Candida auris: A globally emerging multidrug-resistant yeast

Mycotic Diseases Branch
DFWED Friday Seminar
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First report of C. auris from Japan in 2009

Candida auris sp. nov., a novel ascomycetous yeast isolated from the external ear canal of an inpatient in a Japanese hospital

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South Korea 2009 and 2011

- 2009 report on 15 ear infection in patients at 5 hospitals
  • Isolates from 2004–2006
- 2011 report of 3 C. auris bloodstream infections in 1 hospital
  • Isolates from 1996 and 2009
  • First report of invasive C. auris infection

Kim N et al, CID 2009; Lee W et al, JCM 2011

India 2011

- 2011 report of 12 bloodstream infections from 2 Delhi hospitals
  • Isolates collected 2009–2011
- 2015 report candidemia in 19 Indian ICUs
  • Isolates collected 2011–2012

Chowdhary A et al, EID 2013

C. auris basics

- Can cause invasive infections, predominantly fungemia
- Is often multidrug resistant (MDR)
- Cannot distinguish C. auris from other Candida species with biochemical tests and most conventional diagnostics

C. auris basics
**Pakistan 2014–2015**

- 2014–2015 outbreak ~30 cases at a single hospital
- Initially identified as *Saccharomyces cerevisiae*
- Pakistan requested CDC assistance with outbreak in 2015
- Launched CDC’s international *C. auris* work

**Global emergence during 2009–2015**

**International *C. auris* response**

- Formed an international *C. auris* collaboration
  - Pakistan
  - India
  - South Africa
  - Venezuela
  - Colombia
- Collect epidemiologic data
- Sequence *C. auris* isolates
- Assess resistance

**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
- May occur in conjunction with other *Candida* spp
- Patients on antifungal treatment when *C. auris* isolated
- Median time from admission to infections: 17 days
- Mortality ~60%:
  - 100% in Venezuela in NICU infants
Whole genome sequencing (WGS)

- 47 isolates from 5 countries
- 47 HiSeq + 2 PacBio + 2 genomes from NCBI
- PacBio reference: 20 contigs, N50: 1 Mbp
- Average sequencing depth with Illumina: 235X (50-300X)
- 96-99% genome coverage
- Assembled genome: 12.5 Mbp

WGS relationships among 47 isolates from 4 countries

- WGS relationships among Indian/Pakistani strains
  - ≤5 SNPs
  - <2 SNPs

WGS results

- Profound phylogeographic structure
- Huge genetic differences among geographic clades
- Possible cryptic species
- Very high clonality within the geographic clades
- Recent independent emergence in different places
### Antifungal susceptibility

- 54 patient isolates from Pakistan, India, SA, Venezuela

<table>
<thead>
<tr>
<th>Antifungal</th>
<th>MIC value in µg/mL</th>
</tr>
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<tbody>
<tr>
<td>Fluconazole</td>
<td>0.03 0.06 0.12 0.25 0.5 1 2 4 8 16 32 64 128 256</td>
</tr>
<tr>
<td>Voriconazole</td>
<td>1 1 1 1 1 1 2 7 4 13 28</td>
</tr>
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<td>3 4 9 28 10</td>
</tr>
<tr>
<td>Caspofungin</td>
<td>4 1 5 19 17 6 2</td>
</tr>
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<td>1 9 22 19 1 1 1</td>
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<td>Posaconazole</td>
<td>28 5 28 9 6 4 2</td>
</tr>
<tr>
<td>Echinocandins</td>
<td>17 18 15 4</td>
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<td>Fluconazole B</td>
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**Key:**
- 93% resistant to fluconazole
- 54% resistant to voriconazole
- 35% resistant to amphotericin B
- 7% resistant to echinocandins
- 41% MDR isolates
- 4% resistant to all three major antifungal classes
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
  - Cohorting colonized patients
  - Environmental decontamination
  - Ward closure
- Transmission from environmental sources
  - Preliminary data suggests healthcare workers not major carriers
  - Hospital rooms remain positive despite cleaning

Why are we concerned about C. auris?

- Is multi-drug resistant
  - Some isolates resistant to all three major antifungal classes
- Can be misidentified
  - Usually misidentified as other Candida spp or Saccharomyces, when using biochemical methods (API strips or VITEK-2)
  - 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
  - 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

CDC issued a clinical alert to healthcare facilities – June 2016
Public Health England released an alert on the same day

Public Health Agency of Canada also released an alert in July 2016

PHAC Communication Re: Emerging global HAI-AMR issue – *Candida auris*

PHAC has recently learned of a public health alert from US CDC in relation to the global emergence of invasive infections caused by the Multidrug-Resistant yeast organism, *Candida auris*.

*C. auris* in the United States (n=7)

- 5 bloodstream infections, 1 urine, 1 external ear
- Ages: 44-89 years
- Underlying medical conditions:
  - Leukemia
  - Bone marrow transplant
  - Short gut requiring total parenteral nutrition
  - High-dose steroids
- Outcomes:
  - 3 died
  - 3 alive
  - 1 unknown

Antifungal susceptibility in the U.S.

- Six of seven isolates resistant to fluconazole
- One of seven isolates resistant to amphotericin B
  - Pt from the United Arab Emirates
- No known echinocandin resistance
Is there evidence of transmission in the U.S.?

- Some cases are epi-linked
  - two patients also shared the same long-term acute care hospital
- 1 patient with *C. auris* BSI 3 months earlier was colonized with *C. auris* in groin, axilla, nares, rectum
- Room of patient with *C. auris* colonization + for *C. auris* on mattress and window sill

KPC-producing CRE in the United States

- 2001
- August 2016
**Limitations and Challenges**

- "Buy in" from facilities and health departments
  - Earlier intervention is better than later?
- Resources for investigation
  - State AR funding
  - Regional labs
- Does it work?
  - Slow spread vs. eliminate
  - Future interventions
    - Manipulating the microbiome/decolonization

**mcr-1**

- 4 U.S. human cases identified
  - 2 retrospective (2014 and early 2015)
  - 2 "current"
- PA – extensive long-term healthcare contact
  - Screening cultures collected from patient, household contacts, HCP, PPS
  - All negative but patient, she was negative at 3 months
- CT – child, no inpatient healthcare exposure, recent travel
  - Screening culture of environment and household contacts

**Response plan for C. auris cases in the U.S.**

- Requested health facilities and labs to report of all C. auris cases CDC and state and local health departments
- Case finding efforts (clinical alert, EIP surveillance, ARLN)
- Immediate investigation of all past and current cases
  - Microbiology record review for other cases and possible cases
  - Identify epi links between cases
  - Assess colonization of case-patient
  - Environmental swabs
  - Point prevalence surveys of colonization in shared rooms/wards
  - Swabs of household contacts
Infection Control Recommendations

- Standard and Contact Precautions
- Daily and terminal cleans to reduce environmental burden of organisms with EPA registered disinfectant
- Regional notification to other facilities the patient may be admitted
- Working with EPA and FDA to understand what works for disinfection

International Collaborations: Colombia

- C. auris in Colombia
  - 5 cities with reported cases
  - 5-24 cases at each site
  - Team in Colombia now
  - Case-case Colombia now
  - Environmental investigation
  - Point prevalence survey of colonization

WGS of Colombian strains

Venezuela + Colombia

Japan + Korea

India + Pakistan

Antifungal susceptibilities

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(Colombia, Korea, US)

30 isolates
India Collaboration

- India
  - 5-8% of all candidemia in Indian ICUs due to C. auris
  - Some centers reporting 40% of candidemia now caused by C. auris
  - Team in India now to start work on C. auris

Why are we seeing so much resistance?

- Not typical fluconazole resistance
  - May not have intrinsic resistance to fluconazole
- Ability to develop resistance may be high
  - Not plasmids, mechanisms unknown?
- Seems to have the ability to adapt quickly
- Emerging on several continents all at the same time
  - Different genes confer resistance
  - What role does antifungal use

Globally emerging multi-drug resistant organism but this time it’s a FUNGUS

- Well-established in some parts of the world
  - Working to understand the full extent of its prevalence and the true burden if disease
  - New modes of transmission are more clear but still many questions
  - Control measures need to be identified and tested
  - Continue to monitor situation in the UK

- Emergence in the US is very recent, but concerning
  - To date only isolated cases, none are triple MDR
  - State and local partners beginning to work with hospitals to monitor emergence, understand transmission and identify and implement control measures