



Candida auris: an Emerging Fungal Pathogen

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ABSTRACT *Candida auris* has emerged globally as a multidrug-resistant health care-associated fungal pathogen. Recent reports highlight ongoing challenges due to organism misidentification, high rates of antifungal drug resistance, and significant patient mortality. The predilection for transmission within and between health care facilities possibly promoted by virulence factors that facilitate skin colonization and environmental persistence is unique among *Candida* species. This minireview details the global emergence of *C. auris* and discusses issues relevant to clinical microbiology laboratories, hospital infection control, and antimicrobial stewardship efforts.

KEYWORDS antifungal susceptibility, *Candida auris*, epidemiology, infection control

Candida bloodstream infections (BSIs) are the third to fourth most common cause of health care-associated BSIs (1, 2). *Candida albicans* has historically been considered the most pathogenic species in the genus and remains the most common cause of candidemia. In 2009, a new fluconazole-resistant species, *Candida auris*, was identified in East Asia and has now been isolated on five continents. This global emergence has been attributed to the near-simultaneous appearance of at least 4 geographically restricted clades, with clonal transmission identified both within and across health care facilities. *C. auris* can be challenging to identify in the clinical laboratory, and this species frequently exhibits multidrug resistance. Alarming, invasive infections have been difficult to treat and are associated with high rates of treatment failure. This minireview summarizes what is currently known about *C. auris* infection epidemiology, pathogenesis, diagnosis, and management.

EPIDEMIOLOGY

C. auris was first isolated in 2009 from the external ear canal of a patient in Japan, with ribosomal DNA (rDNA) sequencing and biochemical analyses indicating identification of a novel *Candida* species (3). *C. auris* was subsequently reported the same year from 15 patients with chronic otitis media in South Korea (4). The first three cases of *C. auris* bloodstream infection (BSI) were also reported in South Korea in 2011 (5). A retrospective review of South Korean *Candida* isolates, however, showed that the earliest strain of *C. auris* actually dated back to 1996 and was identified from a BSI in a child (4). The majority of the South Korean isolates displayed elevated fluconazole MICs, which suggested that this new species is largely resistant to fluconazole.

Ensuing reports of *C. auris* infections have come from multiple countries around the world, including India, South Africa, Kuwait, Malaysia, the United Kingdom, Pakistan, Kenya, Norway, Germany, Oman, Spain, Israel, Venezuela, Columbia, Panama, Brazil, the United States, and Canada (6–18). The U.S. Centers for Disease Control and Prevention (CDC) continues to map new case reports and transmission globally (<https://www.cdc.gov/fungal/diseases/candidiasis/tracking-c-auris.html>). Given the flurry of recent reports, a review of >15,000 *Candida* isolates deposited in the international SENTRY repository was conducted to look for previously misidentified strains (12). SENTRY

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began cataloguing *Candida* isolates in 2004, yet only 4 previously misidentified *C. auris* cultures were found in the search, implying that this pathogen has recently emerged.

Clinical *C. auris* isolates have been recovered from a variety of specimen types, including normally sterile body fluids, respiratory sections, urine, bile, tissues, wounds, and mucocutaneous swabs. BSI is the most commonly observed invasive infection, with in-hospital mortality rates reported on the order of 30 to 60% (5, 8, 19). Cases have mainly involved patients with underlying medical comorbidities and significant health care exposure, with infection typically occurring weeks after hospital admission. Overlapping contact with long-term-care facilities or acute-care hospitals in the same geographic region was also common among cases (18, 20). In a recent report from India, the risk for the development of *C. auris* BSI compared to other *Candida* spp. was associated with longer intensive care unit (ICU) stays, underlying respiratory illness, vascular surgery, prior antifungal drug exposure, and lower acute physiology and chronic health evaluation II (APACHE II) scores (21). The majority of the *C. auris* isolates in this study were clonal and came from public hospitals in the northern portion of the country.

Beginning in 2016, the CDC, the European Centre for Disease Prevention and Control (ECDC), and Public Health England, among others, released a series of alerts to inform clinicians, laboratorians, infection prevention practitioners, and public health officials about the emerging health threat posed by *C. auris* and to request that all cases be reported to local, state, or national health departments (see <https://www.cdc.gov/fungal/diseases/candidiasis/c-auris-alert-09-17.html>, https://ecdc.europa.eu/sites/portal/files/media/en/publications/Publications/Candida-in-healthcare-settings_19-Dec-2016.pdf, and <https://www.gov.uk/government/publications/candida-auris-emergence-in-england>). As of September 2017, a total of 127 confirmed and 27 probable cases from 10 states have been reported to the CDC. New York and New Jersey have identified the majority of the confirmed cases, reporting 86 and 26, respectively (<https://www.cdc.gov/fungal/diseases/candidiasis/tracking-c-auris.html>). Increased numbers of isolates from the New Jersey and New York area are possibly related to population density, geographic health care facility interconnectedness, and/or heightened surveillance efforts. Whole-genome sequencing (WGS) analysis with comparison to previously identified international strains found that isolates within reporting states were highly related (18). Investigation of the first isolates from New York found that they were similar to isolates from South Asia, New Jersey isolates were also similar to South Asian isolates but distinct from those identified in New York, and isolates from Illinois were grouped with isolates from South America. Available epidemiologic information suggested that many of these infections were acquired in the United States. Additionally, three of the four existing lineages have been detected in the United Kingdom (7). The observation that different clonal lineages are now distributed over large geographic distances supports the idea of multiple independent introductions of *C. auris* into the United States and U.K., with subsequent local spread.

MICROBIOLOGY

C. auris isolates have been analyzed using a variety of laboratory methods in an attempt to (i) establish phylogenetic relationships with other pathogenic yeasts, (ii) evaluate potential relatedness across strains, (iii) determine virulence, and (iv) characterize antifungal susceptibility profiles.

TAXONOMY

rDNA sequencing of the 26S D1/D2 and 18S internal transcribed spacer (ITS) regions placed the initial Japanese isolate within the Metschnikowiaceae family, most closely related to species of the *Clavispora* clade (3, 22). D1/D2 sequences from the initial isolate clustered most closely with *Candida haemulonii*, *Candida pseudohaemulonii*, and *Candida ruelliae* (85.7, 83.0%, and 82.4% similarity, respectively), and the ITS 1/2 region most closely matched *C. haemulonii*, *C. pseudohaemulonii*, and *C. heveicola* (87.5, 81.4, and 81.3% sequence similarity, respectively). A phylogenetic tree based on ITS 1/2 and

D1/D2 sequences deposited in publically available databases illustrates the position of *C. auris* within the *Clavispora/Candida* clade (Fig. 1).

C. auris isolates from India, South Africa, Brazil, and/or South Korea have also been analyzed with classical typing methods, including pulsed-field gel electrophoresis, M13 phage typing, multilocus sequence typing (MLST), and/or amplified fragment length polymorphism (AFLP) fingerprinting (10, 23–25). These were the first studies to suggest geographical strain clustering, but the inherently low discriminatory power of traditional molecular typing methods precluded comparisons of relatedness among isolates with identical fingerprints.

WGS has also been applied to an international collection of isolates in an effort to better assess the relatedness to other *Candida* species and evaluate clonality among strains (12, 26). The assembled *C. auris* genome is diploid and has a size range between 12.3 and 12.5 Mb, a G+C content of 44.5 to 44.8%, and approximately 6,600 to 8,300 coding sequences (27, 28). Draft genome comparisons revealed that the majority ($\geq 99.5\%$) of *C. auris* genomic reads did not align with previously sequenced *C. albicans*, *Candida glabrata*, *Candida lusitanae*, and *Saccharomyces cerevisiae* strains, which suggests that *C. auris* is highly divergent at the whole-genome level (27). However, compared to each other, *C. auris* isolates can be grouped into geographic-specific clusters, with unique South Asian (India and Pakistan), South African, South American (Venezuela), and East Asian (Japan) clades identified. Each of the 4 geographically distinct clades was separated by tens of thousands of single-nucleotide polymorphisms (SNPs), while the isolates that grouped within each geospatial clade appeared to be clonal (12).

Matrix-assisted laser desorption ionization–time of flight mass spectrometry (MALDI TOF MS) has also been used to examine strain relatedness. Protein profiling with cluster analysis also showed evidence of geographically distinct groups, but this did not correlate perfectly with the results of standard genotyping methods (24). It should be noted that MALDI TOF MS has not necessarily been validated or optimized as a tool for strain typing and is limited in the number of proteins that can be detected for strain characterization relative to higher-resolution MS methods.

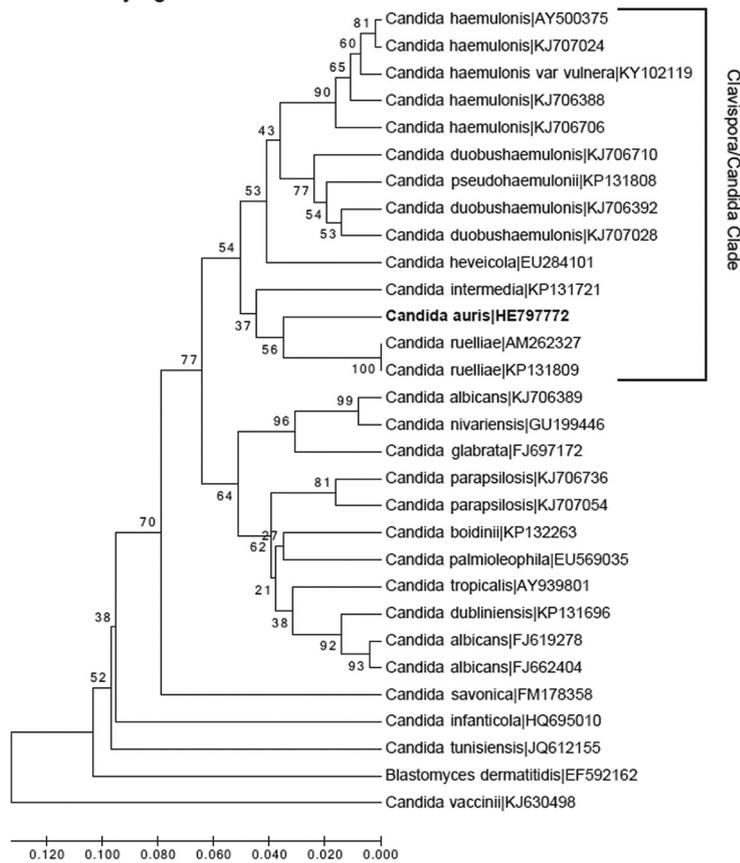
VIRULENCE FACTORS

Several studies have been conducted to characterize *C. auris* virulence determinants. Germination, adherence, biofilm formation, phospholipase, and proteinase production are all known to contribute to *Candida* pathogenesis (27). *C. auris* does not appear to form germ tubes, pseudohyphae, or chlamydospores *in vitro* (5, 9, 28) but may produce phospholipase and proteinase in a strain-dependent manner (29, 30). Although *C. auris* is able to adhere to plastics and form biofilms, these capabilities are significantly reduced relative to those of *C. albicans* (30, 31). An additional intriguing observation is that some *C. auris* isolates grow in clumps (i.e., budding occurs but daughter cells are not released), which results in large aggregates of organisms that cannot be easily disrupted *in vitro* (28). In the *Galleria mellonella* insect model, aggregate-forming strains were found to be significantly less pathogenic than nonaggregating isolates (28). Interestingly, the most virulent nonaggregative forms exhibited pathogenicity on par with *C. albicans*, despite the fact they did not form hyphal or pseudohyphal elements in *G. mellonella* larvae. In a murine model of hematogenous disseminated candidiasis, *C. auris* cell aggregates were also observed in the kidneys of infected animals compared to the invasive hyphal forms of *C. albicans* (6). Additionally, inoculation with *C. auris* was associated with longer median survival than with *C. albicans* (6). Whether these growth characteristics affect the course of infection in other animal models or humans is not known.

IDENTIFICATION IN THE CLINICAL LABORATORY

Candida isolates from normally sterile body sites should be identified to the species level in order to guide initial therapy based on predictable species-specific susceptibility. Additionally, the CDC recommends considering identifying *Candida* isolates from

A. ITS 1/2 Phylogenetic Tree



B. D1/D2 Phylogenetic Tree

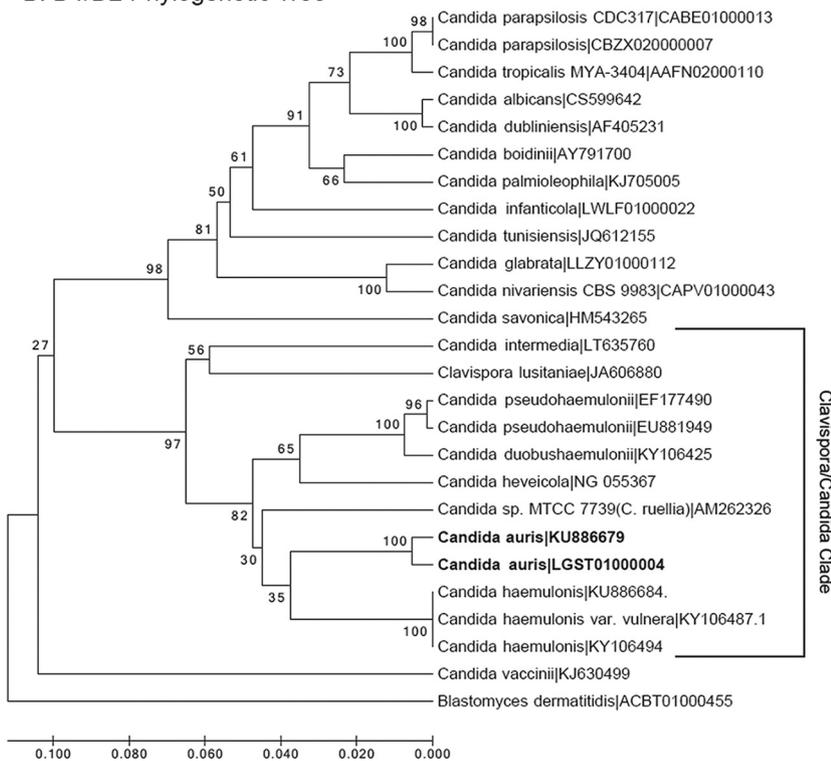


FIG 1 Dendrograms of *Candida auris* with other *Candida* species. Trimmed internal transcribed spacer 1/2 (A) and the long subunit (LSU) D1/D2 sequences (B) were aligned using MEGA7 software. The same (Continued on next page)

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TABLE 1 Common *Candida auris* misidentifications by commercial biochemical test method^a

Biochemical method	Misidentification
All methods	<i>Candida haemulonii</i> <i>Candida</i> spp. not otherwise specified
API 20C AUX	<i>Candida sake</i> <i>Rhodotorula glutinis</i> ^b
BD Phoenix	<i>Candida catenulata</i>
MicroScan	<i>Candida catenulata</i> <i>Candida famata</i> <i>Candida guilliermondii</i> ^c <i>Candida lusitaniae</i> ^c <i>Candida parapsilosis</i> ^c
Vitek2	<i>Candida duobushaemulonii</i> <i>Candida famata</i>

^aAdapted from <https://www.cdc.gov/fungal/diseases/candidiasis/recommendations.html>.

^bWhen the characteristic red/pink pigment is absent and urease reaction is negative.

^cWhen no blastoconidia/pseudohyphae are present on cornmeal agar.

nonsterile sites in select situations, such as when a case of *C. auris* has been identified in a health care facility or when a patient has health care exposure in a location outside the United States where *C. auris* has been reported. Laboratories should also review past records to identify confirmed or suspected cases as well as conduct prospective surveillance. However, accurate identification of *C. auris* infection in the clinical laboratory can be problematic especially when relying on phenotypic characteristics.

PHENOTYPIC CHARACTERISTICS

C. auris strains have been described as nondescript white- to cream-colored colonies on Sabouraud dextrose agar (SDA) and pink to beige on CHROMagar. They form ovoid to elongated budding yeast cells without pseudohyphae on corn meal or rice Tween 80 agar, grow well at 37°C and 42°C, and assimilate *N*-acetylglucosamine, succinate, and gluconate (3, 32). In contrast, *C. haemulonii* and *C. duobushaemulonii* strains produce pseudohyphae, do not grow well at 42°C, and do not assimilate the same sugars. Based on these observations, a small study proposed using temperature tolerance and CHROMagar supplemented with Pal's medium as a means to morphologically separate *C. auris* from members of the closely related *C. haemulonii* complex (33).

BIOCHEMICAL METHODS

Misidentifications of *C. auris* as other *Candida* species by commercial biochemical methods have been widely reported, likely because of a lack of representative organisms in currently available databases. Clinical laboratories should be especially alert to the possibility of *C. auris* when an isolate is identified by biochemical methods as *C. haemulonii*. Table 1 summarizes possible *C. auris* misidentifications grouped by identification method.

MALDI-TOF MS

MALDI-TOF MS is a potentially accurate and rapid method for the identification *C. auris* from pure culture. However, current FDA-cleared libraries for use with the MALDI

FIG 1 Legend (Continued)

software was used to draw the bootstrap (500 replicates) unweighted pair group method using average linkages (UPGMA) dendrograms constructed using a Kimura 2-parameter genetic distances model. Also of note, *C. haemulonii* (synonym *C. haemulonis*) is now considered a species complex composed of two species and one variety: *C. haemulonii sensu stricto*, *C. duobushaemulonii*, and *C. haemulonis* var. *vulnera* (45), and *Clavispora lusitaniae* is the current name for *Candida lusitaniae*. Accession numbers are shown to the right of the organism names.

Biotyper (Bruker, Billerica, MA) and Vitek MS (bioMérieux, Marcy l'Etoile, France) platforms do not include *C. auris* reference spectra. Identification requires the research use only (RUO) databases for these instruments or, alternatively, the creation of custom libraries. *C. auris* was added to the MALDI Biotyper RUO library in 2013 (database version 5627 and later). The Saramis version 4.14 RUO database with the Saccharomycetaceae patch is required for a higher confidence that *C. auris* will not be missed when using the Vitek MS.

A recent multicenter study evaluated the accuracy of current RUO databases for the identification of *C. auris* versus closely related species (34). Both platforms correctly identified 100% of the test isolates; the Vitek MS accomplished this using the direct on-slide extraction method, whereas the MALDI Biotyper required a separate tube extraction to obtain high-confidence scores. In contrast, another report that included only 2 *C. auris* strains observed that the Bruker RUO system correctly identified both isolates, while the Vitek MS RUO reported "no species ID" calls (35). Supplementation of the Vitek MS RUO database with in-house generated spectra subsequently resulted in both *C. auris* isolates being correctly identified to the species level. The variable Vitek MS RUO results may be related to the RUO database employed. Mizusawa et al. did not specify which Vitek MS RUO database version was used in their study (34), while Grenfell et al. reported running version 4.12, which may be why their two *C. auris* isolates were missed (35).

MOLECULAR METHODS

rDNA sequencing of the 28S D1/D2 region or ITS 1/2 will accurately identify *C. auris* to the species level. Additionally, PCR-based methods have also been developed. Kordalewska et al. designed a real-time PCR assay to detect *C. auris* and to differentiate it from *C. haemulonii*, *C. duobushaemulonii*, or *C. lusitaniae* via melt curve analysis (36). The *C. auris* primers showed excellent selectivity versus common fungal pathogens as well as human DNA, but relatively few members of the *Clavispora* clade known to share similar ITS sequences were evaluated. The development of a PCR-based test is of particular interest, especially because this approach may be useful for patient and environmental screening from swabs or for direct detection from other clinical specimens.

ANTIFUNGAL DRUG RESISTANCE

One of the reasons the emergence of *C. auris* has been so alarming is the potential for these organisms to harbor or develop multidrug resistance. In fact, some isolates have demonstrated elevated MICs to all available drug classes, indicating that treatment options for panresistant isolates would be extremely challenging if not impossible.

PHENOTYPIC SUSCEPTIBILITY

Currently, there are no species-specific antifungal susceptibility breakpoints established for *C. auris*. The isolates tested to date have uniformly displayed elevated fluconazole MICs (i.e., $\geq 16 \mu\text{g/ml}$), along with varied susceptibilities to other azoles, amphotericin, and the echinocandins (9, 12, 24, 30, 32, 37). Table 2 summarizes several of the larger drug susceptibility surveys. Posaconazole followed by isavuconazole have generally been the most potent azoles *in vitro*, and fewer isolates have had elevated amphotericin or echinocandin MICs. Of note, overrepresentation of clonal strains in any one study has the potential to skew susceptibility patterns, and several of the larger reports have included a significant proportion of isolates from India. It should also be recognized that falsely elevated amphotericin and caspofungin MICs have been reported using the Vitek 2 susceptibility test method (13, 32).

MOLECULAR RESISTANCE DETERMINANTS

Molecular mechanisms for azole resistance in *C. albicans* have been well defined and include: overexpression of multidrug transporters, mutations in lanosterol demethylase (encoded by *ERG11*), increased expression of *ERG11*, and an alteration in the sterol

TABLE 2 *Candida auris* antifungal MIC ranges determined by the CLSI broth microdilution reference method

Drug	Tentative ^a resistance breakpoints	MIC range ($\mu\text{g/ml}$) ^b		
		MIC	MIC ₅₀	MIC ₉₀
Fluconazole	≥ 32	0.12 to ≥ 64	≥ 64	≥ 64
Voriconazole	NA	0.032 to 16	0.5 to 2	2 to 8
Itraconazole	NA	0.032 to 2	0.06 to 0.5	0.25 to 1
Posaconazole	NA	0.015 to 16	0.016 to 0.5	0.125 to 2
Isavuconazole	NA	0.015 to 4	0.125 to 0.25	0.5 to 2
Anidulafungin	≥ 4	0.015 to 16	0.125 to 0.5	0.5 to 1
Caspofungin	≥ 2	0.03 to 16	0.25 to 1	1 to 2
Micafungin	≥ 4	0.015 to 8	0.125 to 0.25	0.25 to 2
Amphotericin	≥ 2	0.06 to 8	0.5 to 1	2 to 4

^aTentative breakpoints proposed by the CDC (<https://www.cdc.gov/fungal/diseases/candidiasis/recommendations.html>). NA, the CDC has recommended using fluconazole as a surrogate.

^bMIC ranges were compiled from the references 12, 21, 24, and 37. The total number of isolates is 355.

biosynthesis pathway which results in the replacement of ergosterol by other sterols in the cytoplasmic membrane (encoded by *ERG3*). Additionally, mutations in *Candida FKS* genes result in elevated echinocandin MICs and have been linked to treatment failures. WGS analyses have shown that *ERG3*, *ERG11*, *FKS1*, *FKS2*, and *FKS3* homologs were present as a single copy in the *C. auris* genome and that these loci share 78% to 85% similarity with *C. albicans* and *C. glabrata* genes (26, 38). Additionally, a significant proportion of the *C. auris* genome is predicted to encode ATP-binding cassette (ABC) and major facilitator superfamily (MFS) efflux pumps (26, 38).

Molecular characterization of drug resistance mechanisms in *C. auris* has mostly focused on alterations in the lanosterol demethylase enzyme. Lockhart et al. evaluated *ERG11* sequences in a global collection of 54 *C. auris* isolates and determined that substitutions linked to fluconazole resistance in *C. albicans* were also present in *C. auris*, and these mutations were strongly associated with geographic clades (i.e., F126T in South Africa, Y132F in Venezuela, and Y132F or K143R in India/Pakistan) (12). Ben-Ami et al. also observed increased ABC-type transporter activity in *C. auris* compared to that in *C. glabrata* and *C. haemulonii*, which suggests that efflux pumps may additionally be involved in antifungal drug resistance (6).

TREATMENT

The optimal treatment regimen for *C. auris* has not been defined. Because the majority of *C. auris* isolates identified in the United States have been susceptible to echinocandins, treatment with a drug from this class, along with infectious diseases consultation, is suggested for initial therapy. Alternatively, the treatment of colonization without evidence of active infection is strongly discouraged (<https://www.cdc.gov/fungal/diseases/candidiasis/c-auris-treatment.html>). Close monitoring for treatment failure and the emergence of resistance upon treatment is required. Preventing *C. auris* infection altogether is ideal. Many patients with reported *C. auris* infection or colonization received antecedent broad-spectrum antibiotics and/or antifungals. The implementation of antimicrobial stewardship programs is warranted to minimize unnecessary antibiotic use. Stewardship teams can also assist with rapid case identification, appropriate management, and coordinate with infection prevention to minimize transmission.

INFECTION PREVENTION AND CONTROL

The transmissibility of *C. auris* within hospitals, especially critical-care settings, has been established (17). Although the precise mode of transmission has yet to be defined, spread from the patient or their environment to the hands of health care workers seems highly plausible. Skin or mucosal colonization of affected patients appears to be common, and the organism has been recovered from a variety of patient contact points, such as mattresses, furniture, sinks, and medical equipment (17, 18). *Candida*

spp. can be transferred from environmental surfaces to hands (39, 40), and *C. auris* has been shown to persist on plastics *ex vivo* for at least 14 days, with viability testing indicating that cells are also capable of entering a metabolically active, but nonculturable, state that persisted for 4 weeks (41).

Given the propensity for *C. auris* to cause outbreaks, the CDC has emphasized adherence to good hand hygiene combined with standard and contact precautions, housing of infected patients in private rooms, performance of thorough daily cleaning, and terminal room disinfection with an agent that is effective against *Clostridium difficile* (<https://www.cdc.gov/fungal/diseases/candidiasis/c-auris-infection-control.html#disinfection>). Recent evaluations suggest that nonsporocidal hydrogen peroxide and chlorine-based disinfectants are also effective against *C. auris* (42–44), but the widely used quaternary ammonium products have relatively poor activity (43). Iodine-based skin cleansers and chlorhexidine (depending on the formulation) also have demonstrated effective *C. auris* killing (42, 44). However, patients continued to be colonized with *C. auris* despite daily chlorhexidine washes in a prolonged outbreak setting, potentially as a result of reinfection from the environment or due to reduced chlorhexidine susceptibility (17). Additional work is required to determine the optimal approach to reducing skin colonization.

SUMMARY

C. auris infections continue to be reported across the globe, often with high associated morbidity and mortality. Accurate species-level identification is crucial for case detection and the implementation of appropriate infection prevention measures. Clinical laboratories should have a high suspicion for *C. auris* when certain yeasts (e.g., *C. haemulonii* or *Candida* spp.) are identified by FDA-cleared biochemical or MALDI-TOF MS methods. rDNA sequencing remains the reference method for *C. auris* species-level identification, but RUO MALDI-TOF MS databases and/or well-designed PCR assays are potentially more rapid alternatives. Suspected and confirmed cases should be reported to public health authorities, with antifungal susceptibility testing performed for invasive infections even though there are no established species-specific breakpoints. Based on available MIC data, the echinocandins appear to be the best choice for initial treatment. Partnerships between clinical laboratories, antimicrobial stewardship, and hospital infection prevention and control are essential for optimizing diagnosis and management and curtailing nosocomial spread.

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