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PEARLS OF LABORATORY MEDICINE

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TITLE: *Candida auris*

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Hello, my name is Seunghyug Kwon. I am the medical microbiology fellow at the University of Chicago Medicine and Northshore University Health system. Welcome to this Pearl of Laboratory Medicine on *"Candida auris*."

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Candida is a genus of yeast. *Candida* is part of the normal human microbiota of the mouth, throat, gastrointestinal tract, and vagina. *Candida* usually does not cause infections in immunocompetent individuals. However, when someone becomes immunocompromised *Candida* infections can occur and is called Candidiasis. When the infection is in the mouth or throat it is called thrush or oropharyngeal candidiasis, in the vagina a yeast infection, and in the bloodstream and internal organs it is called invasive candidiasis, which includes overlapping syndromes of deep-seated candidiasis and candidemia.

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According to the CDC, the incidence is approximately 25,000 cases per year nationwide. Up to 95% of all invasive candidiasis are caused by these 5 species: *C. albicans, C. glabrata, C. parapsilosis, C. tropicalis*, and *C. krusei* with *C. albicans* leading the way.

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The CDC's surveillance data indicates that in-hospital all-cause (crude) mortality among people with invasive candidiasis is approximately 25 %. The caveat though is that these patients are typically already sick with other medical conditions thus the direct attribution of death due to the *Candida* infection and in turn the true mortality is unknown. However, in recent years there has been a new *Candida* species that has been emerging globally and that is *Candida auris*.

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C. auris was first reported in 2009 from the ear discharge of a patient in Japan and the first documented blood stream infection d in a South Korean patient in 2011 who had persistent fungaemia while on fluconazole and amphotericin B. As of March 2020, the organism has been isolated from several body sites in multiple countries on five continents. To give you some context on how alarming this spread has been, in Sub-Saharan Africa, between 2010-13, *C. auris* was the most common cause of hospital-onset fungemia, consisting of 38 % of all fungemia. In South America, between 2012-13, *C. auris* was the 6th most common cause of bloodstream infections. In India, a study covering 27 intensive care units in 2011-2012 reported *C. auris* as the fifth most common species isolated from patients with ICU-onset candidemia, and in London the prevalence of the organism is now about 0.04 % in cardiothoracic centers. The U.S. was also among the countries that *C. auris* has infiltrated.

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Starting in 2015, there has been a sudden increase in cases and has been steadily increasing overtime. For the most part, states with large metropolitan areas such as New York, New Jersey, Illinois, Florida, and California have seen the most cases, especially in long term care facilities. New cases, however, have also been popping up in other states as well. As of May 2020, the total number of confirmed reported CDC cases were 1,167 in 20 States.

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Clinical symptoms for invasive *C. auris* is not unique compared to other *Candida* species, from minimal fever to a full-blown sepsis syndrome. Types of infections reported in the literature include blood, central venous catheter tip, central nervous system, upper and lower respiratory tracts, urogenital system, abdominal, skin, wounds, soft tissue, and bone. Like other *Candida* species, critically ill patients are infected and thus the true mortality is also difficult to determine. Based on various studies, the mortality is certainly higher than other *Candida* species, ranging about 30 – 60 %.

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A unique characteristic of *C. auris* is its' ability to colonize and transmit to other patients unlike other *Candida* species. *Candida* have not historically been thought to spread in healthcare settings. There have been incidences of transmission due to contaminated equipment but not between patients. *C. auris* appears distinct among yeast in that it readily spreads in healthcare settings.

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C. auris, unlike other *Candida* species, has been able to colonize the skin of patients and healthcare workers, particularly the axilla and groin, and has shown to persist for many months. Transmission between patients has been thought to be via healthcare worker colonization. In the US, 12 % of close healthcare contacts of *C. auris* patients were colonized. Thus, it is now required that *C. auris* patients be contact isolated.

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Unsurprisingly, environmental spread has also been noted as well. People infected or colonized with *C. auris* shed the organism. In laboratory studies, *C. auris* has been shown to persist on various surfaces for at least 7 days including moist surfaces, dry linens, and dry steel disks. Sodium hypochlorite (bleach) and hydrogen peroxide have shown to have the greatest reduction, thus hospitals should have a standard decontamination procedure of patient rooms (including bed, chairs, windowsills, countertops), hallways outside patient rooms, and all medical equipment used for care of the patient.

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The organism has been shown to grow easily on Sabouraud dextrose agar plates, appearing as light-colored colonies as seen here, and on chromogenic agar candida medium, as pink to beige colored colonies. Microscopically, *C. auris* shows ovoid to elongated budding yeast which seldom forms rudimentary pseudohyphae. In essence, macroscopically or microscopically, *C. auris* does not show any distinct features to differentiate it from other *Candida* species. Thankfully, there are more sophisticated systems to identify fungi these days. Unfortunately, *C. auris* is still able to evade many of these systems.

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As noted in this table, many of the identification systems that have been used misidentified *C. auris*. Even the more recent systems, like Vitek MS and MALDI that utilize mass spectrometry, were misidentifying the organism when it first appeared. This has been since remedied for the mass spec systems with updated databases. For the laboratories that utilize the biochemical systems listed, the CDC has provided algorithms if *C. auris* is suspected and has since advised to confirm via molecular methods or use one of the mass spec systems.

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One of the major concerns of *C. auris* comes from its' antifungal resistance. In the CDC's report on 'antibiotic resistance threats in the US' published in 2019, more than 2.8 million cases of antibiotic resistance cases are reported resulting in more than 35,000 deaths every year nationwide. While many of us are familiar with bacterial antibiotic resistance and the many measures taken to combat them, far less is being done for fungi. That will have to change, as *C. auris* has been labelled one of the urgent threats in this report.

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The antifungals can be divided into three classes; the triazoles (which include fluconazole), polyenes (which included amphotericin B), and echinocandins (which include Caspofungin). Among the 54 isolates of *C. auris* from the various countries, over 90% have been fluconazole resistant, 35 % amphotericin B resistant and 7% echinocandin resistant. This is also reflected in the U.S. according to the CDC reported data, although this can differ depending on region (Chicago isolates tend to be less resistant compared to New York). Among the U.S. isolates, 41 % were resistant to at least two drug classes and two isolates were pan-resistant.

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The resistance mechanism of *C. auris* remains under investigation, however, there have been some clues to propose some possible ways. For the triazoles, twelve Erg11 mutations have been identified, three of these mutations have been directly linked to drug resistance, specifically to fluconazole, in *C. albicans*. Efflux pump activity has been speculated to further contribute to the triazole resistance, however, the extent of this contribution remains unknown. FKS mutations have also been identified and most likely contributes to the echinocandin resistance. As for amphotericin B resistance, though unconfirmed at this time, it is suspected that this is likely due to a reduction in ergosterol, the target for amphotericin, in the cellular membrane.

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So far there are no definitive antifungal minimum inhibitory concentration, or MIC, break points for *C. auris* to evaluate for resistance. The CDC has provided some tentative break points based on epidemiologic cut off values from other *Candida* species and model distribution of MICs of approximately 100 isolates from diverse geographic locations. These breakpoints are informational only and have not been approved by any regulatory agency or standardization committee.

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The current recommended first-line treatment has been echinocandins due to most isolates showing low resistance, however, it has been noted in two U.S. cases where *C. auris* evolved pan-resistance in response to treatment, thus monitoring of the MIC is recommended while treating or re-treating patients. As for other options, unfortunately all are still under development. Antifungal combinations, like micafungin and fluconazole, have shown promises in vitro but no clinical studies have been conducted. New drugs, like Ibrexafungerp(SCY-078), show great promise but are still in clinical trials.

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In summary, *C. auris* has become a fungus of interest due to its' sudden emergence globally, its' ability to colonize and transmit to others in healthcare settings, misidentification from many systems old and new, and potential to gain pan resistance to antifungals.

Slide 19: References

Slide 20: Disclosures

Slide 21: Thank You from www.TraineeCouncil.org

Thank you for joining me on this Pearl of Laboratory Medicine on "*Candida auris*."