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Candida auris: An emerging multidrug-resistant pathogen

David Sears*, Brian S. Schwartz

Division of Infectious Diseases, University of California, San Francisco, USA

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ABSTRACT

*Candida auris*is an emerging multidrug-resistant pathogen that can be difficult to identify using traditional biochemical methods. *C. auris* is capable of causing invasive fungal infections, particularly among hospitalized patients with significant medical comorbidities. Echinocandins are the empiric drugs of choice for *C. auris*, although not all isolates are susceptible and resistance may develop on therapy. Nosocomial *C. auris* outbreaks have been reported in a number of countries and aggressive infection control measures are paramount to stopping transmission.

Introduction

Candida auris was first identified from samples of external ear drainage from one Japanese patient (Satoh et al., 2009) and 15 Korean patients in 2009 (Kim et al., 2009). This organism can be challenging to identify using standard microbiologic techniques and frequently exhibits multidrug-resistance. In the eight years since these initial cases, *C. auris* has become an emerging global health threat, implicated in a host of invasive infections and outbreaks in healthcare facilities. To date, cases have now been identified in India (Sarma et al., 2013; Chowdhary et al., 2013), South Africa (Magobo et al., 2014), Kuwait (Emara et al., 2015), the United Kingdom (Schelenz et al., 2016), Venezuela (Calvo et al., 2016), Brazil (Prakash et al., 2016), the United States (Vallabhaneni et al., 2016), Colombia (Morales-López et al., 2017), Pakistan (Lockhart et al., 2017), Spain (Ruiz Gaitán et al., 2017), Germany (European Centre for Disease Prevention and Control, 2016), Israel (Ben-Ami et al., 2017), Norway (European Centre for Disease Prevention and Control, 2016), and Oman (Al-Siyabi et al., 2017). This review will detail the microbiology, clinical features, therapeutic options, and infection control measures relevant to *C. auris* infection.

Microbiology and diagnosis

C. auris is phylogenetically related to *Candida haemulonii* and *Candida ruelliae* (Satoh et al., 2009). Four distinct clades have been identified from separate geographic origins, suggesting a recent and nearly simultaneous emergence of different clonal populations (Lockhart et al., 2017). *C. auris* grows readily at 37–42 °C and forms light pink colonies on chromogenic media (Chowdhary et al., 2014; Kathuria et al., 2015). Unlike *C. haemulonii*,*C. auris* does not form pseudohyphae. Only some *C. auris* strains produce the virulence factors phospholipase and proteinase, which may account for the variability in pathogenicity demonstrated in a murine model (Borman et al., 2016; Larkin et al., 2017). *C. auris* is capable of forming biofilms (Oh et al., 2011) and adhering to catheter material, although not to the same degree as *Candida albicans* (Larkin et al., 2017).

Traditional biochemical methods of identification commonly misdiagnose *C. auris* as other yeast. The United States Centers for Disease Control and Prevention (CDC) recommends further testing for *C. auris* whenever *C. haemulonii* is identified or in a number of other scenarios depending on the organism reported and the method of identification (Table 1). Accurate identification can be performed with VITEK MS and Bruker Biotyper matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) devices using their "research use only" databases. Molecular sequencing of the D1–D2 domain of the 28s rDNA can also identify *C. auris* (CDC, 2017). For laboratories without the capability to perform these tests, Kumar et al. propose a low-cost alternative that can accurately distinguish *C. auris* from *C. haemulonii* using CHROMagar medium supplemented with Pal's medium (Kumar et al., 2017).

* Corresponding author at: 513 Parnassus Ave., Box 0654, San Francisco, CA 94143, USA. Fax: +1 415 476 9364.
E-mail address: david.sears@ucsf.edu (D. Sears).

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Table 1
When to suspect *Candida auris* based on the organism presumptively identified and the method of identification (CDC, 2017).

Organism reported	Method
Candida haemulonii	Any
Candida spp.	Any validated identification method
Rhodotorula glutinis	API 20C if red color is not present
Candida sake	API 20C
Candida catenulata	BD Phoenix
Candida catenulata	MicroScan
Candida famata	MicroScan
Candida guilliermondii	MicroScan
Candida lusitaniae	MicroScan

Source: US Centers for Disease Control and Prevention.

Clinical features

Risk factors for *C. auris* infection appear to be similar to infections from *Candida* in general. These include immunosuppressed state, significant medical comorbidities, central venous catheters, urinary catheters, recent surgery, parenteral nutrition, exposure to broad spectrum antimicrobials, intensive care unit admission, and residence in a high-acuity skilled nursing facility (Vallabhaneni et al., 2016; Sarma and Upadhyay, 2017). In a case-control study investigating risk factors for *C. auris* fungemia compared to bloodstream infection from other *Candida* species in Indian ICUs, those with *C. auris* fungemia were more likely to have had longer antecedent hospitalizations, underlying respiratory conditions, vascular surgery, prior antifungal exposure, and low APACHE II scores. Patients with *C. auris* fungemia in this study were also more frequently from public-sector ICUs from the north of India (Rudramurthy et al., 2017).

C. auris has been recovered in samples from blood, catheter tips, cerebrospinal fluid, bone, ear discharge, pancreatic fluid, pericardial fluid, peritoneal fluid, pleural fluid, respiratory secretions (including sputum and bronchoalveolar lavage), skin and soft tissue samples (both tissue and swab cultures), urine, and vaginal secretions. Clinically, it has been implicated as a causative agent in fungemia, ventriculitis, osteomyelitis, malignant otitis (including otomastoiditis), complicated intra-abdominal infections, pericarditis, complicated pleural effusions, and vulvovaginitis (Satoh et al., 2009; Kim et al., 2009; Sarma et al., 2013; Magobo et al., 2014; Emara et al., 2015; Schelenz et al., 2016; Calvo et al., 2016; Vallabhaneni et al., 2016; Morales-López et al., 2017; Lockhart et al., 2017; Ruiz Gaitán et al., 2017; Ben-Ami et al., 2017; Al-Siyabi et al., 2017; Borman et al., 2016; Lee et al., 2011; Khillan et al., 2014; Choi et al., 2017; Chowdhary et al., 2017; Tsay et al., 2017). Much like other *Candida* species, there is uncertainty about the ability of *C. auris* to cause true respiratory, urinary, and skin and soft tissue infections despite being isolated from such samples.

While one study reported no *C.* auris attributable deaths among nine patients with fungemia, crude mortality rates for *C. auris* fungemia have otherwise ranged from 28 to 66% across a wide range of healthcare settings and patient populations (Chowdhary et al., 2013; Calvo et al., 2016; Vallabhaneni et al., 2016; Morales-López et al., 2017; Lockhart et al., 2017; Al-Siyabi et al., 2017; Chowdhary et al., 2014; Rudramurthy et al., 2017; Lee et al., 2011).

Antifungal therapies

Source control measures, including removal of indwelling catheters, are likely as important to the successful treatment of invasive *C. auris* infections as they are to other forms of invasive candidiasis. Regarding antifungal therapy, there are no Clinical and Laboratory Standards Institute (CLSI) or European Committee for Antimicrobial Susceptibility Testing (EUCAST) defined breakpoints for *C. auris* susceptibility. CDC recommends that all *C. auris* isolates undergo susceptibility testing and provides guidance for MIC breakpoints based on related *Candida* species and expert opinion (Table 2) (CDC, 2017). Fluconazole (tentative MIC breakpoint ≥32) is associated with high minimum inhibitory concentrations (MICs) and is likely almost always resistant. Susceptibility testing from four studies involving between 54 and 123 clinical isolates revealed MIC50 results between 64 and 128 mg/L and MIC90 results between 64 and 256 mg/L by CLSI microbroth dilution. Echinocandins (tentative MIC breakpoint ≥4 for anidulafungin and micafungin, ≥2 for caspofungin) appear to be most active in these studies with favorable results for anidulafungin (MIC50 range 0.125–0.5, MIC90 range 0.5–1), caspofungin (MIC50 0.25–0.5, MIC90 1), and micafungin (MIC50 0.125–0.25, MIC90 0.25–2). Amphotericin B (tentative MIC breakpoint ≥2) susceptibility testing exhibits a wider range of MIC results (MIC50 0.5–1, MIC90 2–4) and is likely less reliable as empiric therapy (Prakash et al., 2016; Lockhart et al., 2017; Kathuria et al., 2015; Arendrup et al., 2017). Regarding second generation triazole susceptibility, fluconazole susceptibility can be used as a surrogate although fluconazole-resistant isolates may occasionally respond to other triazole antifungals (CDC, 2017). In comparison to CLSI microbroth dilution, similar MIC50 and MIC90 results can likely be obtained by the EUCAST method (Arendrup et al., 2017), although caution should be used when interpreting Etest and Vitek antifungal susceptibility testing results (Kathuria et al., 2015).

Based on these results, echinocandins are the empiric drugs of choice for *C.auris* infections in adults and children over the age of 2 months. Amphotericin B–while less reliable–should be considered for patients not responding to echinocandin therapy, depending on MIC results. A mouse model testing antifungal therapy on nine strains of *C. auris* suggested that micafungin may be particularly fungicidal and more active than tentative MIC breakpoints may suggest (Lepak et al., 2017), however further clinical studies in humans are needed. It is important to note that resistance may develop on therapy and close clinical follow-up and potentially repeat MIC testing may be indicated for patients who are responding poorly to antifungal therapy.

Table 2
Tentative MIC (mg/L) breakpoints for *Candida auris* susceptibility (CDC, 2017) and published MIC ranges by CLSI microbroth dilution (Prakash et al., 2016; Lockhart et al., 2017; Kathuria et al., 2015; Arendrup et al., 2017).

Antifungal drug	Tentative MIC breakpoint	Published MIC50 range	Published MIC90 range
Fluconazole	≥32	64–128	64–256
Voriconazole[a]	N/A[b]	0.5–2	4–8
Amphotericin B	≥2	0.5–1	2–4
Anidulafungin	≥4	0.125–0.5	0.5–1
Caspofungin	≥2	0.25–0.5	1
Micafungin	≥4	0.125–0.25	0.25–2

[a] Also applies to other second generation triazole antifungals.
[b] Consider using fluconazole susceptibility as a surrogate, although fluconazole-resistant isolates may occasionally respond to other triazole antifungals.