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Candida auris: What We Need to Know in Healthcare Settings

Cima Nowbakht, DO[*]
Luis Ostrosky-Zeichner, MD

Address
[*]University of Texas, 6431 Fannin Street, MSB 2.112, Houston, TX, 77030, USA
Email: cima.nowbakht@uth.tmc.edu

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Abstract

Purpose of review Candida auris is an emerging pathogen characterized for its difficult identification, rapid nosocomial spread, and limited treatment options. Data is currently limited; however, this will change as the pathogen's prevalence increases. The goal of this review is to provide a concise summary of the available data to manage a possible *C. auris* infection.
Recent findings Candida auris has been rapidly spreading globally and has been evading popular identification methods with MALDI-TOF being the only successful modality as long as the "research use only" database is used. Echinocandins are the treatment of choice; however, all isolates should have susceptibilities performed as there have been reports of resistance to all antifungal classes. Several hospital outbreaks have occurred; thus, all patients should be isolated with appropriate terminal cleaning.
Summary Atypical or suspicious *Candida* isolates should be identified by MALDI-TOF. Most *Candida auris* strains are resistant to azoles; therefore, the suggested empirical treatment is an echinocandin. Echinocandin-resistant strains have been reported, and in those cases, a polyene is preferred. Strict contact precautions are recommended while in the hospital due to high levels of nosocomial transmission.

Introduction

With a growing immunosuppressed population and more widespread use of broad spectrum antimycotics as prophylaxis, non-albicans Candida species have increasing prevalence as invasive pathogens [1]. As they become ubiquitous, especially in hospital environments, a shift towards multi-drug resistance creates treatment challenges.

Candida auris is a rapidly emerging pathogen causing invasive, mostly nosocomial, infections since first being described and isolated from the external ear

discharge of an elderly Japanese patient in 2009 [2]. Shortly afterwards, 15 isolates were published from patients between 2004 and 2006 with chronic otitis media in South Korea from five university hospitals though its clinical implication was still in question (no histopathological diagnosis of invasive infection) [3, 4]. This question was answered when three cases of *C. auris* nosocomial fungemia were reported in South Korea [4]. Interestingly, one of the cases was found from a 1996 unidentified yeast blood isolate [4]. Since then, cases have been published from Brazil, Colombia, India, Israel, Kenya, Kuwait, Pakistan, South Africa, Venezuela, the United Kingdom, and the USA [5–8].

Identification

Outside of its quick spread geographically, one of the major challenges with *C. auris* is identification. Using current modern diagnostic method upwards of 90% of isolates are misidentified [9•, 10, 11]. A significant shortfall is the lack of species identification of many isolated *Candida* species in microbiology labs world-wide [11]. Without distinguishing the species, infection prevention measures and appropriate treatment regimens are delayed, possibly leading to high chances of adverse events or outbreaks.

Far from foolproof, the appearance and color of *C. auris* colonies on culture plates has been suggested to aid in discerning it from other species and possibly alerting technicians [12]. *C. auris* is a budding yeast, rarely forms pseudohyphae, and does not form germ tubes [12]. On typical agars, it will form white to cream-colored colonies while on chromogenic agars, they can appear pink, white, or red [13]. Morphology and growth patterns are grossly unreliable, as are popular commercial biochemical identification platforms. Matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS) systems are currently the standard for identification [10, 14, 15].

It is recommended that yeast identified as any of the aforementioned in Table 1 should be further investigated via state public health entities or reference laboratories.

Treatment and infection prevention strategies

Pharmacologic treatment

Currently, there are no clinical breakpoints available for antifungals against *C. auris* [16]. However, Table 2 shows the suggested breakpoints from the Centers for Disease Control and Prevention to make therapeutic decisions.

Triazoles

Triazoles inhibit the C-14α demethylation of lanosterol by binding to one of the cytochrome P-450 enzymes ultimately reducing the concentration of ergosterol which is needed for a functioning cytoplasmic membrane. Several drugs are available, including fluconazole, itraconazole, voriconazole, and isavuconazole.

In general, this class has several advantages. They are available in intravenous and oral formulations, have great tissue penetration, and are generally, well tolerated. More common adverse events include gastrointestinal upset such as nausea and vomiting and hepatotoxicity. Because this class impedes P-450

Table 1. Misidentification of *C. auris* by commonly used instruments

Diagnostic technique	Database (if applicable)	Able to identify *C. auris*	Misidentification
Microscan		No	*C. lusitaniae* *C. guilliermondii* *C. parapsilosi* *C. famata* *C. albicans* *C. tropicalis* *Candida* spp. not identified
Vitek 2 YST		No	*C. haemulonii* *C. duobushaemulonii* *C. lusitaniae* *C. fatama* Candida spp. not identified
API 20C		No	*Rhodotorula glutinis* *C. sake* *Candida* spp. not identified
BD phoenix		No	*C. catenulata* *C. haemulonii* *Candida* spp. not identified
Bruker Biotyper MALDI-TOF	RUO (research use only)	Yes	Some isolates may not be identified
	FDA	No	
bioMerieux VITEK MS MALDI-TOF	RUO	Yes	
	FDA	No	
API Candida		No	*C. famata*

Table 2. Suggested MIC breakpoints

Antifungal class	Suggested CDC MIC breakpoints
Triazoles	
Fluconazole	≥ 32
Second generation-azoles	N/A; decision to use other triazoles should be made on a case-by-case basis as isolates resistant to fluconazole may still respond to other triazoles
Polyenes	
Amphotericin B	≥ 2
Echinocandins	
Anidulafungin	≥ 4
Caspofungin	≥ 2
Micafungin	≥ 4

Recommendations for identification of Candida auris. Adapted from Center for Disease Control and Prevention. Retrieved from https://www.cdc.gov/fungal/diseases/candidiasis/recommendations.html. Copyright 2017 by CDC

enzyme functioning, drug-drug interactions are common. Voriconazole also has propensity to cause hallucinations as well.

Widely used as a first-line, empiric antifungal, multiple studies have shown consistent, almost universal (89% of isolates) resistance to fluconazole (MIC of 16 to > 64 μg/ml) from C. auris [10]. There is report of a fluconazole sensitive treatment failure of one patient in the USA [12]. Itraconazole, however, had favorable susceptibility (MIC 90 0.5 μg/ml) to all tested isolates 1 [10]. Voriconazole did have a higher MIC 90 at 8 μg/ml with 58% of isolates having an MIC of ≥ 1 μg/ml [10]. Fortunately, posaconazole and isavuconazole hade favorable MIC 90 s at 2 μg/ml and, of note, only one isolate had MIC ≥ 1 μg/ml [10, 16].

In summary, of the triazoles, fluconazole should not be considered for treatment. The other-azoles can be considered as options for therapy; however, susceptibilities must be done with close, clinical monitoring to assess patient improvement. They are generally well tolerated and drug-drug interactions may limit their use in this ill population.

Echinocandins

The echinocandins are a class of antifungal agents that inhibit the synthesis of 1,3-β-d-glucan leading to decreased wall integrity and abnormal cell morphology causing cell rupture and death. In general, it is favored as empiric therapy or invasive candidiasis prior to sensitivity availability.

Only available intravenously, the three available drugs, caspofungin, micafungin, and anidulafungin, are generally well tolerated with low adverse event rates and have similar spectra. A significant limitation is the poor penetration into eye tissue, cerebral spinal fluid, prostate, and little drug in urine.

A pharmacokinetic/pharmacodynamic study of C. auris candidemia in a neutropenic mice model did favor echinocandins, specifically micafungin, over fluconazole and amphotericin B; however, only nine isolates were studied with all MICs < 4 μg/ml [17, 18]. In another study where 90 isolates were tested for echinocandin susceptibility, micafungin did have the lowest MICs followed by anidulafungin and then caspofungin [10]. Alarmingly, in seven isolates, all echinocandins had no activity with MICs > 4 μg/ml [10]. There was investigation into whether the isolates contained C. glabrata echinocandin-resistance FKS genes which were not found [10].

Echinocandins should be considered as empiric therapy in patients suspected of or have confirmed C. auris invasive infections with pending susceptibilities.

Others

Flucytosine, or 5-fluorocytosine, is a fluorine analogue of cytosine and causes aberrant transcription. It is generally used in combination with other antimycotics due to induced resistance when used as monotherapy. In susceptibility testing, 88% had reduced MICs where the other isolates had highly elevated MICs ≥ 32 μg/ml [10]. Only available in oral formulation, doses must be adjusted to renal function. It is generally tolerated well with infrequent adverse events notably rash, diarrhea, and hepatic dysfunction.

Amphotericin B is a polyene antifungal that inserts into the cytoplasmic membrane causing increased membrane permeability leading to increased potassium ion activity (low drug concentrations) or membrane pore formation impairing viability. It is available in intravenous and inhaled forms. Though a majority would be considered susceptible, there are isolates with high MICs of ≥ 2 μg/ml in a similar theme to the other antimycotics listed before [10, 16, 19].

Infection prevention and control

Unlike other species of *Candida*, *C. auris* has a penchant for causing prolonged hospital outbreaks. The first published interhospital, clonal outbreak occurred in India in two hospitals between 2009 and 2011 with 12 cases of fungemia that included adult, pediatric, and neonates across wards and ICU settings [20]. Though not detailed, there were no shared healthcare workers [20]. The propensity for persistence in the hospital environment was demonstrated in another outbreak at a cardio-thoracic specialty surgical center in London over a 16-month period [21].

Isolation

All patients with confirmed infection or colonization should be placed in single rooms or if space is limited, at the very least in a cohort. They should be on strict standard and contact precautions. *C. auris* is highly transmissible in the healthcare environment quickly contaminating the floor and surrounding equipment and was even picked up in an air sample [21]. Persistence in colonized patients has been attributed to low level environmental contamination that can even lead to recolonization after documented clearance [21].

If manageable, staff should be limited, and proper hand hygiene must be strongly enforced. In an outbreak, one healthcare worker developed nasal colonization likely due to inadequate hand cleansing due to an alcohol gel skin allergy [21]. We recommend standard hand hygiene practice with an alcohol-based sanitizer and washing with soap and water if the hands are visibly soiled [22–24, 25••].

Environmental disinfection

The most common infection with this fungus is candidemia that is thought to stem from skin colonization contaminating central venous catheters [21]. Direct patient-to-patient transmission can occur, but the environment of colonized patients can quickly become a durable supply for further spread lasting at minimum 28 days to 3 months [12, 24].

Currently, there are some recommendations available on best daily and terminal cleanings. The CDC and the European Centre for Disease Controls suggest using an Environmental Protection Agency registered hospital-grade disinfectant effective against Clostridium difficile spores for daily and terminal cleaning [22, 23]. Outbreaks in London and Spain performed cleanings three times per day with 1000 ppm chlorine-based product or disposable chlorhexidine towels respectively [21, 25••]. Though aggressive, this may be necessary to slow and control the spread of infection during an outbreak. This method appeared to have worked as well.

One study, done by those with outbreak experience, looked at in vitro susceptibility of *C. auris* to certain disinfectants specifically H2O2 vaporization and found that it was 96.6–100% effective at killing isolates [21, 25••, 26–29].

Decolonization

Skin colonization is thought be a major risk factor for the spread of C. auris during outbreaks as skin shedding is the likely source of further environmental contamination. The risk of fungal invasion is also increased by skin colonization as deep central lines, surgical wound sites, and urinary catheters are potential sources of life-threatening infections especially in the setting of biofilm formation [29].

A European study performed in vitro evaluation of several skin decolonization methods utilized during their own outbreak [30]. It was found that 4% liquid chlorhexidine products used on patient's skin and healthcare members' hand decontamination were effective at subduing the spread of C. auris [31]. However, concentrations of chlorehexidine at 2% may not be sufficient to inhibit the growth [32]. Iodine povidone at 10% was used as preoperative surgical skin preparation in colonized patients undergoing surgery with the advantage of being more inhibitory at < 3 min than chlorhexidine [33].

Conclusions

Given the rapid rise of *Candida auris* as a resilient pathogen leading to invasive, nosocomial infections, it is important that healthcare institutions remain on alert. The first step is always education to implement appropriate methods starting with species identification of non-albicans Candida. Once found, patients should be treated empirically with an echinocandin, and susceptibilities should be performed. Strict precautions should be started with daily cleanings, terminal cleanings, and decolonization. Data is currently limited; however, as more isolates are identified, we will be able to more precisely treat and prevent the spread of *C. auris*.

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Compliance with ethical standards

Conflict of interest

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Human and animal rights and informed consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

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