Worldwide epidemiology and the burden of *Candida auris*

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Disclosures

* Research grants–advisory boards–speaker

* last 3 years
• Epidemiology (global, USA) and risk factors
• Few words regarding colonization
• Few words regarding pathogenesis, in vitro resistance and treatment challenges
• I am not going to talk about infection control!
DEADLY GERMS, LOST CURES

A Mysterious Infection, Spanning the Globe in a Climate of Secrecy

The rise of Candida auris embodies a serious and growing public health threat: drug-resistant germs.

April 6, 2019
Candida Auris

A deadly, drug-resistant fungus is infecting patients in hospitals and nursing homes around the world. The fungus seems to have emerged in several locations at once, not from a single source.

**COUNTRIES WITH**
- Multiple cases of Candida auris infection
- One reported case

**EUROPE**
The first large outbreak in Europe involved 72 cases in a London hospital in 2015–16.

**CENTRAL AND SOUTH AMERICA**
The first documented outbreak in the Americas was from 2012–13 at a medical center in Venezuela. Five of 18 infected patients died.

**SOUTH AMERICA**
A genetically distinct strain of Candida auris in South Africa infected at least 451 patients from 2012–18.

**JAPAN**
Candida auris (left) was discovered in 2009 in the infected ear of a 70-year-old Japanese woman.

**INDIA AND PAKISTAN**
The two countries have some of the highest case counts in the world. A distinct strain appeared in Pakistan as early as 2008 and in Delhi by 2009.

**EUROPE**
The first large outbreak in Europe involved 72 cases in a London hospital in 2015–16.

**SOUTH AFRICA**
A genetically distinct strain of Candida auris in South Africa infected at least 451 patients from 2012–18.

**JAPAN**
Candida auris (left) was discovered in 2009 in the infected ear of a 70-year-old Japanese woman.


Sources: Centers for Disease Control and Prevention; Emerging Infectious Diseases; Emerging Microbes & Infections; Clinical Infectious Diseases; Journal of Infection; Mycoses; Doherty Institute. Image from Kazuo Satoh et al., Microbiology and Immunology.
Simultaneous emergence in disparate geographic regions

- First described from an ear canal of a patient in Japan in 2009 (Satoh et al. Microbiol Immunol 2009)
- 4 glades (WGS data, evolutionary distance of thousands of years): S Asia, S Africa, S America, E Asia
- Rose independently and simultaneously!
- No know animal or environmental reservoir!
- Unique attributes of *C. auris* (frequent MDR resistance, geographic presences, ability to grow in high salinity and high temperatures) are clues
- Reasons are unknown? Pesticide use (theory)

Lockhart et al. CID 2017, Fosberg K et al. Med Mycol 2019
Examples of the global impact of *C. auris* pandemic: the last 5 years

- Hit a neonatal unit in Venezuela
- Swept through a hospital in Valencia Spain (372 pts colonized, 85 pts with invasive infections)
- Forced the closure of ICU in a British medical center
- Taken root in India, Pakistan, South Africa, South America
- Since 2013 (first case in May 6, 2013) there were 587 cases in US, 309 in NY, 104 in NJ, 144 in IL—CDC alert (canndidaauris@cdc.gov)
Candida auris by State

Most cases in the United States have been in nursing homes in New York City, Chicago and New Jersey.

Source: Centers for Disease Control and Prevention
C. auris clinical cases reported by state — United States, 2013–August 2018

~425 clinical cases
~1180 clinical + screening cases
Epidemiologic Characteristics of U.S. Cases

- Median age: 70; ~30% 30-day mortality
- Multiple underlying conditions, indwelling devices
  - Tracheostomy, central line, gastrostomy tube
- Extensive healthcare exposure
  - Acute care hospitals, LTACHs, SNFs
- Patient have multiple other MDROs
  - CP-CRE is the most common co-colonizer

Initial culture site of *C. auris*

Antifungal resistance of *C. auris*
Healthcare abroad is risk factor for *C. auris*

- US *C. auris* cases are a result of initial introductions from abroad followed by local transmission
Isolates from U.S cases cluster to all four *C. auris* clades

African clade

South Asian clade

East Asian clade

South American clade

>300 clinical cases

> 700 additional patients colonized

Chow NA et al, Lancet ID 2018
CT, CA, and OK travel-related cases – South Asian clade

WGS has emerged as a powerful epidemiological tool for travel-related cases

Chow NA et al, Lancet ID 2018
Potential for missed identification and misidentification of *Candida auris*

- Difficult to distinguish from other *Candida* species
- *C. auris* closest phylogenetic relationship is with *C. haemulonii*

<table>
<thead>
<tr>
<th>Organism</th>
<th>Microscopic</th>
<th>Sabouraud dextrose agar</th>
<th>CHROMagar Candida</th>
<th>Growth temperature</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Candida auris</em> (N=90)</td>
<td>Elongated budding yeast occurring singly or in pairs</td>
<td>Smooth, white to cream colored colonies</td>
<td>Pink</td>
<td>Yes</td>
</tr>
<tr>
<td><em>C. haemulonii</em> (N=7)</td>
<td>Pseudohyphae with blastocondia</td>
<td>Smooth, white to cream colored colonies</td>
<td>Pink</td>
<td>Yes</td>
</tr>
<tr>
<td><em>C. duobushaemulonii</em> (N=5)</td>
<td>Pseudohyphae with blastocondia</td>
<td>Smooth, white to cream colored colonies</td>
<td>Pink</td>
<td>Yes</td>
</tr>
</tbody>
</table>

*C. auris* were positive for assimilation of N-acetylglucosamine, succinate, and gluconate

Kathuria et al. JCM 2015
Current Laboratory Identification of *Candida auris*: A work in progress

<table>
<thead>
<tr>
<th>Identification Method</th>
<th>Database /Software</th>
<th>C. auris, if initial identification C. auris</th>
<th>Possible C. auris Needs further workup</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bruker Biolyzer MALDI-TOF</td>
<td>RUO library</td>
<td>C. auris</td>
<td>n/a</td>
</tr>
<tr>
<td></td>
<td>FDA library</td>
<td>C. auris</td>
<td>n/a</td>
</tr>
<tr>
<td>bioMerieux VITEK MS MALDI-TOF</td>
<td>RUO library</td>
<td>C. auris</td>
<td>C. haemulonii, No identification</td>
</tr>
<tr>
<td></td>
<td>IVD library</td>
<td>n/a</td>
<td>C. haemulonii, No identification</td>
</tr>
<tr>
<td>VITEK 2 YST</td>
<td>C. auris Version 8.01</td>
<td>C. haemulonii, C. duobushaemulonii Candida spp. not identified</td>
<td></td>
</tr>
<tr>
<td>API 20</td>
<td>n/a</td>
<td>Rhodotorula glutinis (red pigment not present), C. sake Candida spp. not identified</td>
<td></td>
</tr>
<tr>
<td>BD Phoenix</td>
<td>n/a</td>
<td>C. catenulata, C. haemulonii Candida spp. not identified</td>
<td></td>
</tr>
<tr>
<td>Microscan</td>
<td>n/a</td>
<td>C. lusitaniae, C. guilliermondii, C. parapsilosis, C. famata Candida spp. not identified</td>
<td></td>
</tr>
<tr>
<td>RapID Yeast Plus</td>
<td>n/a</td>
<td>C. parapsilosis Candida spp. not identified</td>
<td></td>
</tr>
</tbody>
</table>
C. auris cases are nationally notifiable in 2019
When to speciate looking for *C auris* in non-sterile sites? (CDC recommendations)

- As clinically indicated
- A case of *C auris* colonization has been detected in the unit or facility
- A patient had an overnite stay in a healthcare facility outside US in the previous year in a country with documented *C auris* transmission

Fosberg K et al. Med Mycol 2019
C. *aurantis* colonization
C. auris colonization

- Patients remain persistently colonized
  - NYS has followed a few hundred patients
    - 60% 90-day mortality
    - Some colonized for over a year
    - Only ~16 have “cleared” colonization

- Colonization means patients are:
  - At risk for developing invasive infection
    - 30 cases of BSI in ~600 colonized patients who are being followed 2016-2018
  - Source of transmission to others
**Screen for C. auris colonization**

- Most sensitive (>90%) and cost-effective swab: axilla and groin
  - Nares, rectal, and oral swabs have also been positive, but not as consistently as axilla/groin swabs
- Enrichment broth method
  - High salt/temperature
  - ~25% more sensitive than direct plating
  - Must hold plates for 10 days

- Reusable skin surface axillary temperature probes as a source in UCIU transmission (UK) (Eyre DW. NEJM 2018)
Decolonization/source control

- Chlorhexidine?
- Antifungals? –terbinafine?
- Remove pressure of antibiotics and antifungals?
In vitro data on chlorhexidine looks promising

**Chlorhexidine activity**

- *C. auris* was effectively inhibited by chlorhexidine (Hibiscrub, Ecolab, UK) *in vitro* at concentrations below 2 and 4% for skin decolonization.
- Iodinated povidone (Videne, UK) demonstrated an even greater activity much below the average 10% concentration used as antiseptic.

**BUT**

In vivo studies on reduction in burden of colonization have not been done. Facilities where *C. auris* outbreaks have occurred have not seen improvements in incidence of colonization even when using CHG bathing.
Specific questions regarding pathogenesis and management of candidiasis due to \textit{C. auris}

- Like other uncommon (391 US cases as per Aug 18, CDC) \textit{Candida} species, there are no breakpoints for non-susceptibility and sparse clinical data in a background noise of very sick patients (Lamoth F & Kontoyiannis DP. JID 2017)

- Unclear if there is correlation of virulence/resistance with “aggregate” type of \textit{C. auris} isolates (Borman AM et al. Bioshere 2016)

- Unclear if there is correlation of virulence/resistance with geographic clades or specific clones of \textit{C. auris} isolates

- Unclear if there is correlation of virulence/resistance biofilm-forming capacity \textit{C. auris} isolates (Sherry L et al. EID. 2017)

- Various PCR methods (e.g., Kordalewka M et al. JCM 2017), T2 Magnetic Resonance assay (Sexton DJ et al, Mycoses) not been adequately validated in patients
Rapid diagnostics

Development and Validation of a Real-Time PCR Assay for Rapid Detection of Candida auris from Surveillance Samples

Evaluation of a new T2 Magnetic Resonance assay for rapid detection of emergent fungal pathogen Candida auris on clinical skin swab samples

Real-time PCR
Treatment for *C. auris*

- Optimal drug treatment has not yet been defined

- For most clinical isolates, MICs of echinocandins are in the susceptible range (especially the UK isolates - Ruiz-Guitan A et al. Mycoses 2018)

- Indian isolates are typicallyazole resistant, and 40% non-susceptible (MIC>1) to echinocandins (Chowdhary A et al. Eur J Clin Microbiol Infect Diseas 2014)

- Echinocandins are currently recommended by the CDC (for US cases) as empiric treatment of *C. auris* infections, with step down therapy is based on in vitro susceptibility, however, there are limited or no clinical data to support this recommendation

Ben-Ami R. J Fungi 2018
Global *C. auris* antifungal resistance

<table>
<thead>
<tr>
<th>Antifungal</th>
<th>% Resistance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Echinocandins</td>
<td>0%</td>
</tr>
<tr>
<td>Amphotericin B</td>
<td>20%</td>
</tr>
<tr>
<td>Fluconazole</td>
<td>80%</td>
</tr>
</tbody>
</table>

*N=848*

Slide courtesy T Chiller, CDC
Resistance is clone-specific

- **Southeast Asia**
  - Nearly universally Flu$^R$, 40% AmpB$^R$

- **South America**
  - Colombian isolates 25% Flu$^R$ + AmpB$^R$
  - Venezuelan isolate are universally Flu$^R$
  - Overall 8% Echino$^R$ but higher in Venezuela

- **Africa**
  - Variable resistance, mostly Flu$^R$, some AmpB$^R$

- **East Asia**
  - Universally susceptible
MDR \textit{C. auris}

- Pan resistant
- 2 or more classes
- 1 or more class
- Pan susceptible

N=848

Slide courtesy T Chiller, CDC
Are echinocandins the answer for *C. auris*?

- *C. auris* is tolerant to echinocandins (Ben-Ami R et al. OFID 2017: 4, abst 145)

- Exposure to echinocandins was consistently found to be a risk factor for infection with *C. auris* and breakthrough infection on echinocandins has been noted (Rudramurthy SM et al. JAC 2017)

Ben-Ami R. J Fungi 2018
Experimental data regarding treatment of *C. auris*

In vitro and animal data support the use of liposomal AMB, alone or in combination with flucytosine, for patients with known or suspected *C. auris* infection (Ben-Ami R et al. Open Forum Infect. Dis. 2017)


APX001A (Arendrup MC et al. AAC 2018, Lepak AJ et al. AAC 2018), SCY-078 (Larkin E et al. AAC 2018), rezafungin (Hager CL et al. JAC 2018) have activity

POSA has activity (for both POSA-S and POSA-R *C auris*) in a Tl-deficient Drosophila *C auris* model (Wuster S… Kontoyiannis DP. JAC 2019)

Nitroglycerine-Citrate–Ethanol (NiCE) catheter lock solution is highly effective for prevention of *C auris* biofilm formation (Vargas–Cruz N, Kontoyiannis DP. Raad I. ID week 2018)
Posaconazole has activity in a Tl deficient fly model of *C. auris* infection

AR 0381: PCZ MIC: 0.06, FCZ MIC: 4
AR 0386: PCZ MIC: 0.5, FCZ MIC: > 256

Is it because PCZ is immune cell-associated (haemocytes)?

Bandi A...Kontoyiannis DP. ID Week 2018 abstract #73236
Need for individualized antifungal therapy for MDR *C. auris*

- Antifungal Resistance?
- Prior antifungal exposures
- PK/PD & drug dosing of monotherapy?
- ? Sanctuary sites involvement, abscesses, catheters
- Timing, intensity and type of immunosuppression or metabolic dysregulation
- Certainty of diagnosis
- Concomitant infections
## A lot of things to learn regarding *Candida auris*

<table>
<thead>
<tr>
<th>Hallmark</th>
<th>Threat</th>
<th>Control/Prevention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased prevalence, unknown origin</td>
<td>Continuous increase in the future leads to emergence of <em>C. auris</em> as a frequent cause of nosocomial infections</td>
<td>Investigate potential sources/reservoirs, conduct epidemiological surveys in large prospective cohorts</td>
</tr>
<tr>
<td>Simultaneous emergence on different continents</td>
<td>Worldwide dissemination leads to pandemics of <em>C. auris</em> infection</td>
<td>Investigate environmental sources/reservoirs</td>
</tr>
<tr>
<td>Misidentification by diagnostic laboratories</td>
<td>Lack or delayed recognition of clinical cases leads to occult outbreaks</td>
<td>Improve development and access to new diagnostic tools (MALDI-TOF mass spectrometry, molecular techniques), improve training of laboratory personnel</td>
</tr>
<tr>
<td>Biofilm formation, persistence/survival in the environment</td>
<td>Inter-human transmission leads to nosocomial outbreaks</td>
<td>Screen patients, create hospital hygiene plans (isolation/disinfection), improve decontamination of surfaces (sporicidal agents)</td>
</tr>
<tr>
<td>Antifungal resistance (intrinsic or rapidly inducible)</td>
<td>Emergence of multidrug- or pan-drug-resistant strains leads to outbreaks with high mortality rate</td>
<td>Limit antifungal drug overuse, develop of novel antifungal</td>
</tr>
</tbody>
</table>

Lamoth F & Kontoyiannis DP. JID 2018
Special thanks to Tom Chiller, MD, MPHTM
Chief, Mycotic Diseases Branch, CDC
and
Kristie Johnson, PhD, Univ of Maryland
21st ICHS Symposium on
Infections in the Immunocompromised Host

7–9 June, 2020
Melbourne, Australia

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