Containing Novel Resistance

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Outline

- Introduction to novel resistance
  - Carbapenemase-producing carbapenem-resistant Enterobacteriaceae (CP-CRE)
  - Carbapenemase-producing non-Fermenters (CP-NF)
  - mcr
  - Candida auris
- AR Laboratory Network (ARLN) overview
- Containment guidance
- Emerging issues in carbapenem-resistant organisms
- Texas investigations
Antimicrobial Resistance (AR)

- 2013 CDC Antibiotic Resistance Threats in the United States
  - Estimated more than 2 million antibiotic-resistant infections resulting in at least 23,000 deaths in US each year
  - Urgent threat: Carbapenem-resistant Enterobacteriaceae (CRE)
  - Serious threats: ESBLs, multidrug-resistant *Pseudomonas aeruginosa*, multidrug-resistant *Acinetobacter*
- Containment of novel or targeted multidrug-resistant organisms (MDROs) is a CDC priority
- Emergence of new MDROs
Gram-Negative Rods

- Encompass large number of pathogenic and non-pathogenic bacteria
- Glucose fermenters
  - Includes gut commensals and pathogens
  - Enterobacteriaceae: e.g., *Escherichia coli*, *Klebsiella pneumoniae*, *Salmonella* spp.
- Glucose non-fermenters
  - Opportunistic pathogens
  - *Pseudomonas aeruginosa*, *Acinetobacter baumannii*
  - Intrinsically non-susceptible to many commonly used antimicrobials
Enterobacteriaceae

- Large family of gram negative rods with >25 recognized genera
- Normal gut flora & opportunistic pathogens
- Most common family encountered in clinical microbiology labs
  - Most common are *Klebsiella* spp., *Escherichia coli*, and *Enterobacter* spp.
  - Also *Proteus*, *Providencia*, and *Morganella*

*K. pneumoniae*, scanning electron micrograph
http://www.ppdictionary.com/bacteria/
Carbapenems

- Many Enterobacteriaceae are very susceptible to many antibiotics including members of the penicillin family
- Some have enzymes called β-lactamases that lead to reduced susceptibility to penicillins
- 1990s - emergence and spread of extended-spectrum β-lactamases (ESBLs)
- Carbapenems: broad-spectrum “antibiotics of last resort”
  - Used to treat highly resistant infections
  - Four approved agents in US (imipenem, meropenem, doripenem, ertapenem)
- Carbapenem-resistant Enterobacteriaceae (CRE)
  - Often multidrug resistant; cause infections with high mortality rates
How Common are CRE in the United States?

- Among HAIs submitted to National Healthcare Safety Network (NHSN)
  - ~3-4% of Enterobacteriaceae NS to a carbapenem during 2011 to 2014*
    - In 2001, only 1.2% NS to a carbapenem
- In 2014, 7.8% of short-stay acute care hospitals doing surveillance for CAUTI or CLABSI had at least one CRE**
  - 24% of long-term acute care hospitals (LTACHs)
- Facilities reported 0-13 LabID CRE Events per month in 2015***
  - High incidence states: mean 1.5 events/month
  - Low incidence states: mean 0.08 events/month

**Walters, M et al. SHEA oral abstract, 2016
***Vasquez, A. et al., ID Week Poster, 2016
Annual Incidence of CRE Compared to Other MDROs

- CRE: 2.93 per 100,000 population
- Methicillin-resistant *Staphylococcus aureus*: 25.1 per 100,000 population
- *Clostridium difficile*: 147.3 per 100,000 population

Source: CDC Emerging Infections Program
Carbapenem Resistance Mechanisms

- Carbapenemases
  - Enzymes that breakdown carbapenems

- Non-carbapenemase-producing carbapenem-resistant Enterobacteriaceae (non-CP-CRE)
  - Extended – spectrum cephalosporinase + porin loss
    - Extended-spectrum β-lactamases (ESBLs)
    - AmpC
  - 1986-1990 in NNIS 2.3% of Enterobacter NS to imipenem
    - Appear to have remained relatively stable

- Carbapenemase-producing CRE (CP-CRE)
Carbapenemases

- Enzymes that degrade carbapenem antibiotics
- Usually found on plasmids, which can lead to rapid spread
- 5 enzymes of primary public health concern
  - *K. pneumoniae* carbapenemase (KPC)
  - New Delhi Metallo-β-lactamase (NDM)
  - Verona Integron Mediated Metallo-β-lactamase (VIM)
  - Imipenemase (IMP)
  - OXA-48-type
- Other carbapenemases less frequently encountered
  - Chromosomally encoded (e.g., SME in *Serratia*)
  - No spread beyond country of origin (e.g., SPM, GIM, SIM)
Why Are Plasmid-Encoded Carbapenemases a Public Health Priority?

- Cause infections associated with high mortality rates
- Resistance is highly transmissible
  - Between organisms – plasmids
  - Between patients
- Treatment options are limited
  - Pan-resistant strains identified
  - Could be decades before new agents are available to treat
- Potential for spread into the community
  - *E. coli* common cause of community infection
- Has spread rapidly (CP-CRE) throughout US and world
CP-CRE Examples

- Potential for swift, epidemic spread
- Can dramatically increase proportion of resistant isolates
- Examples
  - Israel: KPC outbreak
    - 11% carbapenem resistant in 2006
    - 22% carbapenem resistant in 2007
  - Greece: Dissemination of VIM
    - <1% carbapenem resistant in 2001
    - 20%-50% carbapenem resistant in 2006

Isolate collected in 1996 during an ICU surveillance project from NC
Why Are Plasmid-Encoded Carbapenemases a Public Health Priority?

States with KPC-CRE Reported to CDC

2001

2016
CP-CRE reported to the Centers for Disease Control and Prevention (CDC) as of January 2017

- NDM
- OXA-48
- VIM
- IMP

https://www.cdc.gov/hai/organisms/cre/trackingcre.html
Carbapenemases In the U.S.

CP-CRE Reported through ARLN, 2017

87%

KPC  NDM  OXA  VIM  IMP

Data are preliminary and subject to change
CRE Surveillance

- Emerging Infections Program (EIP) Multi-site Gram-negative Surveillance Initiative (MuGSI)

- Population-based surveillance in nine metropolitan areas

- 15.1 million persons under surveillance in 2017
EIP MuGSI Surveillance

- Proportion of carbapenemase-producing isolates in CRE varies regionally
  - From 15.4% (Oregon) to 76.5% (Maryland)
  - Overall 47.9%

- Location of culture collection: 66.1% outside of short-stay acute care hospitals

- 75.1% of cases had acute care hospitalization in prior year

Carbapenemase-Producing Non-Fermenters
Carbapenem-Resistant Non-Fermenters

- Carbapenemase-producing non-fermenters (CP-NF)
- Can have chromosomal or plasmid-mediated carbapenem resistance
- Carbapenem-resistant *Pseudomonas aeruginosa* (CR-PA)
  - Brazil 1998-2012: 39% of CRPA produced carbapenemase
  - Europe 2009-2011: 20% of CRPA produced carbapenemase
  - Denmark 2011: 7% of CRPA produced carbapenemase
  - U.S. 2015: 2% of CRPA tested produced carbapenemase
- VIM is most commonly reported worldwide
  - IMP, KPC, and NDM also reported in U.S

CP-NF Isolates Reported to CDC, by Organism and Mechanism, January 2009-December 2016, N=53

Number of Isolates

<table>
<thead>
<tr>
<th>Organism</th>
<th>NDM</th>
<th>VIM</th>
<th>IMP</th>
<th>KPC</th>
<th>KHM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Achromobacter xylosoxidans</td>
<td></td>
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<tr>
<td>Acinetobacter spp.</td>
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<tr>
<td>Pseudomonas aeruginosa</td>
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<td></td>
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<tr>
<td>Pseudomonas stutzeri</td>
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</tbody>
</table>

Cluster associated
Patients with CP-NF Isolates Reported to CDC, by Year, N=51
Patients with CP-NF Reported to CDC, by State, January 2009-December 2016, N=51
CP-NF: Considerations for Public Health Response

- Carbapenemase-producing non-fermenters are rare in the U.S.
  - VIM *Pseudomonas* most frequently reported
  - Other carbapenemases, including KPC, less frequently identified
  - Unknown proportion associated with travel

- Responses should consider different attributes of these organisms
  - *Acinetobacter*: Environment can plan substantial role in transmission
  - *Pseudomonas*: Water bug, moist environments
Colistin Resistance and mcr
Colistin and emergence of mcr in the U.S.

- Mobile colistin resistance (mcr)
  - First reported in 2015 isolates from China*
  - Now identified in isolates from across globe**
- Mobile resistance to Polymyxin class of antibiotics (colistin, polymyxin B)
- Antibiotic used to treat serious, highly resistant infections
- 26 cases (24 mcr-1 and 2 mcr-3) identified as of August 31, 2017
- 14 *E. coli* (including 1 STEC), 10 *Salmonella*, 2 *Klebsiella pneumonia*
  - Only one CP-CRE (NDM)

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Colistin and emergence of *mcr* in the U.S.

https://www.cdc.gov/drugresistance/tracking-mcr1.html
Key Findings from mcr Investigations

- 22/26 had international travel in year prior
  - Bahrain, Cambodia (n=2), China (n=2), Columbia, Dominican Republic (n=6), Jamaica/St. Vincent/Bahamas, Lebanon, Mexico (n=2), Portugal, Thailand, Vietnam (n=3)

- 11/26 had known inpatient healthcare exposure in year prior (3 unknown)
  - Currently investigating 1 potential transmission in healthcare

- Concern for spread in healthcare settings

- [https://emergency.cdc.gov/han/han00390.asp](https://emergency.cdc.gov/han/han00390.asp)
Candida auris
Recent Emerging Threat: Candida auris (C. auris)

- Fungus that causes invasive infections, high mortality, can be resistant to multiple antifungal drugs
- Unlike most other Candida species:
  - Colonizes intact skin and readily contaminates environmental surfaces for long periods (e.g., bedrails, bedside tables, chairs)
  - Often misidentified by clinical labs (e.g. C. haemulonii), requires special lab methods and training (MALDI-TOF)
  - Appears to be supplanting other Candida spp. in facilities where found more frequently
Recent Emerging Threat: *Candida auris* (C. auris)

- 153 cases as of 8/31/2017 (126 confirmed; 27 probable)
- 10 states
- Majority of clinical isolates were from blood
- Resistance (n=127)
  - 91% to fluconazole
  - 29% to amphotericin B
  - 6% to echinocandins
- Majority from skilled nursing facilities (SNFs) or LTACHs
Recent Emerging Threat: *Candida auris* (C. auris)

Recent Emerging Threat: *Candida auris* (C. auris)

- **Candida auris** Recommendations for Healthcare Facilities and Laboratories
  - [https://www.cdc.gov/fungal/diseases/candidiasis/recommendations.html](https://www.cdc.gov/fungal/diseases/candidiasis/recommendations.html)

- Suspect *C. auris* when isolate identified as:
  - *Candida haemulonii, Candida duobushaemulonii* by Vitek 2 YST
  - *Rhodotorula glutinis* by API 20C (when red color not present)
  - *Candida sake* by API 20C
  - *Candida catenulata, Candida haemulonii* by BD Phoenix
  - *Candida parapsilosis*, *Candida famata, Candida guilliermondii*, or *Candida lusitaniae* by MicroScan
  - *Candida spp.* not identified by a valid identification method

*if no hyphae/pseudohyphae present on cornmeal agar*
Recent Emerging Threat: *Candida auris* (C. auris)


- Reporting: [candidaauris@cdc.gov](mailto:candidaauris@cdc.gov)
Detection of Targeted MDROs
Detection

- Problem: restricted capacity to detect and respond to emerging resistance if CDC is the only sentinel surveillance program for AR
- Limited state capacity for AR testing
- In clinical labs, data is not often connected to public health action
Solution: CDC’s AR Laboratory Network (ARLN)

- Transform the national lab infrastructure with regional laboratories and local labs with gold-standard methods and technology
  - species identification and confirmatory antimicrobial susceptibility testing
  - phenotypic screening for carbapenemase production
  - carbapenemase mechanism testing
- Enhanced testing capacity in all 50 states and five local jurisdictions
- Faster detection for rapid and improved public health response
- Communication channels to engage clinical laboratory partners
- Real-time, actionable data to combat AR threats
AR Solutions at Every Level

- The ARLN ensures more consistent and improved communication, coordination, and tracking at all levels every time.
- When resistance threats are detected within healthcare facilities or state/local labs, regional labs can provide support to characterize, support response, and track these discoveries.
- Flexibility in surveillance testing to focus on the next emerging threat.
- CDC’s ARLN team and Programs provide logistics support, subject matter expertise, and tailored solutions.
ARLN Regional Lab Core Testing

- CRE/CRPA Isolate Characterization
- Targeted surveillance
  - Carbapenem-R Acinetobacter spp.
  - ESBL-producing Enterobacteriaceae
  - Isolate testing for mcr-mediated colistin resistance

Outbreak Response

CRE Colonization Screening from Rectal Swabs
- Confirms CRE
- Submits to HAI Coordinator
- Identifies Patient Contacts
- Coordinates Swab Collection

Results to Facility, Epidemiologist, and Lab in 2 Days
ARLN: Laboratory Support for Containment

Hospitals/Clinical Laboratories

Public Health Laboratories
50 States
5 Local Health Departments

May include:
Species identification
Confirmatory AST
Phenotypic screening for carbapenemase production
Carbapenemase mechanism testing

CRE/CRPA isolates
Colonization screening in ARLN

Rectal swabs from CP-CRE+ patient contacts

Swabs positioned regionally for rapid deployment to facilities where screening taking place

Rapid PCR-based detection from swab (Cepheid)
Colonization screening in ARLN

Swabs from CP-CRE+ patient contacts

≤1 day turnaround

Report within 1 working day of results

Regional lab

Provide or request assistance; Initiate investigation

Report within 1 working day of results
<table>
<thead>
<tr>
<th>Test TYPE</th>
<th>Method</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacterial Species Identification</td>
<td>- Matrix assisted laser desorption ionization-time of flight mass spectrometry (MALDI-TOF)</td>
</tr>
<tr>
<td></td>
<td>- API 20 is MALDI-TOF result not definitive</td>
</tr>
<tr>
<td></td>
<td>- Conventional biochemicals</td>
</tr>
<tr>
<td>Antimicrobial Susceptibility Testing (AST)</td>
<td>- Disk Diffusion</td>
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<tr>
<td></td>
<td>- Etest</td>
</tr>
<tr>
<td></td>
<td>- Broth Microdilution (coming soon)</td>
</tr>
<tr>
<td>Carbapenemase Production Testing</td>
<td>mCIM, CarbaNP</td>
</tr>
<tr>
<td>Mechanisms of Resistance Testing</td>
<td>- Cepheid panel</td>
</tr>
<tr>
<td></td>
<td>- CDC PCR protocol: KPC/NDM, OXA-48 like, VIM, mcr-1/mcr-2</td>
</tr>
<tr>
<td>Whole Genome Sequencing</td>
<td>Illumina MiSeq</td>
</tr>
</tbody>
</table>

*Provided by TX regional lab*
CRE by the Numbers
January – July 2017 CRE data reported as of September 5, 2017

- 2,207 isolates tested
- 645 confirmed as carbapenemase-producers
- 3 mcr-1 cases confirmed by the AR Lab Network
- 89 AR Lab Network alerts, informing local epi response
- 26 public health labs reporting
Containment of Targeted MDROs
Containment Strategy

- **Goal:** slow spread of novel or rare multidrug-resistant organisms or mechanisms
- Systematic, aggressive response to single cases of high concern antimicrobial resistance
  - Focus on stopping transmission
- Response activities have tiered approach based on organism/mechanism attributes
- Complements existing guidance
  - CRE Toolkit
  - VRSA Investigation Guide

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

- Tier 1
  - resistance mechanisms novel to the United States (i.e., not or only very rarely identified in the United States) or
  - organisms for which no current treatment options exist (pan-resistant)
  - organisms and resistance mechanisms for which experience in the United States is extremely limited and a more extensive evaluation might better define the risk for transmission

- Tier 2
- Tier 3
Response Tiers

- Tier 1
- Tier 2
  - MDROs primarily found in healthcare settings but not found regularly in the region; these organisms might be found more commonly in other areas in the United States
- Tier 3
Response Tiers

- Tier 1
- Tier 2
- Tier 3
  - MDROs targeted by the facility/region that are already established in the United States and have been identified before in the region but are not thought to be endemic
Targeted Pathogens for Containment

- *Candida auris* (tier 1)
- *mcr*-1 producing Enterobacteriaceae (tier 2)
- Vancomycin-resistant *Staphylococcus aureus* (tier 1)
- Pan-resistant isolates (tier 1)
- Carbapenemase-producing carbapenem-resistant Enterobacteriaceae (particularly non-KPC) (tier 2)
- Carbapenemase-producing *Pseudomonas* sp. (tier 2)
- Carbapenem-resistant Enterobacteriaceae producing *Klebsiella pneumoniae* carbapenemase (tier 3)
- Other isolates might be important in some areas
## Containment Response Elements

<table>
<thead>
<tr>
<th>Infection control assessment</th>
<th>Prospective surveillance</th>
<th>Lab Lookback</th>
<th>Screening of healthcare roommates</th>
<th>Broader screening of healthcare contacts</th>
<th>Household contact screening</th>
<th>Environmental sampling</th>
<th>Healthcare personnel screening</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tier 1</td>
<td>Tier 2</td>
<td>Tier 3</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Novel resistance mechanisms, PanR</td>
<td>Mechanisms and organisms not regularly found in a region</td>
<td>Mechanisms and organisms regularly found in a region but not endemic</td>
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</tbody>
</table>
Approach to screening healthcare contacts

https://www.cdc.gov/hai/outbreaks/mdro/index.html
Infection Control Considerations

- Notify patients of their results
- Educate and inform healthcare personnel and visitors
- Ensure adequate supplies are available and appropriate infection control practices in place
  - hand hygiene
  - transmission-based precautions
  - environmental cleaning
- Flag patient record
- Ensure patient’s status and infection control precautions are communicated at transfer
- If MDRO present at admission, notify transferring facility
Emerging Issues in Epidemiology of CP-Organisms
Emerging Issues in Epidemiology of CP-Organisms

#1: Increase of non-KPC carbapenemases reported in Enterobacteriaceae other than *Klebsiella*, *Enterobacter*, and *E. coli*

<table>
<thead>
<tr>
<th>Organism</th>
<th>Number of Isolates</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Proteus mirabilis</em></td>
<td>5</td>
</tr>
<tr>
<td><em>Providencia rettgeri</em></td>
<td>5</td>
</tr>
<tr>
<td><em>Morganella morganii</em></td>
<td>4</td>
</tr>
<tr>
<td><em>Citrobacter freundii</em></td>
<td>3</td>
</tr>
<tr>
<td><em>Serratia marcescens</em></td>
<td>3</td>
</tr>
<tr>
<td><em>Salmonella seftenberg</em></td>
<td>1</td>
</tr>
<tr>
<td><em>Providencia stuartii</em></td>
<td>1</td>
</tr>
<tr>
<td><strong>Grand Total</strong></td>
<td><strong>22</strong></td>
</tr>
</tbody>
</table>
Emerging Epidemiologic Trends

- #2: Increased detection of IMP, VIM, and OXA-48
Emerging Issues in Epidemiology of CP-Organisms

#3: CP-CRE in U.S. patients without healthcare or international travel

- Colorado: 6/10 recent NDM community-associated*
  - 2 had recent international travel
- Source currently unknown
  - CP-CRE found in community sources in U.S.
    - OXA-48 in municipal water that failed fecal coliform testing$    
    - IMP-27 in environmental samples on pig farm#

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$ Tanner, W.D., poster presentation

Emerging Issues in Epidemiology of CP-Organisms

#4: New modes of transmission: sink drains and hoppers

- Hospital sink drains and hoppers can become colonized with CP-CRE and contaminate the patient environment.
- Characteristic outbreak “signature”
  - Single mechanism in multiple genus and species
  - Cases persist despite infection control interventions for person to person transmission and environmental cleaning.
- Lab work ongoing to describe extent of spread and to evaluate ways to prevent (e.g., lids on hoppers).
- Keep patient supplies away from sink splash zone.
Antimicrobial Resistance In Texas
Texas CP-CRE and Carbapenemase-Producing *Pseudomonas aeruginosa* (CP-PA)

- 347 isolates submitted from TX to regional lab for characterization reported to CDC as of 8/31/2017
  - 97 CP-CRE identified (96 KPC, 1 OXA-48)
  - 13 CP-PA identified (6 VIM-*Pseudomonas*, 2 IMP-*Pseudomonas*, 5 no gene currently identified)

### Number CP of isolates, by organism

<table>
<thead>
<tr>
<th>Organism</th>
<th>Number of Isolates</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Klebsiella pneumoniae</em></td>
<td>92</td>
</tr>
<tr>
<td><em>Enterobacter cloacae</em></td>
<td>2</td>
</tr>
<tr>
<td><em>Enterobacter cloacae complex</em></td>
<td>1</td>
</tr>
<tr>
<td><em>Escherichia coli</em></td>
<td>2</td>
</tr>
<tr>
<td><em>Pseudomonas aeruginosa</em></td>
<td>13</td>
</tr>
<tr>
<td><strong>Grand Total</strong></td>
<td><strong>110</strong></td>
</tr>
</tbody>
</table>
TX CP-PA

- **VIM-PA**
  - 8 cases identified in 4 facilities in 2016 and 2017
  - Cases primarily in West Texas/Panhandle
  - 1 patient screened as a result
  - No additional cases identified from screening

- 4 MDR-*Pseudomonas* cases among pediatric patients at burn hospital
  - 2 patients identified with IMP-PA
  - Investigation suggests importation and transmission
mcr-1 from ESBL E. coli in urine from a 49 yo without international travel
  — 20th U.S. case (1st in TX)
  — Admitted to ACH, LTACH, and IRF

First OXA-48 identified in \textit{E. coli} from a wound culture at a rehab facility
  — Screened 3 healthcare contacts in close proximity to patient’s room (all negative)
Summary

- Containment of MDROs is complex
- Guidance available
  - [https://www.cdc.gov/hai/outbreaks/mdro/index.html](https://www.cdc.gov/hai/outbreaks/mdro/index.html)
- Coordination between lab and epi is critical
- TX organisms for containment
  - Carbapenemase-producing PA (VIM and IMP)
  - CP-CRE (OXA-48 and NDM)
  - mcr-1
  - *C. auris*
  - Be on the lookout for others (*e.g.* IMP and VIM producing-CRE)
Thank you

For more information, contact CDC
1-800-CDC-INFO (232-4636)

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.