National Center for Emerging and Zoonotic Infectious Diseases

Emerging Resistance Updates

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Objectives

- Describe emergence and potential importance of Enterobacteriaceae with *mcr-1*
- Discuss world-wide dissemination of *Candida auris*
- Discuss identification of resistance to ceftazidime/avibactam
- Describe regional approach to emerging MDROs

mcr-1

Plasmid-mediated colistin resistance (*mcr-1* gene)

- Colistin from polymyxin family of antibiotics (Polymyxin B and E)
  - Broad activity against Gram-negative bacteria
  - Humans: Used topically and IV for highly-resistant organisms
  - Used in animals in U.S. for treatment (rarely)
  - Toxicities have limited its human IV use to highly-resistant Gram-negatives (e.g., CRE)
  - Resistance
    - Chromosomal
    - About 11% of CDC ESBLs have Colistin MIC>=4 mcg/ml
    - Some Enterobacteriaceae can have baseline elevated MICs

Liu YY et al. *Lancet Infect Dis.* 2016; 16(2):161-8.
Skov RL, Monnet DL. *Euro Surveil.* 2016; 21(9)

Plasmid-mediated colistin resistance (*mcr-1* gene)

- First report of plasmid-mediated colistin resistance November 2015 (China)
  - Found in (*E. coli*):
    - 78/523 (15%) raw meat samples
    - 166/804 (21%) animal samples
    - 16/1322 (1%) human healthcare samples

Liu YY et al. *Lancet Infect Dis.* 2016; 16(2):161-8.
Skov RL, Monnet DL. *Euro Surveil.* 2016; 21(9)

Plasmid-mediated colistin resistance (*mcr-1* gene)

- Subsequent retrospective reviews and prospective surveillance:
  - Earliest isolates identified 1980s (chickens, China)
  - Earliest human isolate from Vietnam 2008
  - Species
    - *Escherichia coli* (primarily)
    - *Klebsiella pneumoniae*
    - *Salmonella enterica* (multiple serotypes)
    - *Shigella sonnei*
  - Very high transmission rate for plasmids

Liu YY et al. *Lancet Infect Dis.* 2016; 16(2):161-8.
Skov RL, Monnet DL. *Euro Surveil.* 2016; 21(9)

Plasmid-mediated colistin resistance (*mcr-1* gene)

- Found globally (>20 countries)
  - Isolated from:
    - Food animals
    - Environment (river water)
    - Meat, vegetables
    - Ill patients
    - Asymptomatically colonized (travel)

Skov RL, Monnet DL. *Euro Surveil.* 2016; 21(9)

Why is mcr-1 potentially important?

- Plasmid-mediated with high propensity for spread
- Although many isolates to date are treatable with other antibiotics, has potential to add colistin-resistance to isolates with high levels of resistance
  - Further limits or eliminates treatment options

mcr-1 gene in the United States

- May 2016: Department of Defense (DoD) reported *E. coli* with *mcr-1* gene (PA)
- Now 4 known human *mcr-1* in the US under investigation
  - NY, NJ, PA, CT
    - Earliest 2014 (NJ)
  - 1 potentially travel-associated
  - 3/4 isolates are susceptible to carbapenems (ESBLs, AmpC)
    - One NDM
  - All *E. coli*
- 2 porcine *E. coli* isolates carrying *mcr-1* identified (IL, NC)

PA *mcr-1*

- Woman with multiple comorbidities and recent admissions
  - No travel in 9 months
- Screening
  - Household contacts
  - HCP at two facilities
  - PPS at one facility
  - Patient
    - Negative at 3 months
- Prospective surveillance – negative

CT *mcr-1*

- Pediatric patient
- Recent travel to Caribbean
- Screening:
  - Household contacts
  - Environment
  - Patient
    - Negative twice

mcr-2

- Report from Belgium of second gene with about 77% homology with *mcr-1*
- *mcr-2* was actually more common in the porcine/bovine E. coli (MIC 4 to 8 mcg/ml) than *mcr-1*
- Current CDC pcr does not identify this

Recommendations – HAN June 13, 2016

- **Infection Prevention:** Healthcare providers should follow Standard and Contact Precautions
- **Laboratory Testing:** Enterobacteriaceae isolates with a minimum inhibitory concentration (MIC) to colistin of 4 µg/ml or higher should be tested for confirmation and the presence of *mcr-1*
  - Exceptions:
    - intrinsic resistance (*Morganella*, etc.)
    - *Enterobacter spp.*
  - Testing when needed for clinical care
- **Validation of Laboratory Testing:** CDC is making test-bacteria with elevated colistin MICs, available through the FDA-CDC AR Bacteria Isolate Bank
- **Environmental Cleaning**: Healthcare facilities should ensure rooms where patients with antibiotic-resistant infections have been placed receive thorough daily and terminal cleaning
- **Report isolates to Public Health**

Candida auris

C. auris basics

- Candida - yeast, cause healthcare and community infections
- Can cause invasive infections, predominantly fungemia
- *C. auris* can be multidrug-resistant (MDR)
- Cannot distinguish *C. auris* from other *Candida* species with biochemical tests and most conventional diagnostics

UK 2015–2016 outbreak

- **An adult critical care unit in the UK with >40 patients either colonized or infected with *C. auris***
  - ~20% of these patients had candidemia
- **Outbreak difficult to control despite intensive IC efforts:**
  - Regular patient screening in the ICU
    - Rarely present at admission
  - Cohorting colonized patients
  - Environmental decontamination with high concentration bleach
  - Ward closure
  - Screening HCP
- **Transmission from environmental sources**
  - Preliminary data suggests healthcare workers not major carriers
  - Hospital rooms remain positive despite cleaning
  - Frequent high-level colonization of skin sites

C. auris early epidemiology

- **Patients of all age ranges (NICU infants→ elderly)**
- **Similar risk factors as for other *Candida* spp.**
  - Diabetes
  - Antibiotic use
  - Recent surgery
  - Presence of a central venous catheter
- **Patients on antifungal treatment when *C. auris* isolated**
- **Median time from admission to infections: 17 days**
- **Mortality in some settings ~60%;**
  - 100% in Venezuela in NICU infants

Why are we concerned about *C. auris?*

- **Is multidrug-resistant**
  - Some isolates resistant to all three major antifungal classes
- **Can be misidentified**
  - Usually misidentified as other *Candida* spp or *Saccharomyces*
  - MALDI-TOF can detect *C. auris*
- **Causes outbreaks in healthcare settings**
  - Unlike other *Candida* spp., seems to colonize healthcare environments and skin
  - Major infection control challenges

Is it in the United States?

- **EIP Candidemia Surveillance Program**
  - >7000 *Candida* isolates collected in U.S. 2008 –2016
  - No *C. auris*
- **SENTRY system** (Private collection funded by pharma)
  - >6000 North American isolates collected from the US since 2004
  - 1 *C. auris* isolate from 2013

Findings from U.S. Investigations

- Lots of contamination of rooms in which there are known patients
- No evidence of persistent contamination following terminal cleaning
- Persistent contamination of index patients (skin and nares)
- Probable transmission but no outbreaks
- No one clone

CDC issued a clinical alert to healthcare facilities – June 2016


Fungal Diseases

Fungal Diseases
Types of Fungal Diseases −
Aspergillosis +
Blastomycosis +
Candidiasis −
Oropharyngeal / Esophageal Candidiasis
Genital / vulvovaginal candidiasis
Invasive candidiasis
Candida auris Q&A
***Candida auris* Alert**
Coccidioidomycosis +
C. neoformans Infection +
C. gattii Infection +
Fungal Eye Infections +

CDC > Fungal Diseases > Types of Fungal Diseases > Candidiasis

Clinical Alert to U.S. Healthcare Facilities

Global Emergence of Invasive Infections Caused by the Multidrug-Resistant Yeast *Candida auris*

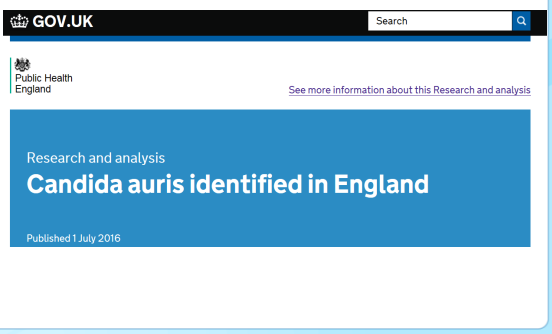
Summary: The Centers for Disease Control and Prevention (CDC) has received reports from international healthcare facilities that *Candida auris*, an emerging multidrug-resistant (MDR) yeast, is causing invasive healthcare-associated infections with high mortality. Some strains of *C. auris* have elevated minimum inhibitory concentrations (MICs) to the three major classes of antifungals, severely limiting treatment options. *C. auris* requires specialized methods for identification and could be misidentified as another yeast when relying on traditional biochemical methods. CDC is aware of one isolate of *C. auris* that was detected in the United States in 2013 as part of ongoing surveillance. Experience outside the United States suggests that *C. auris* has high potential to cause outbreaks in healthcare facilities. Given the occurrence of *C. auris* in nine countries on four continents since 2009, CDC is alerting U.S. healthcare facilities to be on the lookout for *C. auris* in patients.

Background

Candida auris is an emerging multidrug-resistant (MDR) yeast that can cause invasive infections and is associated with high mortality. It was first described in 2009 after being isolated from external ear discharge of a patient in Japan [1]. Since the 2009 report, *C. auris* infections, specifically fungemia, have been reported from South Korea [2], India [3], South Africa [4], and Kuwait [5]. Although published reports are not available, *C. auris* has also been identified in Colombia, Venezuela, Pakistan, and the United Kingdom.

It is unknown why *C. auris* has recently emerged in so many different locations. Molecular typing of strains performed by CDC suggests isolates are highly

Public Health England released an alert on the same day



Candida auris recommendations: Health Alert June 24, 2016

- **Reporting**: healthcare facilities with known or suspected *C. auris* should notify public health (candidaauris@cdc.gov)
- **Laboratory:** difficult to differentiate except by MALDI-TOF. *C. haemulonii* and other Candida species isolates can be sent to CDC for further identification
- **Infection control:** until further info available, CDC recommends Contact and Standard Precautions and single rooms
- **Environment**: Aggressive attention to daily and terminal room cleaning using a hospital grade disinfectant with a fungal claim

Link to Health Alert: http://www.cdc.gov/fungal/diseases/candidiasis/candida-auris-alert.html

Ceftazidime/avibactam

Ceftazidime/avibactam

- Antibiotic approved in 2015
- Broad activity against Gram-negative bacteria including those producing ESBLs, AmpC β-lactamases, and even class A carbapenemases (e.g. , KPC)
- Resistance among KPC had not been identified
- Shortage of avibactam
  - Antibiotic might not be available again until early 2017

Ceftazidime/avibactam

- Review demonstrated resistance in only 11/>20,000 US Enterobacteriaceae tested in one large study
  - Some of these had MBLs
- Resistance reported among 2 KPC-producing CRE
  - California
  - Maryland
- Mechanism of resistance not clearly understood

Ceftazidime/avibactam

- Report of use in 37 patients with CRE (primarily KPC, no MBLs)
  - Clinical success rate 57%
  - 3/37 (8%) developed resistance during use
  - Microbial failure 10/37 (27%)
    - 3/10 (30%) developed resistance
- Bottom line:
  - Success rates similar to other regimens
  - Possibly better tolerated
  - Resistance might be quick to develop
    - Consider screening sites (e.g., urine) for resistant CRE before use

CRE updates

Community-associated CP-CRE

- In EIP surveillance, about 8% of CRE patients did not have identifiable CRE risk factors
- In other countries more appears to be community-associated
- 2012 – hospital cased outbreak of NDM-producing CRE
  - Since 2012, 10 additional NDM-producing CRE noted
  - 6/10 community-associated
    - 2 with travel (no healthcare)
  - WGS of 7/10 isolates demonstrated that only 2 were related

Non-KPC carbapenemases

- NDM – remains most common
  - 188 isolates reported to CDC
  - IL by far has most - related to duodenoscope outbreak
- OXA-48 – increasingly common
  - 2010 – August 2015
    - 52 isolates from 43 patients in 19 states
    - Weak carbapenemase - may be susceptible to third-generation cephalosporins
    - 66% with international travel (india)
    - 55% with overnight healthcare stay outside US
    - Several clusters including UCLA ERCP cluster

Non-KPC carbapenemases

- VIM – 17 isolates as of April 2016
  - Cluster in KY/IN (n=10)
    - Plasmid mediated outbreak
- IMP – 10 isolates as of April 2016
  - Most reported from California
  - pcr is poor for IMP – most only detect IMP-1
- When detected most non-KPC should be considered novel and should result in a response to identify and halt transmission
  - Mechanism testing to become more common
  - Test isolates in patients with risk factors
    - Aztreonam susceptible CRE
    - Healthcare outside US (still rare with just travel)

Response to novel resistance

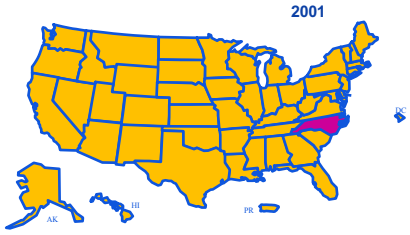
Antimicrobial Agents and Chemotherapy, Apr. 2001, p. 1151–1161 Vol. 45, No. 4
0066-4804/01/$04.00+0 DOI: 10.1128/AAC.45.4.1151–1161.2001

Novel Carbapenem-Hydrolyzing β-Lactamase, KPC-1, from a Carbapenem-Resistant Strain of *Klebsiella pneumoniae*

HESNA YIGIT,[1] ANNE MARIE QUEENAN,[2] GREGORY J. ANDERSON,[1]
ANTONIO DOMENECH-SANCHEZ,[3] JAMES W. BIDDLE,[1] CHRISTINE D. STEWARD,[1]
SEBASTIAN ALBERTI,[4] KAREN BUSH,[2] AND FRED C. TENOVER[1]*

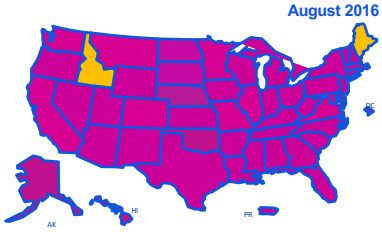
KPC-producing CRE in the United States

2001



KPC-producing CRE in the United States

August 2016



Vancomycin-resistant S. aureus (VRSA)

- First US isolate 2002
- Resistance is plasmid-mediated (*vanA*)
- Resistance was to critical antibiotic in a bacterial species that is important cause of healthcare and community infections
- 14 to date in the US
  - All have resulted in extensive public health investigations
    - Hundreds of patients, household contacts and HCP screened

http://www.cdc.gov/hai/pdfs/VRSA-Investigation-Guide-05_12_2015.pdf

Investigation and Control of
Vancomycin- Resistant
Staphylococcus aureus (VRSA):
2015 Update

Division of Healthcare Quality Promotion
Centers for Disease Control and Prevention
Updated: April 2015

Response to Emerging Resistance

- As of this year all state and some local health departments will be funded to respond to emerging AR threats in their jurisdictions
  - Technical assistance
  - Contact investigations
  - Laboratory support
- More aggressive approach designed to identify outbreaks more rapidly to prevent emergence of novel resistance
- What constitutes novel resistance might vary from region to region

Components of the investigations

- Epi investigation to identify contacts
- Reviewing clinical cultures (Lab look backs)
- Screening cultures (broader initially):
  - Index patient
  - HCP
  - Healthcare contacts
  - Household contacts
  - Community contacts
- Environmental cultures
- Prospective surveillance

AR Lab Network: Detecting Threats with Gold-Standard Lab Capacity

- **Capacity Building** in regional and state labs
- **Pathogen-Specific Solutions** for threats like CRE, *Salmonella*, and GC
- **Public Health Assessments** for threats like *C. difficile* & AR threats
- **Communication/IT Networks & Education** through partners

Regional Labs

&

State or Local CRE labs

Map placement of labs illustrative only. Regional lab awardees anticipated August 2016.

What can facilities and HCP do to help prevent spread of novel resistance?

- Be aware of emerging MDROs, be on look out for these organisms
- Institute recommended IC precautions when suspect organisms identified
- Notify public health
  - Work with public health to implement recommended interventions
- Save isolates
- Implement prospective and retrospective surveillance to identify isolates with similar phenotype (e.g., lab look backs)
- If patient transferred from a facility – notify transferring facility
- If patient being transferred -- notify accepting facility
- Implement a method to identify known colonized/infected patients at readmission

More information available:
http://www.cdc.gov/hai/pdfs/toolkits/Responding-to-New-Forms-of-Antibiotic-Resistance.pdf

Thanks for your attention. Questions?

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