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REVIEW
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Identification of Drug Resistant *Candida auris*

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Candida auris is a multidrug resistant yeast, recognized as a cause of invasive infections and health care associated outbreaks around the world. *C. auris* is of great public health concern, due to its propensity for drug resistance, mode and pace of its transmission, and the possibility that biologic and epidemiologic factors could exacerbate worldwide emergence of *C. auris* infections. Currently, outbreak response is complicated by limited treatment options and inadequate disinfection strategies, as well as by issues (misidentification, long turnaround time) associated with application of commonly used diagnostic tools. Misdiagnosis of *C. auris* is common since many diagnostic platforms available in clinical and public health laboratories depend on reference databases that have not fully incorporated *C. auris*. Moreover, the correlation between minimal inhibitory concentration values (MICs) and clinical outcomes is poorly understood resulting in the absence of *C. auris*-specific breakpoints. New, accurate and fast diagnostic methods have emerged to facilitate effective patient management and improve infection control measures, ultimately reducing the potential for *C. auris* transmission. This review provides an overview of available *C. auris* detection/identification and antifungal susceptibility determination methods and discusses their advantages and limitations. A special emphasis has been placed on culture-independent methods that have recently been developed and offer faster turnaround times.

Keywords: *Candida*, *Candida auris*, diagnostics, identification, detection, antifungal drug resistance

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INTRODUCTION

Over the last few decades, fungal infections are increasingly recognized as a serious concern for human health, especially for immunocompromised patients and those hospitalized with serious underlying diseases. Candidemia and other forms of invasive candidiasis, including infections of normally sterile body fluids, deep tissues, and organs, are the most common nosocomial invasive fungal infections, and are associated with prolonged hospitalization and increased health care costs (Lockhart, 2014; Pfaller et al., 2019). In the US, the most often isolated species is *Candida albicans*, but a trend of increasing number of cases of infection with non-*albicans Candida*, thought to be driven largely by the increasing use of prophylactic antifungal agents such as fluconazole (Deorukhkar et al., 2014), has been reported. Strikingly, non-*albicans Candida* species have been associated with higher mortality and greater antifungal drug resistance than those seen with *C. albicans* infections (Pfaller et al., 2019).

As one of the most prominent emerged pathogens, *Candida auris* has been spreading across the globe causing hospital outbreaks (Meis and Chowdhary, 2018). It is often associated with high level antifungal drug resistance, which limits treatment options. It was first reported in 2009 after being isolated from an external ear canal discharge of a patient in Japan (Satoh et al., 2009). Subsequently, cases of persistent colonization and various types of invasive infections have been reported from many countries located on six continents (**Table 1**). Bloodstream infection has been

the most frequently reported type of invasive infection, with mortality ranging from 30 to 60% (Chowdhary et al., 2017). However, *C. auris* isolates have been recovered from many other types of clinical specimens (**Table 1**). Currently, *C. auris* is divided into four major clades displaying distinct biological and drug resistance properties (Szekely et al., 2019; Welsh et al., 2019): I, South Asian; II, East Asian; III, South African; IV, South American. *C. auris* infections in other parts of the world, such as the United States and United Kingdom have been caused by strains that are genetically related to these clades (**Table 1**). Every major clade except for Clade II has been linked to outbreaks with invasive infections. A molecular epidemiological survey performed by Chow et al. in the US showed that travel-related cases, in which patients probably acquired *C. auris* through health-care exposures abroad, are not common (5/73 clinical cases) and that the current epidemic in the United States is dominated by Clade I and Clade IV. Genetic diversity among isolates from the same patients, health-care facilities, and states indicated local and ongoing transmission (however, no apparent transmission even between adjacent states, NY and NJ) (Chow et al., 2018). Several factors, including widespread antifungal use and climate change, have been recently discussed (Jackson et al., 2019), but the exact reasons why this fungus has started spreading in recent years remain unclear.

Major obstacles impacting the control of *C. auris* spread include common misidentification by diagnostic platforms available in clinical and public health laboratories, a poor understanding of resistance to antifungal drugs and disinfectants, and a high propensity to contaminate health care environments which results in transmission of clonal *C. auris* isolates (spread through contact with affected patients and contaminated surfaces). Ultimately, correct detection and identification of the pathogen and its antifungal susceptibility, followed by strict adherence to appropriate treatment and infection prevention and control strategies is crucial for limiting of the spread of *C. auris*.

The aim of this review is to provide an overview of available *C. auris* detection/identification and antifungal susceptibility determination methods and discuss their advantages and limitations. A special emphasis is put on molecular-based and culture-independent methods that have recently been developed and offer faster turnaround times.

Candida auris IDENTIFICATION AND DETECTION IN CLINICAL SAMPLES

There is a vast variety of fungal identification methods used by clinical and public health laboratories all over the world to detect *C. auris*. However, many of them use systems (e.g., VITEK 2, API 20C) for which misidentification with other yeasts has been reported (**Table 1**). Moreover, because much of the treatment for *Candida* infections is empirical, many institutions do not identify *Candida* to the species level, and if they do it, it is mostly for sterile-site isolates (Lockhart et al., 2017a; Durante et al., 2018). However, the worldwide emergence of *C. auris* heightened public health relevance of the identification of *Candida* to the species level. As broadly discussed by Lockhart et al., species should be determined for isolates recovered from invasive candidiasis cases and selected non-invasive isolates in order to improve detection of *C. auris*. Species identification of isolates from normally sterile body sites enables guidance for initial therapy considering predictable species-specific susceptibility. Moreover, given the emergence of *C. auris*, the Centers for Disease Control and Prevention (CDC) advises species-level identification in the following situations: (1) when clinically indicated in the care of a patient; (2) when a case of *C. auris* infection or colonization has been detected in a facility or unit; (3) when a patient has had an overnight stay in a health care facility in the previous 6 months in a country with *C. auris* transmission. Laboratories should also review past records to identify confirmed or suspected cases, as well as conduct prospective surveillance (Lockhart et al., 2017c).

Accurate identification of *C. auris* infection in the clinical laboratory can be problematic especially when relying on phenotypic characteristics. Institutions without appropriate methodology for *C. auris* species characterization or with isolates that are unidentified or suspect for *C. auris* are strongly advised to contact a reference laboratory for guidance (Durante et al., 2018). In the US, the CDC Advanced Molecular Detection (AMD) program[1] addresses gaps in technology and workforce knowledge, helps build capacity and provides training at CDC, as well as state and local public health laboratories across the nation.

It is noteworthy, that *C. auris* identification inaccuracies still persist, which has complicated our understanding of the real global prevalence of infections caused by this yeast. Challenges in *C. auris* identification emphasize the importance of local and international collaboration between hospitals (care team), diagnostic laboratories, public health authorities and researchers to optimize diagnostic capacities for rapid identification of emerging pathogens (Lockhart et al., 2017c; Durante et al., 2018).

Enrichment Culture Protocol for *C. auris* Colonization Screening

The CDC, regional, and state public health laboratories in the United States use Salt Sabouraud Dulcitol enrichment broth procedure for isolation of *C. auris* from clinical skin swabs and environmental sponge surveillance samples. Welsh et al. recommended using dulcitol instead of dextrose as the main carbon source in order to decrease the opportunities of co-incubation of other (non-target) species like *C. glabrata* and *C. parapsilosis* (Welsh et al., 2017).

When screening for *C. auris* colonization, laboratories receive swabs immersed in modified liquid Amies medium. An aliquot (usually 100 μl) of the vortexed swab medium is inoculated into Salt Sabouraud Dulcitol enrichment broth and incubated at 40°C (temperature selective for *C. auris*), with shaking at 250 rpm for at least 5 days. Every sample that becomes turbid is streaked by a loop onto CHROMagar Candida. In a case when a sample remains clear, an aliquot is spread onto CHROMagar Candida. All CHROMagar Candida plates are incubated at 37°C for 48 h and screened for the presence of colony types possible for *C. auris* (Sexton et al., 2018b).

[1] www.cdc.gov/amd

TABLE 1 | Published cases of *Candida auris* (as of April 01, 2019).

Continent	Country	Clade	Isolates source	Reliable identification	Cases of initial misidentification	References
Asia	China	N/A	Blood, urine, catheter, sputum, bronchoalveolar lavage fluid (BAL)	MALDI-TOF MS, rDNA sequencing	*C. haemulonii* by VITEK 2; *C. famata* by API 20C	Tian et al., 2018; Wang et al., 2018
	India	I	Blood, tissue, pus, BAL, catheter tip, swab (axilla, groin, oral, rectal, skin, vaginal), wound	MALDI-TOF MS, rDNA sequencing	*C. haemulonii, C. famata, C. glabrata* by VITEK 2; *C. sake* by API 20C	Chowdhary et al., 2013; Sarma et al., 2013; Chowdhary et al., 2014; Chatterjee et al., 2015; Kathuria et al., 2015; Kumar et al., 2015; Prakash et al., 2016; Sharma et al., 2016; Lockhart et al., 2017b; Rudramurthy et al., 2017; Chowdhary et al., 2018; Mathur et al., 2018
	Iran	N/A	Ear swab	MALDI-TOF MS, rDNA sequencing	No	Abastabar et al., 2019
	Israel	III	Blood, urine, wound, environment	MALDI-TOF MS and rDNA sequencing	*C. haemulonii* by VITEK 2; *C. parapsilosis* by BD Phoenix	Ben-Ami et al., 2017; Belkin et al., 2018
	Japan	II	Ear discharge	MALDI-TOF MS and rDNA sequencing	*C. haemulonii* by VITEK 2; *Saccharomyces kluyveri* by API ID 32C	Satoh et al., 2009; Iguchi et al., 2018
	Kuwait	N/A	Blood, urine, catheter tip, BAL, pus, endotracheal aspirate, abdominal drain fluid	rDNA sequencing, *C. auris*-specific PCR	*C. haemulonii* by VITEK 2	Emara et al., 2015; Khan et al., 2018a; Khan et al., 2018b; Alobaid and Khan, 2019
	Malaysia	N/A	Blood	rDNA sequencing	*C. haemulonii* by VITEK 2; *Rhodotorula glutinis* by API 20C	Mohd Tap et al., 2018
	Oman	N/A	Blood	MALDI-TOF MS	*C. haemulonii* by API 20C and BD Phoenix	Al-Siyabi et al., 2017; Mohsin et al., 2017
	Pakistan	I	Blood, urine, wound	MALDI-TOF MS	*Saccharomyces cerevisiae* by API 20C	Lockhart et al., 2017b
	Russia	I	Blood, urine, tracheal aspirate	MALDI-TOF MS	No	Barantsevich et al., 2019
	Saudi Arabia	I	Blood, pleural tissue	MALDI-TOF MS	*C. haemulonii* by VITEK 2	Abdalhamid et al., 2018
	Singapore	N/A	Blood, femur tissue	rDNA sequencing	No	Tan and Tan, 2018
	South Korea	II	Blood, catheter tip, pelvic Jackson-Pratt drain, ear discharge	MALDI-TOF MS, rDNA sequencing	*C. haemulonii* by VITEK 2	Lee et al., 2011; Choi et al., 2017; Jung et al., 2019; Kwon et al., 2019a
	Taiwan	N/A	Facial lesion	MALDI-TOF MS, rDNA sequencing	*C. haemulonii* by VITEK 2 and BD Phoenix	Tang et al., 2019
	United Arab Emirates	N/A	Blood	MALDI-TOF MS	*C. haemulonii* by VITEK 2; negative result on BioFire's Filmarray1 Blood Culture Identification*	Alatoom et al., 2018
Africa	South Africa	III	Blood, cerebrospinal fluid, serous fluid, tissue, urine, respiratory tract specimen, swab (skin, mucosal), catheter tip	MALDI-TOF MS, rDNA sequencing	*C. haemulonii* by VITEK 2; *R. glutinis* by API 20C	Magobo et al., 2014; Prakash et al., 2016; Lockhart et al., 2017b; Govender et al., 2018

(Continued)

TABLE 1 | Continued

Continent	Country	Clade	Isolates source	Reliable identification	Cases of initial misidentification	References
South America	Brazil	IV	Blood	MALDI-TOF MS, rDNA sequencing	No	Prakash et al., 2016
	Colombia	IV	Blood, urine, cerebrospinal fluid, peritoneal fluid, ocular secretion, swab (axilla, groin, hands, rectum) healthcare environment	MALDI-TOF MS, rDNA sequencing	*C. haemulonii* by VITEK 2 and BD Phoenix; *C. tropicalis* by MicroScan Walkaway; *C. albicans, C. guilliermondii, C. parapsilosis, C. catenulata, Rhodotorula rubra* by MicroScan; *C. famata* by API Candida	Morales-Lopez et al., 2017; Escandón et al., 2018; Parra-Giraldo et al., 2018; Escandón et al., 2019
	Panama	IV	Blood, urine, catheter tip, pleural fluid	MALDI-TOF MS, rDNA sequencing	*C. haemulonii* by VITEK 2	Arauz et al., 2018
	Venezuela	IV	Blood	rDNA sequencing	*C. haemulonii* by VITEK 2	Calvo et al., 2016; Lockhart et al., 2017b
North America	Canada	N/A	Ear swab	MALDI-TOF MS	No	Schwartz and Hammond, 2017
	United States	I, II, III, IV	Blood, urine, BAL, respiratory tract, sputum, bile fluid, wound, catheter tip, bone, ear, jejunal biopsy, swab (axilla, groin, skin, nares), environment	MALDI-TOF MS, *C. auris*-specific qPCR, rDNA sequencing	Not identified by VITEK MS; *C. haemulonii* by VITEK 2	Azar et al., 2017; Tsay et al., 2017; Vallabhaneni et al., 2017; Chow et al., 2018; Leach et al., 2018; Lesho et al., 2018; Park et al., 2019
Europe	Austria	N/A	Ear swab	MALDI-TOF MS, rDNA sequencing	*C. haemulonii, C. duobushaemulonii* by VITEK 2	Pekard-Amenitsch et al., 2018
	Belgium	N/A	Blood	MALDI-TOF MS, rDNA sequencing	*C. haemulonii* by VITEK 2	Dewaele et al., 2018
	Spain	Close to III	Blood, urine, vascular line, respiratory specimen, catheter tip, swab (rectal), healthcare environment	rDNA sequencing	*C. haemulonii, C. lusitaniae* by VITEK MS; *Saccharomyces cerevisiae* by AuxaColor 2; *C. sake* by API 20C	Ruiz Gaitan et al., 2017, Ruiz-Gaitan A. et al., 2018; Ruiz-Gaitan et al., 2019
	Switzerland	N/A	Tracheal aspirate, groin, auditory canal, urine	MALDI-TOF MS, rDNA sequencing	No	Riat et al., 2018
	United Kingdom	I, II, III	Blood, urine, sputum, cerebrospinal fluid, shunt reservoirs, line, arterial line, femoral line, pleural fluid, cerebral tissue and fluid, catheter tip, swab (groin, skin, oropharynx, wound, pustule), hospital environment	MALDI-TOF MS, rDNA sequencing	No	Borman et al., 2016; Schelenz et al., 2016; Borman et al., 2017; Eyre et al., 2018; Rhodes et al., 2018; Khatamzas et al., 2019
Australia		III**	Deep operative sternal bone samples	MALDI-TOF MS and rDNA sequencing	No	Heath et al., 2019

*Countries within continents are listed in an alphabetical order. Clades: I, South Asian; II, East Asian; III, South African; IV, South American. rDNA sequencing: ITS and/or D1/D2 large subunit regions of rDNA sequencing. N/A, information not available. *test detects only five common Candida species (C. albicans, C. glabrata, C. krusei, C. parapsilosis, and C. tropicalis). **a man from Kenya visiting Australia*

Phenotypic and Biochemical Methods for *C. auris* Identification

Candida auris isolates show smooth white to cream-colored colonies on Sabouraud dextrose agar and appear as beige to pink colonies on CHROMagar Candida medium. However, Bentz et al. (2018) described presence of alternate colors: pink, white, and sectored (dark purple) of smooth and glossy colonies (see photographs[2]), and phenotype switching in isolates recovered from swabs through enrichment broth procedure. By no means recovery of aforementioned colony types on CHROMagar Candida medium can be considered as final identification of *C. auris*, since other yeast, including *C. parapsilosis*, can look alike. Recovered colonies should be further analyzed by one of the reliable identification methods, e.g., rDNA sequencing, *C. auris*-specific PCR/qPCR, or MALDI-TOF MS.

Kumar et al. (2017) proposed using temperature tolerance and CHROMagar supplemented with Pal's medium in order to morphologically distinguish *C. auris* from *C. haemulonii* and *C. duobushaemulonii*. *C. auris* strains showed confluent growth of white to cream colored smooth colonies at 37°C and 42°C after 24 and 48 h incubation and did not produce pseudohyphae. Contrarily, isolates of the *C. haemulonii* complex showed poor growth of smooth, light-pink colonies at 24 h while at 48 h the growth was semiconfluent with the production of pseudohyphae (Kumar et al., 2017).

Candida auris has often been misidentified in conventional diagnostic laboratories using standard biochemical identification systems (**Table 1**), primarily due to the lack of *C. auris* references in their databases. As databases are being updated, accurate identification becomes more possible, like it happened with VITEK 2 8.01 software version (BioMérieux) in 2018 (Lockhart et al., 2017a; Govender et al., 2018), however misidentifications of strains from certain clades have been reported and all *C. duobushaemulonii* should be forwarded for further identification[2]. A high vigilance still needs to be in place when identification process results in *C. haemulonii, C. duobushaemulonii, C. famata, C. glabrata* from (not updated) VITEK 2 (bioMérieux), *C. famata*, *C. sake*, *Rhodotorula glutinis, Saccharomyces cerevisiae* from API 20C AUX (bioMérieux), *C. haemulonii*, *C. parapsilosis*, *C. catenulata* from BD Phoenix (Becton Dickinson), or *C. albicans*, *C. parapsilosis, C. tropicalis, C. famata, C. lusitaniae, C. guilliermondii, C. catenulata, R. rubra* from MicroScan (Beckman Coulter) (Lockhart et al., 2017a; Mizusawa et al., 2017). Consequently, it might be necessary to confirm such identification result, especially for high fluconazole minimal inhibitory concentration (MIC) or multidrug resistant isolates, by rDNA sequencing, *C. auris*-specific PCR/qPCR or MALDI-TOF MS.

Identification of *C. auris* by MALDI-TOF MS

The matrix-assisted laser desorption ionization time-of-flight mass spectrometry (MALDI-TOF MS) can be used for rapid and accurate identification of microorganisms. MALDI-TOF MS generates characteristic mass spectra, unique for each microorganism, that can be used as their fingerprints. Since the identification process is based on comparison of spectra acquired for a tested sample and a database of spectra of know species, accurate result is reliant on the presence of the sample organism spectrum in the database. That is why absence of identification or misidentification of fungal species by MALDI-TOF MS is essentially due to absence, mistakes or incomplete reference spectra in the database (Croxatto et al., 2012).

Lack of proper spectra in the databases has resulted in the misidentification of *C. auris* as *C. haemulonii* and *C. albicans*, among others, by MALDI-TOF MS (Kim et al., 2016; Wattal et al., 2017). However, once research-use only (RUO) or manufacturer's databases are updated with *C. auris* and related species spectra, MALDI-TOF MS identification of *C. auris* to the species level appears to be accurate (**Table 1** and Cendejas-Bueno et al., 2012; Girard et al., 2016; Bao et al., 2018; Vatanshenassan et al., 2019). It is crucial that laboratories review the presence of aforementioned spectra in the database and confirm the laboratory detection capacity by testing a panel of reference strains, e.g., "*Candida auris* Panel" offered by CDC & FDA Antibiotic Resistance (AR) Isolate Bank[3], which contains *C. auris* isolates from all clades and other yeast species that are related to *C. auris* or are commonly misidentified as *C. auris*.

Evaluated the viability of *C. auris* after various MALDI-TOF MS extraction protocols (on-plate extraction, quick tube extraction, and extended tube extraction) to determine if isolates processing may expose laboratory workers to infectious agents. *C. auris* was effectively killed in all three methods. Additionally, the authors recommended use of the quick tube extraction method since it gave confidence scores not significantly different from the extended one but better than the on-plate method (Sterkel et al., 2018).

In general, compared with conventional identification methods, MALDI-TOF MS has been shown to confer a significant gain of both technician working time (pre-analytical procedure to prepare samples) and turnaround time (automated analytical procedure to obtain results). MALDI-TOF MS is suitable for high-throughput and rapid microbial identification at low costs and is an alternative for conventional laboratory biochemical and molecular identification systems. Even though the running costs are significantly cheaper than those of conventional identification methods (Croxatto et al., 2012), the amount of money required to purchase a MALDI-TOF MS instrument itself is often an obstacle for laboratories, ultimately preventing implementation of the technique.

In summary, the use of MALDI-TOF MS for the identification of clinically relevant yeasts, including *C. auris*, is rapid and accurate providing that the database is constructed with a comprehensive collection of accurately identified reference strains. Currently, accurate identification of *C. auris* can be achieved by using freely available MicrobeNet database validated by CDC experts[4] or the following MALDI-TOF MS systems: Bruker Biotyper with FDA-approved MALDI Biotyper CA

[2] www.cdc.gov/fungal/candida-auris/recommendations.html

[3] www.cdc.gov/drugresistance/resistance-bank

[4] www.cdc.gov/microbenet

System library (Version Claim 4) or their "research use only" libraries (Versions 2014 [5627] and more recent) and VITEK (MALDI-TOF) MS RUO (with Saramis Ver 4.14 database and Saccharomycetaceae update).

Molecular-Based Methods for *C. auris* Identification

Molecular techniques have greatly enhanced the diagnosis of causal agents of infectious disease, particularly when the causal agent is difficult to culture and identify. Sequencing of genetic loci and PCR/qPCR assays have successfully been applied for identification of *C. auris* (**Table 1**). Especially real-time PCR assays bear incomparable potential of being the most efficient tool for high-throughput screening of surveillance samples. If properly validated, they can deliver the diagnostic result within several hours, since the DNA can be isolated directly from the patient specimen without the need of obtaining a colony.

Sequencing of Genetic Loci

Sequencing of rDNA genetic loci, namely internal transcribed spacer and D1/D2 region of large subunit (LSU), that are amplified with standard primers, provides accurate identification of *C. auris* and differentiation from other yeast (**Table 1**). However, as mentioned by Lockhart et al. sequencing is not routinely used to determine isolate species, since the cost, technical demands, and lengthy turnaround times for those without in-house sequencing capacity can make this technique unsuitable for some laboratories (Lockhart et al., 2017a).

It is also worth to mention, that comparative analysis of rDNA sequences should not be used to define relations between strains due to its insufficient discriminatory power, as revised elsewhere (Jeffery-Smith et al., 2018).

Nucleic Acid-Based Identification Strategies

Various molecular-based assays, from conventional PCR, through real-time PCR, to more complex T2 magnetic resonance or Loop-mediated Isothermal Amplification (LAMP), have been developed, that can be applied based on the available resources (**Table 2**). Most of the assays have the ability to provide rapid results - within several hours from the clinical sample delivery. In comparison, other methods, including biochemical automated systems and MALDI-TOF MS, require culture, that can take anywhere from 4 to 14 days.

Most of the developed assays are highly sensitive, with a detection limit of 1–10 *C. auris* CFU/PCR reaction (**Table 2**). More importantly, the assays are highly specific and no cross-reactivity is observed with all known closely and distantly related yeasts and other pathogens. Currently, at least three assays have been successfully validated on a panel of clinical swabs (Leach et al., 2018; Sexton et al., 2018a,b), which included samples that were negative for *C. auris* DNA but harbored other organisms. No cross-reactivity was observed, further confirming the high specificity of the assays that can be used for direct detection of *C. auris* without a need of prior culture. It is a huge progress from the *status quo* of axilla/groin composite swabs processing (see: 2.1 Enrichment culture protocol for colonization screening). The delay generated by the requirement of culture has been dramatically limiting the opportunity to quickly respond to outbreaks.

Nucleic acid-based identification strategies may have several technical (availability of equipment and separation of sample prep/amplification/analysis areas) and cost (equipment, reagents) limitations depending on the laboratory infrastructure. Another aspect may be considered both a benefit or limitation, depending on the aim of particular study: DNA from both live and dead *C. auris* cells can be detected, which can be a discrepancy with culture, but shouldn't be considered a false positive result. A positive result from a non-sterile specimen (skin swab, environmental sponge) is an indicator of past or present *C. auris* colonization.

DETECTION OF *C. auris* ANTIFUNGAL DRUG RESISTANCE

Antifungal susceptibility testing (AFST) for *C. auris* has been performed using various standardized tests, including Clinical and Laboratory Standards Institute (CLSI) and European Committee on Antimicrobial Susceptibility Testing (EUCAST) broth microdilution methods, the *E*-test gradient diffusion method, and the VITEK 2 antifungal susceptibility system. However, analysis of susceptibility testing results for an emerging fungal species like *C. auris* is complicated by the limited understanding of the correlation between MICs and clinical outcomes (no established breakpoints enabling AFST result interpretation). Currently, CDC provides guidance for *C. auris* MIC interpretation, that based on information gathered for related *Candida* species and expert opinion[5].

Nevertheless, *C. auris* isolates are often characterized by reduced susceptibility to azoles, polyenes, and echinocandins. Results of susceptibility testing performed on Indian isolates revealed their nearly universal resistance to fluconazole. For that reason, *C. auris* was initially suspected to be intrinsically resistant to this azole drug (Chowdhary et al., 2014, 2018; Kathuria et al., 2015; Arendrup et al., 2017). Moreover, reduced susceptibility of *C. auris* to other triazole antifungal drugs, including voriconazole, posaconazole, itraconazole, and isavuconazole was reported (Chowdhary et al., 2014; Arendrup et al., 2017; Ben-Ami et al., 2017; Lockhart et al., 2017b; Morales-Lopez et al., 2017; Vallabhaneni et al., 2017; Khan et al., 2018a; Rhodes et al., 2018; Ruiz-Gaitan et al., 2019). Such situation when reduced susceptibility to azole class drugs is commonly observed is extremely worrying, since azoles are a mainstay in the treatment of *Candida* infections and antifungals other than fluconazole might be unavailable in resource-limited countries. Nowadays, as more susceptibility information has become available for isolates from around the world and fluconazole susceptible isolates (2–8 mg/l MIC) have been reported, it is believed that fluconazole resistance is an acquired phenomenon in *C. auris* (Lockhart et al., 2017a). Furthermore, polyene antifungal drug amphotericin B can show variable activity against *C. auris* isolates (Shin et al., 2012; Sarma et al., 2013; Magobo et al., 2014;

[5]www.cdc.gov/fungal/candida-auris/c-auris-antifungal.html

TABLE 2 | Molecular-based methods for identification and detection of *Candida auris*.

Paper	Purpose	Identification from	DNA extraction	Assay type	Assay specificity	Detection limit
Kordalewska et al., 2017	New assay	Colonies	Quick boiling method (Brillowska-Dabrowska et al., 2010)	PCR and qPCR (SYBR Green)	(1)*C. auris* (PCR and qPCR) (2)*C. auris, C. duobushaemulonii*, *C. haemulonii*, and *C. lusitaniae* (qPCR)	(1) 10 CFU/rxn (2) 1000 CFU/rxn
Sexton et al., 2018b	Validation of the assay	Clinical swabs	Bead beating and DNeasy PowerLyzer Microbial Kit (Qiagen)	qPCR (SYBR Green) from Kordalewska et al., 2017	*C. auris*	4 CFU/rxn
Leach et al., 2018	New assay	Clinical swabs, environmental sponges	Bead beating	qPCR (TaqMan)	*C. auris*	1 CFU/rxn
Ahmad et al., 2019	Validation of rapid extraction method	Clinical swabs	MagNA Pure 96 (Roche)	qPCR (TaqMan) from Leach et al., 2018	*C. auris*	1 CFU/10 μl
Theill et al., 2018	New assay	Colonies	N/A	Duplex PCR	*C. auris* and *C. haemulonii*	N/A
Arastehfar et al., 2018	New assay	Colonies	CTAB method (Gupta et al., 2004)	Tetraplex PCR	*C. auris, C. haemulonii*, *C. duobushaemulonii*, and *C. pseudohaemulonii*,	N/A
Ruiz-Gaitan A.C. et al., 2018	New assay	Colonies	Boiling in 20 mM NaOH	Duplex PCR	*C. auris*	N/A
Khan et al., 2018a	New assay	Colonies	Rapid method using Chelex-100 (Asadzadeh et al., 2015)	PCR	*C. auris*	N/A
Martinez-Murcia et al., 2018	Validation of a commercial kit	Colonies	MagNA Lyser with green beads followed by MagNA Pure 96 (Roche); or GPS DNAcol	GPS MONODOSE dtec-qPCR kit	*C. auris*	5 CFU/rxn
Arastehfar et al., 2019a	New assay	Colonies, spiked serum samples	CTAB method (Gupta et al., 2004)	Tetraplex qPCR (SYBR Green/EvaGreen)	*C. auris, C. haemulonii*, *C. duobushaemulonii*, and *C. pseudohaemulonii*,	10 CFU
Arastehfar et al., 2019b	New assay	Colonies	DNeasy Blood & Tissue Kit (Qiagen) with modifications	Multiplex PCR	21 species including *C. auris*	N/A
Sexton et al., 2018a	Validation of a commercial assay	Clinical swabs	T2Dx	T2 Magnetic Resonance (T2MR) system	*C. auris*	5 CFU/ml
Yamamoto et al., 2018	New assay	Colonies, clinical ear swab, mock environmental samples	Boiling in water (colonies) or Kaneka Easy DNA Extraction kit version 2 (KANEKA Co.) (swabs and environmental samples)	Loop mediated isothermal amplification (LAMP)	*C. auris*	20 CFU/rxn

N/A, information not available. rxn, reaction.

Calvo et al., 2016; Prakash et al., 2016; Sharma et al., 2016; Lockhart et al., 2017b; Vallabhaneni et al., 2017; Khan et al., 2018a; Rhodes et al., 2018; Escandón et al., 2019; Ruiz-Gaitan et al., 2019). The concern about resistance to azoles and amphotericin B has led to the recommendation for the use of echinocandins as a first-line therapy (Chowdhary et al., 2016; Public Health England, 2017). However, reports of *C. auris* isolates showing elevated MIC to one or more echinocandins have been published (Chowdhary et al., 2014, 2018; Sharma et al., 2016; Arendrup et al., 2017; Lockhart et al., 2017b; Vallabhaneni et al., 2017; Kordalewska et al., 2018; Rhodes et al., 2018). Strikingly, some *C. auris* isolates have demonstrated reduced susceptibility to multiple classes of antifungal agents, raising the possibility of pan-drug resistance (Kathuria et al., 2015; Lockhart et al., 2017b).

Broth Microdilution Methods

As already mentioned, at present, there are no antifungal clinical breakpoints reported for *C. auris* by CLSI or EUCAST. Tentative epidemiological cut off values (ECVs) were proposed in a recent study, where MIC distributions of 123 clinical *C. auris* isolates from India were analyzed (Arendrup et al., 2017). The ECV, which defines the upper limit of the wild type susceptible population of clinical isolates, provides a measure of potential drug resistance. Determined ECVs are valuable in the analysis of MICs of isolates from the South Asian clade, yet their application to isolates from other clades may lead to incorrect estimation of potential drug resistance, since there are strong indications that MIC distributions can vary substantially for *C. auris* isolates from different clades (Szekely et al., 2019; Welsh et al., 2019).

We reported a significant challenge with obtaining an accurate AFST MIC readout for caspofungin since all tested isolates exhibited an Eagle effect (also known as the paradoxical growth effect), with the intensities of the Eagle effect varying among the isolates (Kordalewska et al., 2018). However, echinocandins were effective *in vivo* in the treatment of invasive murine candidiasis caused by *C. auris* isolates, despite the presence of the Eagle effect *in vitro* and only determinant impacting the pharmacodynamic response was the *FKS1* genotype. Therefore, as with many *Candida* species, standardized CLSI susceptibility testing with caspofungin should be viewed cautiously or avoided since an Eagle effect results in an overestimation of the resistant population (Kordalewska et al., 2018).

Nearly all laboratories rely on automated systems for routine AFST. These systems are attractive because they can reduce the laboratory workload relative to manual broth microdilution methods, but they often underperform. Although Kwon et al. observed essential (96.7%) agreement between VITEK 2 and CLSI methods in fluconazole AFST (Kwon et al., 2019b), others have reported its suboptimal performance for amphotericin B (Kathuria et al., 2015), and a cautionary approach is warranted for automated AFST systems.

Therefore, an analysis of susceptibility results obtained by phenotypic tests is not always straightforward and may have difficulties defining susceptible or resistant isolates. More knowledge about clade-specific susceptibility patterns (MICs distribution) is crucial to support the global effort to fight *C. auris* infections efficiently.

MALDI-TOF

The MALDI Biotyper antibiotic susceptibility test-rapid assay (MBT ASTRA) for rapid AFST. *C. auris* cells were inoculated into RPMI 1640 with 2-fold serial dilutions of echinocandins (anidulafungin, micafungin, and caspofungin) and incubated at 37°C with shaking for 6 h. Later the cells were washed, lysed and deposited in a grid together with matrix, and spectra were acquired and analyzed. A comparison between MBT ASTRA and the CLSI broth microdilution assay results detected a sensitivity and specificity of 100% and 98% for anidulafungin, and 100 and 95.5% for micafungin, respectively. A categorical agreement of 98% and 96% was calculated for the two methods. For caspofungin, sensitivity and specificity of 100 and 73% were found, respectively, with a categorical agreement of 82%. MBT ASTRA has a potential to detect echinocandin non-susceptible *C. auris* isolates within 6 h, which makes it a promising candidate for AFST in clinical laboratories in the future (Vatanshenassan et al., 2019).

Molecular-Based Methods

Availability of methods for rapid and accurate identification of *C. auris* antifungal drug resistance is of urgent need. Molecular-based tests have the potential to become part of the clinical laboratory routine for resistance detection to help direct therapy and enhance epidemiological surveillance. Since azole and echinocandin resistance in *C. auris* are closely associated with specific *ERG11* and *FKS1* mutations, respectively (Healey et al., 2018; Kordalewska et al., 2018), their analysis can deliver a valuable information on antifungal drug resistance, and facilitate implementation of effective antifungal therapy. Regretfully, at this time there is no clear explanation for the molecular mechanism of *C. auris* amphotericin B resistance. The role of non-synonymous mutations in a transcription factor similar to *FLO8* or membrane transporter described by Escandón et al. (2019) needs to be further investigated. It is also possible that the mechanism of amphotericin B resistance is not mutation-based but regulated at the transcription level (Munoz et al., 2018).

Genetic Basis of *C. auris* Antifungal Drug Resistance

Several groups have sequenced genes encoding targets for azoles (Chowdhary et al., 2018; Healey et al., 2018; Kwon et al., 2019b) and echinocandins (Berkow and Lockhart, 2018; Chowdhary et al., 2018; Kordalewska et al., 2018), while the others performed whole genome sequencing (WGS) (Lockhart et al., 2017b; Rhodes et al., 2018), that led to the discovery of mutations responsible for *C. auris* resistance. Echinocandin resistance is mediated through limited mutations S639P (Berkow and Lockhart, 2018) or S639F (Chowdhary et al., 2018; Kordalewska et al., 2018) in *FKS1*, and

azole resistance through F126L, Y132F, and K143R in *ERG11* (Lockhart et al., 2017b; Healey et al., 2018; Rhodes et al., 2018). To date, these are the only mutations associated with clinical failures due to azole and echinocandin drugs.

It is crucial to remember that not all mutations detected in target genes confer resistance, and some mutations e.g., the ones leading to K177R, N335S, and E343D amino acid substitutions in Erg11, likely represent genetically evolved clade differences, and do not contribute to any decrease in drug susceptibility (Healey et al., 2018). Any newly identified allele should be carefully investigated to resolve its potential involvement in drug resistance. Validation of resistance properties can be done through molecular engineering approaches (creating/repairing mutation in an organism of the same species, cloning a mutated allele into a model organism) and pharmacodynamic studies in animals.

Moreover, as discussed earlier (see section "Sequencing of Genetic Loci"), and even more accurate for WGS, several factors related to the cost, turnaround time, technology and expertise make sequencing impractical for the regular workflow of clinical microbiology laboratories (Lockhart et al., 2017a).

Real-Time PCR Assay for Identification of Mutations in *C. auris ERG11* and *FKS1* Genes

Recently, highly accurate real-time PCR diagnostic platform was developed for rapid identification of mutations in *C. auris ERG11* and *FKS1* genes, conferring azole and echinocandin resistance, respectively. Analysis of melting profiles of molecular beacons, small stem-loop-structured DNA oligonucleotides, was used in conjunction with asymmetric PCR. Since a single-stranded amplicon is generated during asymmetric PCR, the molecular beacon can anneal and generate fluorescence at low temperature. Later, the temperature is increased, and the probe slowly dissociates from the target, which results in the fluorescence intensity decrease. Melting curve analysis (a plot of the fluorescence intensity changes as a function of temperature) enables determination of temperature at which the molecular beacon-target DNA hybrids melt apart (T_m). The T_m value is different in a situation when the target and the probe sequences match perfectly and when they are mismatched, thereby providing an ideal tool for typing single-nucleotide polymorphisms e.g., wild-type (WT)/non-WT discrimination (Zhao et al., 2016).

A duplex *ERG11* assay and a simplex *FKS1* HS1 assay were developed to identify the most prominent resistance-associated mutations (Y132F and K143R in *ERG11*; S639F in *FKS1* HS1) within 2 h. The molecular diagnostic results from the assays were 100% concordant with DNA sequencing results. Advantages of the assays include easy interpretation of the results since the testing strain can be easily identified by comparing the T_m value with those generated by reference strains representing WT and mutant target region; multiplex potential by combining several probes; and expandable readiness for novel/unreported mutation detection, because the assay will be able to pick up a novel mutation by simply incorporating the corresponding genotype into the library without the need for assay redesign (Hou et al., 2019).

This platform may potentially be used for direct detection of *C. auris* antifungal drug resistance markers in clinical swabs, dramatically reducing the time needed to obtain information on isolate susceptibility. Thus, it has the potential to overcome the deficiencies of existing *in vitro* susceptibility-based assays to identify azole- and/or echinocandin-resistant *C. auris* and holds promise as a surrogate diagnostic method to direct antifungal therapy more effectively.

CONCLUSION

Efforts to control *C. auris* have posed multiple challenges that include developing and evaluating new diagnostics, understanding its epidemiology, and identifying means to minimize transmission among patients. With emergence of less common fungal opportunists, newly described species, and species that can exhibit antifungal resistance mechanisms, one must take care to not blindly accept results from commonly available methods. New molecular methods used in tandem with classical methods give the diagnostician a broad and ever-increasing armamentarium at their disposal to provide the clinician with the most reliable information to ensure the best possible patient care and outcome.

AUTHOR CONTRIBUTIONS

MK contributed to the conceptualization and writing the original draft of the manuscript. DP contributed to the reviewing and editing of the manuscript.

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The remaining author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.