various Resistance Mechanisms Utilized by *P. aeruginosa*

Keith A. Rodvold, PharmD, FCCP, FIDSA
Professor of Pharmacy Practice and Medicine
Colleges of Pharmacy and Medicine
University of Illinois at Chicago
Chicago, IL
The Versatility of *P. aeruginosa* Resistance Mechanisms

- *Pseudomonas aeruginosa* possesses intrinsic resistance to many antibiotic classes.
- *Pseudomonas aeruginosa* has the ability to develop resistance by mutations in different chromosomal loci.
- *Pseudomonas aeruginosa* can develop resistance by horizontal acquisition of resistance genes carried on plasmids, transposons or integrons.
- The frequent acquisition of antimicrobial resistance in *Pseudomonas aeruginosa* challenges the use of antibiograms as a tool in epidemiological typing.

Resistance Mechanisms in *Pseudomonas aeruginosa*

- **Mucoid layer**
  - *P. aeruginosa* has a mucoid layer outside the outer membrane; increased thickness of this layer

- **Outer membrane porins**
  - Loss of porins inhibits antibiotic entry

- **Efflux pumps**
  - *P. aeruginosa* can carry efflux pumps in the outer membrane; when present, antibiotics can be pumped out the cell

- **Beta-lactamase upregulation**
  - Regulation of the chromosomal AmpC, which involves a complex relationships between peptidoglycan breakdown, beta-lactam exposure, and gene regulation leading to overexpression of the AmpC enzyme
  - In periplasmic space of the bacteria; able to break down beta-lactam antibiotics and/or beta-lactamase inhibitors

- **PBP alterations**
  - In peptidoglycan layer; altered to prevent interaction of antibiotics with their targets

**P. aeruginosa: Intrinsic Resistance**

- **Inducible chromosomal AmpC β-lactamase**
  - Renders *Pseudomonas aeruginosa* resistant to: ampicillin, amoxicillin, amoxicillin-clavulanate, and first- and second-generation cephalosporins, cefotaxime, ceftriaxone

- **Multidrug efflux systems**
  - Exist in *Pseudomonas aeruginosa* that can result in expulsion of: β-lactams, chloramphenicol, fluoroquinolones, macrolides, novobiocin, sulfonamides, tetracycline, trimethoprim, and aminoglycosides
  - Can also export virulence determinants in *Pseudomonas aeruginosa*, enhancing toxicity to the host

P. aeruginosa: A Variety of Resistance Mechanisms

• Acquired resistance
  - Efflux pumps
  - Impermeability mutations
  - β-lactamases
  - Carbapenemases
  - Aminoglycoside-modifying enzymes
  - Transmissible quinolone resistance

• Adaptive resistance

• Multidrug resistance

P. aeruginosa: Acquired Resistance

- **Efflux pumps**
  - MexAB-OprM is synthesized constitutively in all strains
  - Upregulation or a mutation in the mexR repressor gene (nalB mutant) results in efflux pump overproduction and significant increases in MICs of quinolones, penicillins, cephalosporins, aztreonam, and meropenem (low-level resistance, MIC 8 to 32 µg/mL), but not imipenem
  - Upregulation of efflux pumps (MexCD-OprJ and MexXY-OprM) is an important determinant of resistance to quinolones and aminoglycosides

- **Impermeability mutations**
  - Can result in resistance to carbapenems (e.g., loss of the OprD porin), aminoglycosides, colistin, and quinolones

β-lactamases

- Mutations in the regulatory mechanisms of the chromosomally-encoded AmpC β-lactamase lead to constitutive expression of high-level enzymes
- Confer resistance predominantly to antipseudomonal penicillins, ceftazidime, cefepime, and aztreonam, but not carbapenemems
- Poorly inhibited by clavulanic acid or tazobactam

Carbapenemases

- Nearly all carbapenemases in *P. aeruginosa* belong to Amber class B (commonly referred to as metalloenzymes)
- Metalloenzymes hydrolyze all β-lactam antibiotics except aztreonam, and are associated with high-level (MIC >32 µg/mL) carbapenem resistance

Aminoglycoside-modifying enzymes

- Drug inactivation by plasmid-encoded or chromosomally-encoded enzymes is the most common mechanism for resistance to the aminoglycosides
- Aminoglycoside-modifying enzymes can occur together with impermeability mutations, resulting in broad-spectrum aminoglycoside resistance

Transmissible quinolone resistance

- Plasmid-borne quinolone resistance determinant (qnr)
- Associated with high-level quinolone resistance
- Appears to be associated with integrons that carry determinants for resistance to β-lactams and aminoglycosides

**P. aeruginosa**: Adaptive Resistance

- Is inducible and depends on the presence of either an antibiotic or environmental stimulus
- Triggering factors modulate the expression of many genes, leading to effects on efflux pumps, the cell envelope, and enzymes
- Once the triggering factor or condition is removed, the organism reverts back to its wild-type susceptibility
- Most commonly involved with aminoglycosides, polymyxins, and cationic antimicrobial peptides

MULTIDRUG-RESISTANT PSEUDOMONAS AERUGINOSA

6,700 MULTIDRUG-RESISTANT PSEUDOMONAS INFECTIONS
440 DEATHS

THREAT LEVEL
SERIOUS

This bacteria is a serious concern and requires prompt and sustained action to ensure the problem does not grow.

51,000 PSEUDOMONAS INFECTIONS PER YEAR
Multidrug (3 or more antimicrobial classes) resistance by *P. aeruginosa* is widespread (with geographic variability) and increasing worldwide.

Genetic background of the multidrug- or pan-drug-resistant *P. aeruginosa* has been shown to be a combination of:

- AmpC hyperproduction
- OprD inactivation
- Target mutations conferring high-level fluoroquinolone resistance
- Mutations involved in efflux pump overexpression
- Production of a class 1 integron harboring aminoglycoside-hydrolyzing enzymes

Multiple Mechanisms Render *P. aeruginosa* Infections a Challenge

Study of 120 *P. aeruginosa* isolates from US hospital that were non-susceptible to ceftazidime

<table>
<thead>
<tr>
<th>Resistance Mechanism</th>
<th>% of Isolates</th>
</tr>
</thead>
<tbody>
<tr>
<td>AmpC derepression (10-fold greater than control)</td>
<td>47.5%</td>
</tr>
<tr>
<td>OprD loss (decreased/no band)</td>
<td>45.8%</td>
</tr>
<tr>
<td>Elevated expression of efflux pumps (5-fold greater than control)</td>
<td>32.5%</td>
</tr>
<tr>
<td>-MexAB-OprM</td>
<td>28.4%</td>
</tr>
<tr>
<td>-MexXY-OprM</td>
<td></td>
</tr>
</tbody>
</table>

Summary

• *P. aeruginosa* utilizes various types of resistance mechanisms that are intrinsic, acquired, or adaptive

• Acquired resistance superimposed on intrinsic resistance renders *P. aeruginosa* infections a therapeutic challenge

• Multidrug-resistant *P. aeruginosa* is widespread and increasing worldwide
Antimicrobial-Resistant *P. aeruginosa*: CDC Data from 2011–2014

Keith S. Kaye, MD, MPH
Professor of Medicine
Division of Infectious Diseases
Department of Internal Medicine
University of Michigan Medical School
Ann Arbor, Michigan
Available at: http://gis.cdc.gov/grasp/PSA/MapView.html

Uses data reported to CDC NHSN from 2011 to 2014 from 4403 healthcare facilities

Data collected from procedure- and device-related HAIs: CLABSI, CAUTI, and SSI

31 resistance phenotypes evaluated, including those identified by CDC as urgent or serious threats

CAUTI, Catheter-Associated Urinary Tract Infections; SSI, surgical site infection; CLABSI, Central Line-associated Bloodstream Infection
# Antibiotic-Resistant *P. aeruginosa*,
All HAIs 2011–2014

<table>
<thead>
<tr>
<th>Resistance type</th>
<th>Overall</th>
<th>2011</th>
<th>2012</th>
<th>2013</th>
<th>2014</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbapenem (N=22,593)</td>
<td>19.3%</td>
<td>20.0%</td>
<td>17.8%</td>
<td>20.4%</td>
<td>19.2%</td>
</tr>
<tr>
<td>Cephalosporin (N=26,772)</td>
<td>10.3%</td>
<td>11.7%</td>
<td>9.9%</td>
<td>10.8%</td>
<td>9.5%</td>
</tr>
<tr>
<td>Fluoroquinolone (N=26,897)</td>
<td>21.6%</td>
<td>23.5%</td>
<td>20.8%</td>
<td>22.3%</td>
<td>20.7%</td>
</tr>
<tr>
<td>Aminoglycoside (N=27,197)</td>
<td>9.7%</td>
<td>10.6%</td>
<td>9.1%</td>
<td>9.8%</td>
<td>9.6%</td>
</tr>
<tr>
<td>Piperacillin/tazobactam (N=23,662)</td>
<td>10.0%</td>
<td>12.8%</td>
<td>10.0%</td>
<td>10.1%</td>
<td>9.0%</td>
</tr>
<tr>
<td>Multidrug-Resistant (N=27,289)</td>
<td>14.2%</td>
<td>15.7%</td>
<td>13.3%</td>
<td>14.8%</td>
<td>13.5%</td>
</tr>
</tbody>
</table>

MDR *Pseudomonas aeruginosa*

**National resistance: 14.2%**

# Resistant: 3871  
# Tested: 27,289

MDR Pseudomonas aeruginosa

MDR Pseudomonas aeruginosa – All HAIs – Combined Years (2011 – 2014)

National resistance: 14.2%
# Resistant: 3871
# Tested: 27,289

Carbapenem-Resistant *P. aeruginosa*

Carbapenem Resistant *Pseudomonas aeruginosa* (Resistant or Intermediate) – All HAIs – Combined Years (2011 – 2014)

National resistance: 19.3%

# Resistant: 4365  # Tested: 22,593

Carbapenem-Resistant *P. aeruginosa*

Carbapenem Resistant *Pseudomonas aeruginosa* (Resistant or Intermediate) – All HAIs – Combined Years (2011 – 2014)

National resistance: 19.3%

# Resistant: 4365
# Tested: 22,593

Northwest 8.0%
Midwest 24.0%
TX 23.3%
DE 58.3%

% RESISTANT
- Not Defined
- Insufficient Data
- 2.5 - 14.1
- 14.9 - 18.7
- 18.8 - 22.1
- 22.5 - 58.3

Piperacillin/tazobactam-Resistant *P. aeruginosa*

Piperacillin/tazobactam-Resistant *Pseudomonas aeruginosa* – All HAIs – Combined Years (2011 – 2014)

National resistance: 10%
# Resistant: 2378  # Tested: 23,662
Piperacillin/tazobactam-Resistant *P. aeruginosa*

Piperacillin/tazobactam-Resistant *Pseudomonas aeruginosa* – All HAIs – Combined Years (2011 – 2014)

National resistance: 10%

# Resistant: 2378  # Tested: 23,662

Cephalosporin-Resistant *P. aeruginosa*

Extended-Spectrum Cephalosporin Resistant *Pseudomonas aeruginosa* – All HAIs – Combined Years (2011 – 2014)

National resistance: 10.3%

- # Resistant: 2763
- # Tested: 26,772

Cephalosporin-Resistant *P. aeruginosa*

Extended-Spectrum Cephalosporin Resistant *Pseudomonas aeruginosa* – All HAIs – Combined Years (2011 – 2014)

National resistance: 10.3%

# Resistant: 2763
# Tested: 26,772

# Antibiotic-Resistant *P. aeruginosa* by Specific HAI, 2011–2014

<table>
<thead>
<tr>
<th>Resistance type</th>
<th>All HAI</th>
<th>CAUTI</th>
<th>CLABSI</th>
<th>SSI</th>
</tr>
</thead>
<tbody>
<tr>
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</tr>
</tbody>
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HAI, hospital-acquired infection; CAUTI, Catheter-Associated Urinary Tract Infections; SSI, surgical site infection; CLABSI, Central Line-associated Bloodstream Infection

Carbapenem-Resistant *P. aeruginosa*, CAUTI

Carbapenem Resistant *Pseudomonas aeruginosa* (Resistant or Intermediate) – CAUTI– Combined Years (2011 – 2014)

<table>
<thead>
<tr>
<th>State</th>
<th>% Resistant</th>
</tr>
</thead>
<tbody>
<tr>
<td>CT</td>
<td>Not Defined</td>
</tr>
<tr>
<td>DE</td>
<td>Insufficient Data</td>
</tr>
<tr>
<td>DC</td>
<td>5.4 - 16.3</td>
</tr>
<tr>
<td>MD</td>
<td>16.5 - 20.8</td>
</tr>
<tr>
<td>AR</td>
<td>21.9 - 26.2</td>
</tr>
<tr>
<td>GA</td>
<td>26.4 - 38</td>
</tr>
<tr>
<td>TX</td>
<td>23.2%</td>
</tr>
</tbody>
</table>

National resistance: 23.2%

# Resistant: 2970
# Tested: 12,815

Carbapenem-Resistant *P. aeruginosa*, CAUTI

Carbapenem Resistant *Pseudomonas aeruginosa* (Resistant or Intermediate) – CAUTI– Combined Years (2011 – 2014)

National resistance: 23.2%

# Resistant: 2970
# Tested: 12,815

Multidrug-Resistant *P. aeruginosa*, CAUTI

National resistance: 18%

- # Resistant: 2791
- # Tested: 15,464

Carbapenem-Resistant \textit{P. aeruginosa}, CLABSI

Carbapenem Resistant \textit{Pseudomonas aeruginosa} (Resistant or Intermediate) – CLABSI– Combined Years (2011 – 2014)

National resistance: 25.8%

# Resistant: 830
# Tested: 3219

Carbapenem-Resistant P. aeruginosa, CLABSI

Carbapenem Resistant Pseudomonas aeruginosa (Resistant or Intermediate) – CLABSI– Combined Years (2011 – 2014)

National resistance: 25.8%
# Resistant: 830  # Tested: 3219

Carbapenem-Resistant *P. aeruginosa*, CLABSI

Carbapenem Resistant *Pseudomonas aeruginosa* (Resistant or Intermediate) – CLABSI – Combined Years (2011 – 2014)

National resistance: 25.8%

# Resistant: 830
# Tested: 3219

Multidrug-Resistant *P. aeruginosa*, CLABSI

MDR *Pseudomonas aeruginosa* – CLABSI – Combined Years (2011 – 2014)

National resistance: 18.8%

- # Resistant: 693
- # Tested: 3686

Multidrug-Resistant *P. aeruginosa*, SSI

National resistance: 4.8%

# Resistant: 387
# Tested: 8139

Treatment Principles for *P. aeruginosa* Infections

**Empiric therapy**

Coverage for *P. aeruginosa* recommended for patients with certain risk factors, including recent healthcare exposure.

- Typically 2 agents from different classes are used for empiric coverage for *P. aeruginosa* to increase the likelihood of providing effective empiric therapy
  - Often β-lactam + aminoglycoside or fluoroquinolone
Treatment Principles for *P. aeruginosa* Infections

Definitive therapy

Once *P. aeruginosa* has been identified and antimicrobial susceptibilities have been determined, therapy can be modified appropriately

- Therapy is challenging for many cases of MDR *P. aeruginosa*
  - In some cases of extreme drug resistance (XDR), older toxic agents such as colistin have been used
Utilizing Antibiograms

- Annual summary of susceptibility rates for a healthcare institution
- Can help inform empiric antimicrobial choices
  - Particularly important for resistant bacteria, such as *P. aeruginosa*
- Unit-level antibiograms helpful
  - Provide data even more locally than institution-wide antibiogram
  - Often differences in susceptibility between intensive care unit and ward unit
- Combination antibiogram
  - Provides susceptibility rates for a combination of antimicrobials (i.e. for a given pathogen, the rates of susceptibility to at least one agent in a given combination)
  - Particularly valuable for *P. aeruginosa* given the high rates of antimicrobial resistance

Utilizing Antimicrobial Stewardship

- **Appropriate use of antimicrobials**
  - The right agent, dose, timing, duration, route

- **Optimize clinical outcomes**
  - Optimize time to effective therapy
  - 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 of antimicrobial-resistant bacteria
    - Particularly important for MDR Gram-negative bacilli, such as *P. aeruginosa*

Summary

• *P. aeruginosa* is a common healthcare-associated pathogen

• MDR *P. aeruginosa* is increasing in frequency and is associated with poor clinical outcomes
  – Resistance complicates therapy and limits antimicrobial options

• Knowing local resistance trends, through surveillance studies and institutional antibiograms, can help guide empiric treatment decisions

• Antimicrobial stewardship strategies are important in preventing the emergence and spread of MDR *P. aeruginosa*
Pseudomonas aeruginosa
Susceptibility Profile

Keith A. Rodvold, PharmD, FCCP, FIDSA
Professor of Pharmacy Practice and Medicine
Colleges of Pharmacy and Medicine
University of Illinois at Chicago
Chicago, IL
## Antibiotic Resistance Threats

<table>
<thead>
<tr>
<th>Gram-Negative Organism</th>
<th>Cases (%)</th>
<th>Deaths (%)</th>
<th>Threat Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>ESBL-producing Enterobacteriaceae</td>
<td>26,000 (1.93)</td>
<td>1700 (7.44)</td>
<td>Serious</td>
</tr>
<tr>
<td>Carbapenem-resistant Enterobacteriaceae</td>
<td>9300 (0.69)</td>
<td>610 (2.67)</td>
<td>Urgent</td>
</tr>
<tr>
<td><strong>Multidrug-resistant <em>Pseudomonas aeruginosa</em></strong></td>
<td><strong>6700 (0.5)</strong></td>
<td><strong>440 (1.92)</strong></td>
<td><strong>Serious</strong></td>
</tr>
<tr>
<td>Multidrug-resistant <em>Acinetobacter</em> spp.</td>
<td>7300 (0.54)</td>
<td>500 (2.18)</td>
<td>Serious</td>
</tr>
</tbody>
</table>

Estimated annual incidence of infection due to notable antimicrobial-resistant organisms
Total: 1,349,766 cases and 22,840 deaths
ESBL, extended-spectrum beta-lactamase

MDR *Pseudomonas aeruginosa*
All HAIs, 2011–2014

National resistance: 14.2%

# Resistant: 3871
# Tested: 27,289

CDC Antibiotic Resistance Patient Safety Atlas

- Allows users to visualize and download antimicrobial resistance data at national, regional, and state levels
- Includes device- and procedure-related infections reported to NHSN from 2011–2014 from over 4400 healthcare facilities
- Publicly available at: [http://gis.cdc.gov/grasp/PSA/MapView.html](http://gis.cdc.gov/grasp/PSA/MapView.html)

NHSN, National Healthcare Safety Network
MDR *Pseudomonas aeruginosa*
All HAIs, 2011‒2014

National resistance: 14.2%

# Resistant: 3871
# Tested: 27,289

% RESISTANT
- Not Defined
- Insufficient Data
- 3.1 - 9.3
- 9.4 - 12.5
- 12.6 - 15.7
- 15.8 - 46.9

MDR *Pseudomonas aeruginosa*

All HAIs, 2011–2014

National resistance: 14.2%

MDR *Pseudomonas aeruginosa*

All HAIs, 2011–2014

National resistance: 14.2%

# Resistant: 3871
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MDR *Pseudomonas aeruginosa*
All HAIs, 2011–2014

Publicly available at: [http://gis.cdc.gov/grasp/PSA/MapView.html](http://gis.cdc.gov/grasp/PSA/MapView.html)
Antibiotic Treatment of Resistant Gram-Negative Organisms

- Infections caused by resistant Gram-negative organisms are associated with increased morbidity and mortality compared to susceptible counterparts.
- Choice of empiric therapy has become more difficult for serious infections because antimicrobial resistance to first-line agents.
- Clinicians also have the dilemma between choosing:
  - an agent that is inactive versus broad-spectrum agent
  - monotherapy versus combination therapy
  - determining the role of adjunctive therapy
  - newer versus older agents
In vitro Activity of Antimicrobial Agents Against *P. aeruginosa*

Antimicrobial susceptibility patterns of *Pseudomonas aeruginosa* isolates from intensive care unit (ICU) and non-ICU patients from US Hospital (2012–2013):

<table>
<thead>
<tr>
<th>Antimicrobial Agents</th>
<th>% Susceptible</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ICU n = 842</td>
</tr>
<tr>
<td>Ceftazidime</td>
<td>77.7</td>
</tr>
<tr>
<td>Cefepime</td>
<td>79.8</td>
</tr>
<tr>
<td>Piperacillin–tazobactam</td>
<td>71.2</td>
</tr>
<tr>
<td>Meropenem</td>
<td>76.6</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>76.4</td>
</tr>
<tr>
<td>Amikacin</td>
<td>98.6</td>
</tr>
<tr>
<td>Colistin</td>
<td>100.0</td>
</tr>
</tbody>
</table>

Newer Antipseudomonal Agents

Ceftolozane-tazobactam\textsuperscript{1-3}

- Demonstrated \textit{in vitro} activity against \textit{Pseudomonas aeruginosa} isolates tested that had:
  - Chromosomal AmpC \textit{or}
  - Loss of outer membrane porin (OprD) \textit{or}
  - Up-regulation of efflux pumps (MexXY, MexAB)
- Not active against bacteria producing metallo-\(\beta\)-lactamases

Ceftazidime-avibactam\textsuperscript{3-5}

- Demonstrated \textit{in vitro} activity against \textit{Pseudomonas aeruginosa} in the presence of:
  - some AmpC beta-lactamases \textit{or}
  - certain strains lacking outer membrane porin (OprD)
- Not active against bacteria producing metallo-\(\beta\)-lactamases and may not have activity against Gram-negative bacteria that overexpress efflux pumps or have porin mutations

In vitro Activity of Ceftolozane-Tazobactam Against *P. aeruginosa* Isolates from Hospitalized Pneumonia Patients (2012)

Current FDA susceptibility interpretive criteria for ceftolozane/tazobactam

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Minimum Inhibitory Concentrations (µg/mL)</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Susceptible (S)</td>
<td>Intermediate (I)</td>
<td>Resistant (R)</td>
<td></td>
</tr>
<tr>
<td><em>Pseudomonas aeruginosa</em></td>
<td>≤ 4 / 4</td>
<td>8 / 4</td>
<td>≥ 16 / 4</td>
<td></td>
</tr>
</tbody>
</table>

Ceftolozane-tazobactam activity against *P. aeruginosa* resistance phenotypes

<table>
<thead>
<tr>
<th><em>P. aeruginosa</em> resistance phenotype</th>
<th>Cumulative (%) inhibited at MIC in µg/mL of:</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>4</td>
<td>8</td>
<td>16</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All <em>P. aeruginosa</em> isolates (n=1019)</td>
<td>92.6</td>
<td>94.1</td>
<td>94.6</td>
<td>0.5 / 4</td>
<td></td>
</tr>
<tr>
<td>Ceftazidime-non-S (n=269)</td>
<td>72.1</td>
<td>77.7</td>
<td>79.6</td>
<td>4 / &gt;32</td>
<td></td>
</tr>
<tr>
<td>Cefepime-non-S (n=239)</td>
<td>70.7</td>
<td>77.0</td>
<td>79.1</td>
<td>4 / &gt;32</td>
<td></td>
</tr>
<tr>
<td>Meropenem-non-S (n=268)</td>
<td>75.7</td>
<td>78.0</td>
<td>79.9</td>
<td>2 / &gt;32</td>
<td></td>
</tr>
<tr>
<td>Piperacillin-tazobactam-non-S (n=311)</td>
<td>76.5</td>
<td>81.4</td>
<td>83.0</td>
<td>2 / &gt;32</td>
<td></td>
</tr>
<tr>
<td>CAZ &amp; MEM &amp; P/T-non-S (n=158)</td>
<td>60.1</td>
<td>63.9</td>
<td>67.1</td>
<td>4 / &gt;32</td>
<td></td>
</tr>
<tr>
<td>Leovofloxac-in-non-S (n=307)</td>
<td>81.4</td>
<td>82.7</td>
<td>84.4</td>
<td>2 / &gt;32</td>
<td></td>
</tr>
<tr>
<td>Gentamicin-non-S (n=197)</td>
<td>71.6</td>
<td>73.1</td>
<td>75.1</td>
<td>2 / &gt;32</td>
<td></td>
</tr>
<tr>
<td>Multidrug-resistant (MDR) (n=246)</td>
<td>72.4</td>
<td>75.6</td>
<td>77.6</td>
<td>2 / &gt;32</td>
<td></td>
</tr>
<tr>
<td>Extensively drug-resistant (XDR) (n=174)</td>
<td>63.2</td>
<td>66.1</td>
<td>69.0</td>
<td>4 / &gt;32</td>
<td></td>
</tr>
</tbody>
</table>

In vitro Activity of Ceftazidime-Avibactam Against *P. aeruginosa* Isolates from Hospitalized Patients (2012-13)

Current FDA susceptibility interpretive criteria for ceftazidime-avibactam

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Minimum Inhibitory Concentrations (µg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Susceptible (S)</td>
</tr>
<tr>
<td><em>Pseudomonas aeruginosa</em></td>
<td>≤ 8 / 4</td>
</tr>
</tbody>
</table>

Ceftazidime-avibactam activity against *P. aeruginosa* by site and resistance phenotypes

<table>
<thead>
<tr>
<th><em>P. aeruginosa</em> isolates, by site and resistance phenotype</th>
<th>Cumulative (%) inhibited at MIC in µg/mL of:</th>
<th>MIC(<em>{50}) / MIC(</em>{90}) (µg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All <em>P. aeruginosa</em> isolates (n=3082)</td>
<td></td>
<td>2 / 4</td>
</tr>
<tr>
<td>non-ICU (n=2240)</td>
<td>91.7</td>
<td>2 / 4</td>
</tr>
<tr>
<td>ICU (n=842)</td>
<td>93.2</td>
<td>2 / 4</td>
</tr>
<tr>
<td>VAP (n=185)</td>
<td>87.9</td>
<td>2 / 4</td>
</tr>
<tr>
<td>Ceftazidime-non-S (n=482)</td>
<td>92.4</td>
<td>2 / 4</td>
</tr>
<tr>
<td>Meropenem-non-S (n=537)</td>
<td>60.2</td>
<td>4 / 16</td>
</tr>
<tr>
<td>Multidrug-resistant (MDR) (n=436)</td>
<td>67.8</td>
<td>4 / 16</td>
</tr>
<tr>
<td>Extensively drug-resistant (XDR) (n=247)</td>
<td>57.3</td>
<td>4 / 16</td>
</tr>
<tr>
<td></td>
<td>46.6</td>
<td>8 / 32</td>
</tr>
</tbody>
</table>

Activity Summary

• MDR *P. aeruginosa* is widespread and increasing worldwide

• Susceptibility to traditional agents can vary considerably based on regional and local factors, necessitating the use of combination therapy

• Newer antipseudomonal agents may offer an effective option against MDR isolates

• Antimicrobial stewardship strategies can potentially improve clinical outcomes and reduce resistance development