Regional Emergence of VIM producing carbapenem resistant Pseudomonas aeruginosa (VIM CRPA)

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Objectives:

Review timeline of antibiotic introduction, development of resistance - How did we get here?

Describe VIM gene
- Resistance mechanisms
- History and previous containment efforts
- Patient risk factors

Discuss role of the environment in potential spread

List other considerations for control of the spread of this organism
Background on *P. aeruginosa*

- Gram-negative found in most environments
  - Soil, water, plants, animals

- Seen in community and hospital-acquired infections (HAIs)
  - Much more common in HAIs
    - 5th most common pathogen in all HAIs
    - Leading cause of respiratory infections
      - 2nd most common in ventilator-associated pneumonias (VAPs)

- Admission to ICU, burns, neutropenia, or cystic fibrosis (70-80% chronically infected) are significant risk factors
P. aeruginosa

- Rates of P. aeruginosa are higher in LTACHs
  - 19% of CAUTIs (10% in ICUs)
  - 35% of VAPs (17% in ICUs)
- Older, frail population with prolonged healthcare exposure
Background on *P. aeruginosa*

- Clinical diseases:
  - Bloodstream infection - 60% mortality
    - Mortality rate higher with MDRO strains
  - Ecthyma gangrenosum
  - Infective endocarditis (IV drug users)
  - Pneumonia (most common GN form of VAP)
  - Bone and joint infections
  - Skin and soft tissue infections (pools, hot tubs)
  - Ear infections → prolonged infection and hearing loss
  - Eye infections (contact lenses)
  - Urinary tract infections
Background on *P. aeruginosa*

- Second most common MDRO found on healthcare workers during routine patient care (17.4%)
  - Recovered in 22% of ICU rooms

- Environmental reservoirs contribute to spread
  - Water or humidity related
    - Showers, sinks, artificial nails, ultrasound gel, soap dispensers
  - Forms biofilms - prevents penetration of cleaning agents; difficult to eradicate
MDRO *P. aeruginosa*

- Many resistance mechanisms exist
  - High rate of multidrug resistance compared to other organisms

- Resistance rates from 2010 (NHSN):
  - 10% aminoglycosides
  - 28% extended-spectrum cephalosporins
  - 34% fluoroquinolones
  - 30% carbapenems
  - 18% Pipercillin-tazobactam

- Resistance rates higher in LTACHs than ICUs
## Carbapenemase Classifications

<table>
<thead>
<tr>
<th>Enzyme</th>
<th>Classification</th>
<th>Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>K. pneumoniae</em> carbapenemase (KPC)</td>
<td>Class A</td>
<td>Hydrolyzes all β-lactam agents</td>
</tr>
<tr>
<td>New Delhi Metallo-β-lactamase (NDM)</td>
<td>Class B: metallo-β-lactamase (MBL)</td>
<td>Hydrolyzes all β-lactam agents except aztreonam</td>
</tr>
<tr>
<td>Imipenemase (IMP)</td>
<td>Class A</td>
<td>Hydrolyzes all β-lactam agents</td>
</tr>
<tr>
<td>Verona Integron Mediated Metallo-β-lactamase (VIM)</td>
<td>Class A</td>
<td>Hydrolyzes all β-lactam agents</td>
</tr>
<tr>
<td>OXA</td>
<td>Class D</td>
<td>Hydrolyzes carbapenems but not active against 3rd generation cephalosporins</td>
</tr>
</tbody>
</table>
Location of Resistance Genes is Important

- Chromosomal mutations
  - Can pass resistance vertically but not horizontally
  - Examples include mutations affecting efflux pumps, porins
  - Often incur fitness defect

- Plasmid encoded
  - Can pass resistance vertically and horizontally
  - Examples include Extended Spectrum $\beta$-lactamases (ESBLs) and carbapenemases
  - No/minimal fitness defect
Carbapenemases Can Spread Rapidly

Carbapenemase producing CRPA

- NHSN 19.3% of *P. aeruginosa* is carbapenem R/I
  - (23.3% in Texas)
- MuGSI: 9% of CRPA produce carbapenemase
- ARLN: 3% of CRPA produce carbapenemase
  - VIM is the most common (53%)
CRE and CRPA Tested through ARLN, January 1 - December 31, 2017

*Carbapenemase-producing defined as positive for carbapenemase production using a phenotypic test or positive for one of 5 carbapenemases by molecular assay

#Sum >100% due to some isolates with >1 carbapenemase

<table>
<thead>
<tr>
<th>Carbapenemase producing*</th>
<th>CRE N=6891 No. (%)</th>
<th>CRPA N=3699 No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2311 (34)</td>
<td>98 (3)</td>
</tr>
<tr>
<td>KPC</td>
<td>2056 (89)</td>
<td>11 (11)</td>
</tr>
<tr>
<td>NDM</td>
<td>185 (9)</td>
<td>3 (3)</td>
</tr>
<tr>
<td>OXA-48-type</td>
<td>77 (4)</td>
<td>0</td>
</tr>
<tr>
<td>VIM</td>
<td>24 (1)</td>
<td>52 (53)</td>
</tr>
<tr>
<td>IMP</td>
<td>24 (1)</td>
<td>8 (8)</td>
</tr>
</tbody>
</table>
Antimicrobial Resistance Laboratory Network (ARLN): Laboratory Support for Containment

Hospitals/Clinical Laboratories

Public Health Laboratories
50 States
5 Local Health Departments

Species identification
Confirmatory AST
Phenotypic screening for carbapenemase production
Carbapenemase mechanism testing
mcr-1 testing (some labs)

CRE/CRPA isolates

Rectal Swabs

CRE and CRPA Colonization Screening
Bird’s Eye View of Lubbock

- Four cases of VIM-CRPA identified in Lubbock - August, 2017
- No clear links among cases
- Surveillance expanded
Bird’s Eye View of Lubbock

- Now, 25 cases identified with 29 isolates
- Prior hospitalization is a common finding, but four cases received only outpatient care
Bird’s Eye View of Lubbock

- PFGE on 29 isolates identified 15 unique patterns
  - No clear relationship
- WGS performed
Bird’s Eye View of Texas

- Total cases of CP CRE in Texas
  - *Klebsiella* spp.
  - *Escherichia coli*
  - *Enterobacter* spp.
- Lubbock: 8
- Houston/Galveston: 82
Bird’s Eye View of Texas

Total cases of VIM CRPA in Texas

Lubbock with 29
Houston with 5
Epidemic stages

- 0 – No cases reported
- 1 – Sporadic occurrence – single cases not epidemiologically related
- 2 - Single facility outbreaks - ≥2 epi-linked cases in one facility
- 3 – Regional spread - >1 facility cluster within one referral network
- 4 – Interregional spread – multiple clusters occurring within different referral networks
- 5 – Endemic – most facilities are repeatedly seeing cases admitted from unrelated sources

Without an obvious epidemiologic link, there is concern for ongoing transmission and undetected spread in the larger Lubbock healthcare network and beyond.

Epi-Aid initiated with goals to:
- Identify common exposures in patients with VIM CRPA isolates through chart abstraction and interviews
- Describe regional epidemiology of VIM CRPA through laboratory data
- Perform infection control consultations at facilities with linkage to identified patients or health-care systems
- **Long-term goal:** Develop and implement a regional prevention strategy to limit the spread of VIM CRPA.
Cluster of VIM-CRPA in TX

- **Case definitions**
  - **Confirmed cases:** A person with *Pseudomonas aeruginosa* isolated from any site from June, 2017 or later with mechanism testing showing VIM.
  
  - **Probable case:** A person with CRPA isolated from any site from June, 2017 or later that is non-susceptible to meropenem or imipenem and intermediate/resistant to one third or fourth-generation cephalosporin.
  
  - **Possible case:** A person with any CRPA isolated from any site from June, 2017 or later that has not had mechanism testing.
Patient Risk Factors

- Past hospitalization
- Critical illness
- Surgery
- ICU stays
- Presence of invasive devices
- Prior exposure to antimicrobial treatments

Characteristics

- 27 cases identified
  - 1 occurred in NM
  - Remainder detected in Lubbock

- Most cultures from wounds or urine
  - 50% with chronic wounds on admission

- 81% on any antibiotic before culture

<table>
<thead>
<tr>
<th></th>
<th>Number (N = 26)</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex (male)</strong></td>
<td>16</td>
<td>62%</td>
</tr>
<tr>
<td><strong>Age</strong> (median, 25th and 75th percentile)</td>
<td>63</td>
<td>46,72</td>
</tr>
<tr>
<td><strong>Culture source</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urine</td>
<td>11</td>
<td>42%</td>
</tr>
<tr>
<td>Wound</td>
<td>10</td>
<td>38%</td>
</tr>
<tr>
<td>BAL, tracheal aspirate or sputum</td>
<td>5</td>
<td>19%</td>
</tr>
<tr>
<td><strong>Clinical history</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wounds on admission</td>
<td>13</td>
<td>50%</td>
</tr>
<tr>
<td>Ventilator during admission</td>
<td>12</td>
<td>46%</td>
</tr>
<tr>
<td>Central line</td>
<td>15</td>
<td>58%</td>
</tr>
<tr>
<td>Catheter during admission</td>
<td>12</td>
<td>46%</td>
</tr>
<tr>
<td>Tracheostomy during admission</td>
<td>7</td>
<td>27%</td>
</tr>
<tr>
<td>Dialysis, prior year</td>
<td>4</td>
<td>15%</td>
</tr>
<tr>
<td>Invasive procedure, prior year</td>
<td>25</td>
<td>96%</td>
</tr>
<tr>
<td>Died during stay or discharged to hospice</td>
<td>4</td>
<td>15%</td>
</tr>
<tr>
<td>Antibiotics during admission prior to positive culture</td>
<td>21</td>
<td>81%</td>
</tr>
<tr>
<td>Carabapenem</td>
<td>7</td>
<td>27%</td>
</tr>
<tr>
<td>Fluoroquinolones</td>
<td>6</td>
<td>23%</td>
</tr>
<tr>
<td>Fourth generation cephalosporin</td>
<td>7</td>
<td>27%</td>
</tr>
<tr>
<td>Piperillin-tazobactam</td>
<td>6</td>
<td>23%</td>
</tr>
<tr>
<td>MDRO flag on medical record after VIM isolated</td>
<td>18</td>
<td>69%</td>
</tr>
</tbody>
</table>
Containment Strategies
Containment Strategy

- **Goal:** slow spread of novel/rare MDROs or mechanisms

- Systematic, aggressive response to single cases of high concern

- Tiered approach based on organism/mechanism

https://www.cdc.gov/hai/outbreaks/mdro/index.html
Containment Response Elements

Infection control assessment
Prospective surveillance
Lab Lookback
Screening of healthcare roommates
Broader screening of healthcare contacts
Household contact screening
Environmental sampling
Healthcare personnel screening
Containment Strategy
Systematic public health response to slow the spread of emerging AR

**Single case** of emerging resistance (e.g., pan-R, carbapenemase or MCR-producing Gram negatives)

Onsite assessment using standardized tools

Regular infection control assessments and point prevalence surveys until transmission stops

Available through ARLN
Example of Regional Containment - Israel

• In 2007, rates of KPC in known CRE isolates reached 22%

• Implemented hand hygiene strategies, standard precautions, PPS, and IP/C assessment
  • Prevalence in known CRE-carriers decreased from 16.8% to 12.5%
  • In unknown CRE-carriers, decreased from 12.1% to 7.9%
  • In skilled nursing units, from 26% to 12.8%

• Risk of carriage inversely correlated with infection control practices of a facility
What is the role of the environment in the spread of VIM CRPA, if any?
Develop policies for cleaning of sink basins, faucets, and surrounding area on at least a daily basis

Flush taps in vacant rooms or treatment areas on a regular basis and as a part of the terminal cleaning process

Validate the longevity of point of use filters within your facility by performing regular HPC testing

Ensure that sink faucets are offset from the drain such that water does not flow from the tap directly into the drain

Sink hygiene - “1 meter zone”

Work with outside source(s) to verify building is not in nitrification
Additional CDC Recommendations

- Evaluate amount of alcohol-based hand rub dispensed
- Develop and implement policies to dedicate noncritical equipment to patients infected or colonized with target MDROs
- Competency-based training related to PPE use
- Implementation of a regional standardized form to communicate MDRO status between facilities
- Simplify isolation precaution signage
- TBD: screening of high-risk patients or admissions; point prevalence surveys; follow-up visits; environmental testing
Possible screening scenarios:

Upon admission to hospitals those with a history of a LTC stay in the last 6 months

Upon admission to hospitals and high-acuity post-acute care facilities those with a history of overnight healthcare admission in the last 6 months

Upon admission to hospitals and high-acuity post-acute facilities for all direct transfers, regardless of history

Upon admission to hospitals any patient with a history of overnight healthcare admissions in the last 6 months along with monthly point-prevalence screenings at high-acuity post-acute care facilities to monitor for additional cases

Upon admission to hospitals, only to ICUs, along with monthly point-prevalence screenings at high-acuity post-acute care facilities
Whole Genome Sequencing

- Core genome of 93% and range from 1-88 SNPs
- Appear to have some more closely related clusters
- Distinct from epidemiologically unrelated cases (other areas of the country)

cgMLST Phylogeny Tree of ST 308 PA

- Lubbock isolates
- Related New Mexico isolate

Mandell, Douglas, and Bennett’s Principles and Practice of Infectious Diseases, 2015, Antibiotic Resistance Threats in the United States, 2013, CDC


Lessons Learned

- Look at your processes and surroundings with “new” eyes
- Do not assume *anything* about what your facility is or is not doing
- Approach these types of investigations as a learning opportunity and present them as such to your Administration and your facility
- Be open and honest during these types of investigations
- Realize we ALL share these patients...what is a *COMMUNITY* issue today may be a *STATE* issue tomorrow and a *NATIONAL* or *GLOBAL* issue next week
Epi-Aid Team

Gillian Blackwell, Region 1 HAI Epidemiologist, DSHS
Mary McConnell, Disease Surveillance Nurse, City of Lubbock Health Department
Support from local, region, and state health departments (thank you!)

Chris Prestel, EIS Officer, CDC
Kathleen Hartnett, EIS Officer, CDC
Lule Rault, Epi-Elective Student, CDC
Lauren Epstein, Medical Officer, Antimicrobial Resistance Team, CDC

Janet Glowicz, Infection Preventionist, Hospital Infection Prevention Team, CDC
Kara Jacobs-Slifka, Medical Officer, Long-term Care Team, CDC

Kate Woodworth, Medical Officer, Antimicrobial Resistance Team, CDC
Maroya Walters, Team Lead, Antimicrobial Resistance Team, CDC