The Biggest Antibiotic Resistance Threats

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AR Threats in the United States - 2013

- First report of AR threats in the United States. Since then...
- Our ability to detect new resistance has expanded
- New threats have emerged (e.g., *Candida auris*) and existing threats have evolved
- Existing threats, like the NDM subtype of carbarpenem-resistant Enterobacteriaceae (CRE) and *Neisseria gonorrhoeae* have become more resistant
Resistant Gram-Negative Bacteria
Hard to Treat Infections

- Very limited treatment options with available drugs
- New drugs coming to market have limited activity
- High mortality (e.g., 50%) with serious infections
Rapid Spread of Carbapenemase-Producing (CP) Enterobacteriaceae in the United States

KPC-CRE found in the US spread from 2 states in 2001 to 49 states, DC, and PR in 16 years

States with *Klebsiella pneumoniae* carbapenemase (KPC)-producing Carbapenem-resistant Enterobacteriaceae (CRE) confirmed by CDC
## Other Types of CP Enterobacteriaceae

<table>
<thead>
<tr>
<th>Carbapenemase</th>
<th>Number of Infections</th>
</tr>
</thead>
<tbody>
<tr>
<td>NDM</td>
<td>379</td>
</tr>
<tr>
<td>OXA-48 like</td>
<td>146</td>
</tr>
<tr>
<td>VIM</td>
<td>57</td>
</tr>
<tr>
<td>IMP</td>
<td>36</td>
</tr>
</tbody>
</table>

Data as of December 2017
Carbapenemase-Producing *Pseudomonas aeruginosa*

<table>
<thead>
<tr>
<th>Carbapenemase</th>
<th>Number of Infections</th>
</tr>
</thead>
<tbody>
<tr>
<td>VIM</td>
<td>86</td>
</tr>
<tr>
<td>IMP</td>
<td>8</td>
</tr>
<tr>
<td>NDM</td>
<td>7</td>
</tr>
<tr>
<td>KPC</td>
<td>6</td>
</tr>
<tr>
<td>OXA–48 like</td>
<td>0</td>
</tr>
</tbody>
</table>

Data as of December 2017
Carbapenem-Resistant *Acinetobacter* spp.

- Differs from Enterobacteriacea and *Pseudomonas*
  - nearly all carbapenem-resistant *Acinetobacter* spp. harbor a carbapenemase
  - The carbapenemases are OXA enzymes. Most common:
    - OXA-51
    - OXA-58
    - OXA-23
  - CRE carbapenemases, KPC and NDM, have been reported but are rare in the U.S.

- Hand hygiene and hospital environmental cleaning are key aspects of infection prevention
## Anticipated Activity of New Antibiotics

<table>
<thead>
<tr>
<th>Drug</th>
<th>CRE</th>
<th>CRPA</th>
<th>CRAB</th>
<th>Stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ceftazidime-avibactam</td>
<td>✓</td>
<td>X</td>
<td>X</td>
<td>FDA Approved</td>
</tr>
<tr>
<td>Meropenem-vaborbactam</td>
<td>✓</td>
<td>X</td>
<td>X</td>
<td>FDA Approved</td>
</tr>
<tr>
<td>Plazomycin</td>
<td>✓</td>
<td>X</td>
<td>X</td>
<td>Submitted to FDA</td>
</tr>
<tr>
<td>Imipenem-relebactam</td>
<td>✓</td>
<td>✓</td>
<td>X</td>
<td>Phase 3</td>
</tr>
<tr>
<td>Eravacycline</td>
<td>✓</td>
<td>✓</td>
<td>X</td>
<td>Phase 3</td>
</tr>
<tr>
<td>Cefiderocol</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>Phase 3</td>
</tr>
<tr>
<td>Omadacycline</td>
<td>X</td>
<td>✓</td>
<td>X</td>
<td>Phase 3</td>
</tr>
<tr>
<td>LYS228</td>
<td>✓</td>
<td>X</td>
<td>X</td>
<td>Phase 2</td>
</tr>
<tr>
<td>Murepavadin</td>
<td>X</td>
<td>✓</td>
<td>X</td>
<td>Phase 2</td>
</tr>
<tr>
<td>Cefepime-AAI101</td>
<td>✓</td>
<td>X</td>
<td>X</td>
<td>Phase 2</td>
</tr>
</tbody>
</table>
Pan-Resistant Infections

Particular Concern: NDM-Producing Carbapenem-Resistant Enterobacteriaceae
2016 Case Report: Infection with Pan-Resistant Bacteria

Notes from the Field

Pan-Resistant New Delhi Metallo-Beta-Lactamase-Producing Klebsiella pneumoniae — Washoe County, Nevada, 2016

Lei Chen, PhD, Randall Todd, DrPH, Julia Kolbenschlag, PhD, Mary Watters, PhD, Alexandre Kalen, MD

On August 25, 2016, the Washoe County Health District in Reno, Nevada, was notified of a patient at an acute care hospital with carbapenem-resistant Enterobacteriaceae (CRE) that was resistant to all available antibiotics. The specific CRE, Klebsiella pneumoniae, was isolated from a wound specimen collected on August 19, 2016. After CRE was identified, the patient was placed in a single room under contact precautions. The patient had a history of recent hospitalization outside the United States. Therefore, based on CDC guidance, the isolate was sent to CDC for testing to determine the mechanisms of antimicrobial resistance, which confirmed the presence of New Delhi metallo-beta-lactamase (NDM).

The patient was a female Washoe County resident in her 70s who arrived in the United States in early August 2016 after an extended visit to India. She was admitted to the acute care hospital on August 18 with a primary diagnosis of systemic inflammatory response syndrome, likely resulting from an infected right hip fracture. The patient developed septic shock and died in early September. During the 2 years preceding this U.S. hospitalization, the patient had multiple hospitalizations in India related to a right femur fracture and subsequent osteomyelitis of the right femur and hip; the most recent hospitalization in India had been in June 2016.

A point prevalence survey, using rectal swab specimens and conducted among patients currently admitted to the same unit as the patient, did not identify additional CRE. Active surveillance for multidrug-resistant bacilli including CRE has been conducted in Washoe County since 2010 and is ongoing; no additional NDM CRE have been identified.

This report highlights three important issues in the control of CRE. First, although CRE are commonly sent to CDC as part of surveillance programs or for reference testing, isolates that are resistant to all antibiotics are very uncommon. Among >250 CRE isolate reports collected as part of the Emerging Infections Program, approximately 80% were susceptible to at least one aminoglycoside and nearly 90% were susceptible to tigecycline. Second, to slow the spread of bacteria with resistance mechanisms of greatest concern (e.g., gene encoding NDM or mcr-1) or with pan-resistance to all drug classes, CDC recommends that when these bacteria are identified, facilities ensure that appropriate infection control contact precautions are instituted to prevent transmission and that health care contracts are evaluated for evidence of transmission. Third, the patient in this report had inpatient health care exposure in India before receiving care in the United States. Health care facilities should obtain a history of health care exposures outside their region upon admission and consider screening for CRE when patients report recent exposure outside the United States or in regions of the United States known to have a higher incidence of CRE.1

1Washoe County Health District, Nevada.2University of Nevada, Reno.3Nevada State Public Health Laboratory.4Division of Healthcare Quality Promotion, National Center for Emerging and Zoonotic Infectious Diseases, CDC

- 70 yo female hospitalized for an infection in her hip
- The patient recently traveled to India and was hospitalized for treatment of a hip fracture
- Infecting isolate: NDM-producing Klebsiella pneumoniae that was pan-resistant (could not be treated by available antibiotics)
- The patient developed septic shock and died
NDM-Producing CRE: Worldwide Dissemination

- There are different types of CRE infections; KPC and NDM are the most common
- All CRE infections are hard-to-treat
- NDM-CRE are found worldwide and predominate in many countries
- In the US, KPC-CRE are more common

Logan et al., J Infect Dis. 2017. Feb 15
We Can’t Rely Upon Drugs Alone to Protect Patients

<table>
<thead>
<tr>
<th>Drugs for MDRO Gram-Negative Infections</th>
<th>Most Common CRETypes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>KPC</td>
</tr>
<tr>
<td>Colistin</td>
<td>?</td>
</tr>
<tr>
<td>Ceftazidime-Avibactam</td>
<td>✓</td>
</tr>
<tr>
<td>Meropenem-Vaborbactam</td>
<td>✓</td>
</tr>
<tr>
<td>Impenem-Relebactam</td>
<td>✓</td>
</tr>
<tr>
<td>Plazomycin</td>
<td>✓</td>
</tr>
<tr>
<td>Aztreonam-Avibactam</td>
<td>x</td>
</tr>
<tr>
<td>Cefiderocol</td>
<td>✓</td>
</tr>
</tbody>
</table>

- New data suggests colistin may provide little clinical benefit
- NDM-CRE usually carry a gene that confers resistance to all aminoglycosides including plazomycin
- Aztreonam-avibactam can be created by treating a patient with ceftazidime-avibactam and aztreonam
Outbreaks of Resistant Fungal Infections in Healthcare Settings

*Candida auris*
Candida auris

- A fungal pathogen causing healthcare facility outbreaks around the world
- Only recently emerged in the United States with nearly all cases occurring after mid 2016.
- *C. auris* is resistant to multiple antifungal drug classes. Pan-resistant isolates have been identified.
- Outbreaks are challenging to control because both the patients and the hospital environment are readily colonized by *C. auris*
Retrospective Analyses Show Rapid Emergence of Different *C. auris* Strains Worldwide

At least 4 strains circulating globally

- S. Africa
- Kenya
- Kuwait
- U.K.
- Pakistan
- Venezuela
- United States
- Colombia

Strain sequences pending

Date Identified


Japan Korea India
An additional 407 asymptotically colonized patients have been identified in four states with clinical cases. If left undetected, colonized patients (without symptoms) could continue spreading *C. auris* in the healthcare facility.
Containing Unusual Resistance

Vital Signs Report April 2018
The Containment Strategy

- Rapid detection in health care facilities
- Infection control assessments led by the health department
- Colonization screenings, when needed
- Coordination between healthcare facilities
- Continued vigilance until spread is controlled
AR Lab Network
Early detection of resistance & testing to support containment
A Pilot Program – Susceptibility Testing of New Drugs

- Closes the gap between new drug approval and the availability of testing methods in hospital laboratories.

- Answers the question, “Will our drugs work?” HP inkjet printer allows for on-demand reference susceptibility testing of new drugs in regional labs of the AR Lab Network.

- Rapid reporting to improve care via AR Lab Network IT reporting to hospitals for tailored patient treatment.
Neisseria gonorrhoeae
Neisseria gonorrhoeae

- Empiric therapy recommendations
  - Ceftriaxone 250 mg IM + Azithromycin 1 gm PO

- All therapy is empiric because disease is diagnosed using PCR

- Resistance to azithromycin and ceftriaxone is emerging
Trends in Resistance

FIGURE 2. Prevalence of tetracycline, penicillin, or fluoroquinolone resistance* or reduced cefixime or azithromycin susceptibility,† by year — Gonococcal Isolate Surveillance Project, United States, 2000–2014
How do we get susceptibility data?

- Gonococcal Isolates Surveillance Program (GISP)
  - Isolates collected from 25 sexually transmitted disease clinics in U.S.
  - Isolates sent to 4 regional labs of the AR Lab Network
  - Antimicrobial susceptibility testing using agar dilution methods
  - Results of testing are used to set treatment guidelines

- Additional detect and protect capacity in public health departments
  - Antimicrobial susceptibility testing of isolates from treatment failures
  - If resistance is found, epidemiological response to track cases and prevent transmission
Clostridium difficile
**Clostridium difficile**

- Is this really an AR threat?
  - Not resistant to treatment
  - Resistant to commonly used antibiotics and can establish GI infections when healthy bacteria are eliminated by these antibiotics

- Significant burden of disease
  - 15,000 deaths per year
  - $3.8 billion in healthcare costs over 5 years
The Importance of the Microbiome
Pathogenesis of \textit{Clostridium difficile} Infection

1. Ingestion of spores transmitted from other patients via the hands of healthcare personnel and environment
2. Germination into growing (vegetative) form
3. Altered lower intestine flora (due to antimicrobial use) allows proliferation of \textit{C. difficile} in colon
4. Toxin A & B Production leads to colon damage +/- pseudomembrane

Managing the Microbiome

- Managing the microbiome could reduce disease (e.g., *Clostridium difficile* infection) or prevent transmission of MDRO colonizer (e.g., CRE)

- Interventions to preserve or restore the microbiome are in development
  - Better probiotics
  - Pills that can absorb or inactivate antibiotics in the GI tract

- Diagnostic tests to assess the microbiome will
  - Help to identify intervention strategies
  - Could be used to determine when interventions are necessary
Summary: The Biggest Threats

- Antibiotic resistance continues to evolve. Two important developments:
  - Pan-resistant CRE infections; NDM-CRE are a particular concern
  - *Candida auris* outbreaks

- The drug pipeline will help, but resistance continues to develop and there are not enough candidates for threats like NDM-CRE. We have to rely on other strategies like containment and improving use of antibiotics.

- CDC has invested in new laboratory capacity
  - For early detection of characterization of AR threats
  - To support containment strategies
  - To provide testing to guide treatment for the most resistant threats
Thank You
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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.