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The emerging pathogen *Candida auris*: A focus on the Middle-Eastern countries

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ABSTRACT

Recent emergence of *Candida auris* as a multidrug resistant fungal pathogen, associated with difficult-to-control nosocomial transmission and high mortality, raises serious concerns for public health. Since it was first reported from Japan in 2009, *C. auris* infections have been diagnosed in several countries from all over the world. However, there is a paucity of reported cases from the Middle East. Literature search resulted in finding only six countries (Kuwait, Israel, Oman, KSA, UAE and Iran) reporting *C. auris* infections in the past three years. All patients were adults with several underlying comorbidities. Majority of the cases presented with bloodstream infection with crude mortality rate of 60%. All isolates were misidentified as *C. haemulonii* by commercial systems requiring specialized methods for identification. In vitro antifungal susceptibility testing showed 100% strains to be resistant to fluconazole (MIC 32 ≥ 256 mg/L) while variable resistance against other antifungal agents.

Contents

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Introduction

There is a growing threat of an emerging multidrug-resistant (MDR) pathogenic yeast *Candida auris* being reported from the world over. Although the first ever case where *C. auris* was identified in a culture from external ear canal in Japan in 2009 [1], subsequent molecular analysis of a 1996 bloodstream isolate in Korea revealed it to be *C. auris* [2]. Since it is found to be phenotypically closely related to *Candida lusitaniae, Candida pseudohaemulonii, Candida duobushaemulonii* and *Candida haemulonii*, an increasing number of *Candida* species causing human infections has created a challenge for clinical laboratories to provide reliable and fast identification, especially for closely related species [3,4]. In 2015, there was an outbreak of bloodstream infections (BSI) and positive urine cultures caused by presumed *Saccharomyces* at a hospital in Pakistan. The isolates were identified as *C. auris,* a species of *Candida* not ever been reported from Pakistan before, at the US Centers for Disease Control and Prevention (CDC) [5].

As already documented for *Candida parapsilosis,* there is growing evidence that *C. auris* has the ability to colonize human skin and persist in the hospital environments [6,7], with the propensity for horizontal transmission in healthcare settings [5,6,8–10]. *C. auris* has been reported to cause invasive candidiasis in susceptible patient population especially those with compromised immune system [11] and co-morbidities with very high associated mortalities [12,13]. In recent years, *C. auris* have been reported from several countries causing a range of infections and outbreaks in healthcare facilities [6,14]. Although outbreaks due to *Candida* spp. were considered uncommon, outbreaks of *C. auris* have been reported from Colombia [15], Venezuela [16], Israel [13] and the United Kingdom [7]. The whole-gene sequence (WGS) analysis of clinical isolates of *C. auris* collected from South Asia (India/Pakistan), Africa, South Africa and East Asia (Korea/Japan) has revealed four highly clonal phylogenetic and geographically distinct clades that have emerged independently of one another namely South India, South America, South Africa and East Asia. [5].

Some strains of *C. auris* can be resistant to multiple antifungal classes, severely limiting treatment options and making infection control and prevention guided by rapid detection in healthcare settings essential [11]. In 2016, government agencies in the USA and the UK issued alerts requesting clinicians, laboratory technicians, infection control practitioners, and public health authorities to report isolation of *C. auris* in their patients [17,18] and an interim guideline for the management of *C. auris* in healthcare facilities in South Africa was issued by the National Institute of Communicable diseases, requesting notification of new outbreaks [19].

The CDC speculates that *C. auris* may be prevalent in many other countries, but that these MDR yeast are under reported due to lack of laboratory methods needed for correct identification and susceptibility testing. In this review, we discuss the trends in emergence of *C. auris* in different parts of the world as well as its virulence determinants, drug resistance, epidemiology, associated risk factors, diagnostic challenges, and therapeutic and infection control management with special attention to Middle Eastern countries.

C. auris: microbiological and molecular characteristics

C. auris produces smooth and white to cream-colored colonies on Sabouraud dextrose agar (SDA). CHROMagar Candida medium supplemented with Pal's agar was tested for ability to differentiate *C. auris* from *C. haemulonii* complex. *C. auris* strains may form pink or beige colored smooth colonies at 37 °C while *C. haemulonii* complex produces poor growth of light-pink colonies on CHROMagar Candida [20,21].*C. auris* is able to grow at 42 °C however, the growth is inhibited by Cycloheximide [20].

C. auris yeast cells are oval round-to-ovoid, germ-tube test-negative and do not form chlamydospores [20]. Several studies reported the inability of *C. auris* to produce pseudohyphae [1,20,22]. However, under different growth conditions such as high concentrations of sodium chloride, *C. auris* might produce pseudohyphae [22].

Due to the close genetic relatedness with *C. haemulonii* complex, *C. auris* is commonly misidentified as *C. haemulonii* in clinical laboratories using biochemical methods. *C. auris* can be misidentified as other *Candida* species or other yeast genera when using commercial systems such as API20C (*Rhodotorula glutinis*, *Saccharomyces cerevisae*), Vitek 2 YST (*C. haemulonii*, *C. duobushaemulonii*), BD Phoenix (*C. haemulonii*,*C. catenulate*), and MicroScan (*C. famata*, *C. guilliermondii*,) [23].

Based on the phenotypic and biochemical characteristics of *C. auris*, efforts were made to design novel media to improve detection in clinical samples. Welsh et al. [11] reported the use of two broths culture media designed for screening *C. auris* from clinical and environmental samples with 100% specificity and sensitivity [11]. In addition, recently Vitek 2 system database was updated and the system can yield a correct identification of *C. auris* using the update VITEK® 2. Matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS) can provide correct and rapid identification of C. *auris* when using updated reference database with *C. auris* spectrum included and by using appropriate extraction method. The MALDI-TOF has been used to correctly identify *C. auris* isolates initially misidentified as other *Candida* species by different systems [18]. MALDI-TOF was found to be equally effective as molecular genotypic tool for typing *C. auris* isolates [24].

Molecular technique is currently considered to be the gold-standard for confirmation of the identity and typing of *C. auris* strains. Conventional PCR is used to amplify ITS and or D1/D2 DNA sequences followed by sequencing the amplicons for confirming the identification of *C. auris* [25]. Sequencing of these genetic loci is also used in phylogenetic analysis and provides the ability to discriminate between the geographic clades [1,22]. Specific PCR assays for *C. auris* and *C. auris*-related species showing promising results with rapid and accurate identification have been developed, which use specific primers to amplify fragments of 5.8S, ITS2 and 28S rDNA, and could identify *C.auris, C. duobushaemulonii*, and *C. lusitaniae auris*, *C. duobushaemulonii* and *C. lusitaniae* within 2.5 h [25]. More recently, a TaqMan-based real-time PCR assay targeting the ITS2 region of the ribosomal gene was developed and validated. The assay, with detection limit of 1 CFU/PCR, was evaluated using 365 clinical samples and 258 environmental sponges, yielding positive results with 89% and 100% clinical sensitivity, respectively. The assay also detected DNA from 1% and 12% of swab and sponge samples with culture-negative results, indicating the presence of culture-impaired *C. auris* [26].

T2 Magnetic Resonance (T2MR), system with detection limit of 5 CFU/mL, was evaluated for detection of *C. auris* using a new *C. auris*-specific T2 assay [27]. Evaluation of skin surveillance swab samples which were tested for the presence of *C. auris* showed sensitivity and specificity of 89% and 98%, respectively [27].

Virulence determinants in *C. auris*

There are several studies, which describe the virulence factors in *C. auris*. Generally, germination, adherence, biofilm formation, hemolysin activity, phospholipase and proteinase production have been shown to contribute to *Candida* pathogenesis by causing invasive fungal infection in the host [20,28]. However, many studies have proved that no chlamydospores, pseudohyphae or germ tubes are formed on cornmeal agar or upon incubation of *C. auris* in fetal bovine serum [20]. Borman et al. [22] have shown that hyphae and pseudohyphae formation are important virulent factors in *Candida*, thereby making *C. albicans*, *C. tropicalis*, and rudimentary pseudohyphae-forming pathogen *C. auris* more virulent and pathogenic than non-hyphae and non-pseudohyphae-forming species [22]. Comparing the virulence of *C. auris* to *C. albicans* it has been shown that the former adheres relatively poorly to catheters, thereby suggesting that adherence to catheters may not play a major role in causing invasive *C. auris* infections and persistence in patients and hospitals [2,24]. *C. auris* may present as two different cellular morphologies based on cell aggregation. Borman et al. [22] showed that non-aggregating cells are equally or little less virulent than *C. albicans* [22]. It is evident from experiments in murine infection models that *C. auris* is far less virulent than *C. albicans* as *C. auris* could not effectively infect and disseminate unless the host was immunocompromised and a larger *C. auris* inoculum (3×10^7 yeast cells/animal) was administered [20]. However, this observation was in contrast to experiments, which assessed the pathogenicity of *C. auris* in killing assays performed in the invertebrate *Galleria mellonella* and compared with that of other *Candida* species. Despite showing similar kill kinetics in this model infection with non-aggregative strain of *C. auris* resulted in 100% death rate in *G. mellonella* larvae exhibiting pathogenicity comparable to that of *C. albicans* [22,29]. Although presence of several virulence genes have been delineated in *C. auris* genomes, not all *C. auris* strains express phospholipases and proteinases and even among strains that do express the virulence enzymes, the degree of activity is varied and highly strain-specific. Whereas the *C. auris* biofilms have been found to be relatively thin and composed mainly of yeast cells and very limited extracellular matrix, *C. albicans* produces highly heterogeneous architecture of biofilms with yeast cells and hyphae embedded within the extracellular matrix. However, *C. auris* has the ability to form antifungal-resistant biofilms, against all three main classes of antifungal agents (azoles, polyenes, and echinocandins) and chlorhexidine and hydrogen peroxide, displaying a less susceptible phenotype than *C. albicans* or *C. glabrata* [30,31].

Molecular resistance determinants against antifungal agents

Resistance toazoles

Molecular characterization of resistant strains of *C. auris* has revealed that resistance to azoles is mediated by overexpression of multidrug transporters, point mutations in lanosterol demethylase (encoded by ERG 11) with substitutions of Y132F, K143R, and F126L, increased expression of ERG 11 and an alteration in the sterol biosynthesis pathway, which results in the replacement of ergosterol by other sterols in the cytoplasmic membrane (encoded by ERG 3) [5,30,31]. Substitutions in ERG 11 sequences linked to fluconazole resistance in *C. albicans* have also been reported in *C. auris* in a study by Lockhart et al. [5]. These mutations have been strongly associated with geographic clades (F126T in South Africa, Y132F in Venezuela and Y132F or K143R in India/Pakistan) [5]. Furthermore, a significant proportion of the *C. auris* genome is predicted to encode ATP-binding cassette (ABC) and major facilitator superfamily (MFS) efflux pumps resulting in antifungal drug resistance [30].

Resistance to echinocandins

Mutations in *Candida* FKS 1 gene, encoding echinocandin drug target 1,3-beta-glucan synthase, result in elevated echinocandin MICs and have been linked to treatment failures. A study from India showed that resistance associated with echinocandins in *C. auris* strains had S639F amino acid substitution equivalent to mutation at S645 of the hot-spot 1 of FKS 1 in *C. albicans* [32]. Micafungin has been found to be the most potent echinocandin in MIC testing and, susceptibility testing with micafungin and or FKS 1 sequence analysis is suggested as better indicators for detection of echinocandin resistance in *C. auris* [33].

Resistance to polyenes

Although the underlying mechanism of amphotericin B resistance has not been defined, it has been found to be significantly associated with four newly identified non-synonymous mutations [34]. Furthermore, reported data on antifungal susceptibility tests (AST) demonstrated that commercial systems (Vitek AST-Y507) may detect falsely elevated MICs against amphotericin B [35].

Drug resistance and susceptibility testing

Reports of antifungal susceptibility data from different geographic locations are varied and some *C. auris* strains exhibit elevated MICs for three major classes of antifungal drugs, i.e, azoles, polyenes and echinocandins. In order to determine the resistance the tentative breakpoints suggested by CDC and Arendrup et al. [37] have been used in most of the studies [36,37]. In a study from India, conducted over an eight year period, it has been shown that 90% of *C. auris* strains were resistant to fluconazole (MIC 32 $\geq$ 64 mg/L), 8% to amphotericin B (MIC $\geq$ 2 mg/L), 2.3% to voriconazole (MIC $\geq$ 16 mg/L) and 2% to echinocandins (MIC $\geq$ 8 mg/L) [30]. In contrast, another study from India showed that 45% of *C. auris* strains isolated from candidemia cases exhibited low MICs to fluconazole [38]. Local evolvement of resistance is suggested for variable antifungal susceptibility data from different geographic regions.

Epidemiology

Since the time of its first isolation in Japan, *C. auris* infections have been reported from several countries including South Korea, Malaysia, Kenya, South Africa, India, Pakistan, Colombia, Venezuela, Panama, United States, Canada, China, Russia and Europe [39]. Among 17 countries listed under the Middle East, invasive *C. auris* infections have only been reported from Kuwait [40–42], Israel [13,43], Oman [44,45], Saudi Arabia [46], United Arab Emirates [47] and Iran [48].

However, the real prevalence and epidemiology of *C. auris* remains uncertain. One of the reasons could be inaccurate identification in the laboratories using conventional diagnostic tools. Soon after the first outbreak of *C. auris*, which occurred in a specialized center in London, UK from April 2015 and July 2016, progressive increase in the number of outbreaks, sporadic infec-

tions and colonized cases has been identified causing great concern because of inter- and intra-hospital spread. The prevalence of *C. auris* candidemia was found to range from 5% to 30% [8,9]. Interestingly, investigation of outbreaks of candidemia in Pakistan revealed clonal relatedness to Indian *C. auris* strains as demonstrated by WGS [5]. Based on available epidemiological information, most of the cases that were reported from the United States appeared to be imported from South America and South Asia [5,49]. Sporadic cases and outbreaks have also been reported from African continent, mostly from South Africa and Kenya [50,51]. Some of the *C. auris* isolates in these areas were phylogenetically distinct from India, Pakistan and Venezuela but had sequence similarity with those from the UK [5,52]. One of the reference hospitals in Kenya has reported 38% of candidemia episodes due to *C. auris* over a nearly 3-year period [51].

Although the isolation rate has been found to be higher in male patients (64.76%) in many studies, the differences between male and female *C. auris*-infected patients were marginal in most countries except South Africa where females outnumbered male patients [53]. The number of *C. auris* cases has been soaring in the past few years with most strains being isolated from blood cultures during a period of five years (2012–2017).

Most importantly, it has been observed that patients infected or colonized with *C. auris* invariably present with serious underlying medical conditions such as, diabetes mellitus, sepsis or bloodstream infections, pulmonary diseases, renal pathologies, immunosuppressive conditions, malignancies and cardiovascular diseases. Most of *C. auris* infections are reported in hospitalized patients on prior broad-spectrum antibiotics and with invasive medical devices, urinary catheter, parenteral nutrition, etc. [12,13]. Crude mortality in *C. auris* associated infections has been reported to vary from 33.33% to 100% word-wide [53].

C. auris in the Middle-East

Kuwait

The first case of *C. auris* candidemia was recognized in Kuwait in 2014 [40]. The isolate was identified as *C. haemulonii* by Vitek 2. However, it was later confirmed to be *C. auris* by sequencing of ITS and D1/D2 domains of rDNA. Interestingly, genomic sequencing for these regions revealed 99%–100% shared identity with sequences for corresponding regions of several *C. auris* strains from India [40]. In a recent report from Kuwait, a retrospective study investigated the occurrence of *C. auris* among yeast isolates recovered from diverse clinical samples during a 3.5-year period, in which a total of 280 isolates that formed pink-colored colonies on CHROMagar Candida were subjected to phenotypic and molecular characterization [54]. Of these, 166 were identified as *C. haemulonii* by Vitek 2 Yeast Identification System. For molecular characterization, a simple species-specific PCR was developed for rapid molecular identification of *C. auris* isolates and the results were confirmed by PCR-sequencing of rDNA. PCR amplification of DNA performed with CAURF and CAURR primers confirmed only 158 isolates to be *C. auris*. These strains were isolated from various clinical samples from 56 (31 male and 25 female) patients who were admitted on different wards including ICUs. The patients' age ranged from 13 to 89 years with none being from pediatric age group. Majority (53%) of *C. auris* strains were isolated from patients$\geq$ 65 years of age. Seven of 56 patients remained colonized with *C. auris* for an extended period of time, ranging from 70 days to 11 months. AST data showed that 100% of *C. auris* isolates were resistant to fluconazole (MIC 128 $\geq$ 256 mg/L) while 73.2% isolates were resistant to voriconazole. Resistance to amphotericin B (MIC $\geq$ 2 mg/L) was observed in 23.2% isolates whereas only one isolate was found to be resistant to caspofungin and micafungin (MIC = 4 mg/L) [41]. Yet another study from Kuwait has described the risk factors in 17 patients with invasive *C. auris* infection and antimicrobial susceptibility of the clinical isolates from these patients [42]. Tables 1 and 2 showing patients characteristics, identification methods and susceptibility profile.

Israel

Emergence of *C. auris* as a cause of nosocomial BSI was first reported from Israel in 2017. *C. auris* was identified in the blood cultures of four patients during May-October 2014 at a Tel Aviv center and later another strain was isolated from a candidemia case in 2015 [13]. Conventional methods such as growth characteristics on CHROMagar Candida, the Vitek2 YST ID System and thermotolerance at 42 °C on Sabouraud dextrose agar (SDA) plates were used for phenotypic identification. Sequence-based species identification was performed by amplifying and sequencing ITS and D1/D2 large subunit (LSU) rDNA segments. *C. auris* strains from Israel shared 98.6% and 98.3% similarity of ITS and LSU sequences, respectively with the *C. auris* type strain CBS10913^T. Based on ITS and LSU sequences, it was shown that *C. auris* isolates from Israel were distinct from other isolates from East Asia, Africa, and the Middle East although these shared 98.6%, 96.2% and 96.7% similarity with India clone, South Korea clone and CH1 strain from Kuwait, respectively [13]. Of five *C. auris* isolates, which represented BSI, 3 patients had vascular catheter related candidemia and 2 had primary nosocomial candidemia of unclear origin. Table 1 and 2. AST of these isolates revealed that all *C. auris* strains had fluconazole MICs > 32 mg/L. MICs to other azoles were: itraconazole (MIC_{50} 0.5 mg/L); voriconazole (MIC_{50} 0.5 mg/L); posaconazole (MIC_{50} 0.25 mg/L) while amphotericin B MIC ranged from 1 to 2 mg/L for *C. auris* isolates and low MICs were noted for echinocandins: anidulafungin (MIC 0.03 mg/L), micafungin (MIC 0.12–0.25 mg/L) and caspofungin (MIC 0.5 mg/L). All isolates except one were susceptible to flucytosine [43].

Recently, another report from Israel described nosocomial transmission of *C. auris* infection [43]. Environmental contamination has been linked to *C. auris* spread within medical facilities. Also, international travel is being increasingly recognized as a risk factor for infection and dissemination with drug-resistant pathogens. The wide genetic variability between country-specific clades allows the use of rDNA typing as a tool for identifying the geographic footprint of the specific *C. auris* isolates.

Oman

Two cases of candidemia due to *C. auris* were reported from Oman in 2017. In both the cases, the blood culture samples yielded growth of yeast, which was identified as *C. haemulonii* by API20C-AUX. The two isolates of *C. auris* were maintained on slants of glucose-yeast-peptone agar (GYPA), incubated at 25 °C and deposited in the reference collection of the CBS-KNAW Westerdijk Fungal Biodiversity Institute, Utrecht, Netherlands. Further confirmation of the species was performed by MALDI-TOF and the strains were identified as *C.auris*. PCR for ITS and LSU partial genes revealed that both genes possessed enough polymorphism, and therefore, proved to be excellent markers with 99–100% accuracy for the identification of *C. auris* [44]. The ITS phylogenetic analyses showed that the reported clinical isolates were found to be identical to many other clinical strains of *C. auris* from all over the world. Amplified fragment length polymorphism (AFLP) typing of *C.auris* isolates showed that while one isolate nested within the Indian cluster, the other nested within the UK cluster.

Also, between December 2016 and February 2017, five patients admitted to a hospital in Oman developed candidemia due to *Candida* species that were phenotypically identified as *C. haemu-*

Table 1
Demographic and clinical characteristics of patients from the Middle East infected with *C. auris*.

Country	Report	No. of patients	Age (yr.)	Gender	Admission	Counts & infections	Hospital days to candidemia	Treatment	Outcome
Kuwait	Emara M et al. [40]	1	27	F	ICU	Lobar pneumonia, RF, Ciliary dyskinesia BS-abx	12	LAMB	died
	Khan et al. [41]	56	13–89	31 M25 F	ICU/ Other wards	–	–	–	–
	Khan et al. [42]	15	33–82	9M 6F		ulcerative colitis, TPN, GI surgery, HIV, CA colon, CA prostate, DM, hypertension	5-94	Fluconazole, Voriconazole, LAMB alone or various combinations	9 died (*1 received no Rx and survived)
Israel	Ben-Ami et al. [13]	5	42–91	3 M 2F	Medical unit Neurology	CVA, VAP, HBV, HCV, IHD, DM, PVD	?	Fluconazole Anidulafungin Voriconazole	2 died
	Belkin et al. [43]	1	25	M	ICU	ARDS,VAP,BS-abx, caspofungin		Ampho B	survived
Oman	Al-siyabi et al. [45]	5	31–71	3 M 2 F	ICU (4)	DM, CVA, obstructive uropathy, CMV, pneumonitis, SLE, CKD, Acute limb ischemia, kidney transplant, CA	(29-62) Median 42	Anidulafungin	3 died
	Mohsin et al. [44]	2	70–77	1 M 1 F	ICU	Hypertension, DM, CHF, CKD, mechanical ventilation, BS-abx	22-33	Anidulafungin, Caspofungin	11 died
Saudi Arabia	Abdalhamid et al. [46]	3	28–53	3 F	ICU	DM, hypertension, CHF, acute pancreatitis, empyema, lupus nephritis, CVC, BS-abx	12-91	LAMB + Micafungin, Anidulafungin	1died
United Arab Emirates	Alatoom et al. [47]	1	84	F	ICU/ other ward	CRF, chronic atrial fibrillation, hypertension	90	Caspofungin, Ampho B	died
Iran	Abastabar et al. [48]	1	14	F	Outpatient (otomycosis)	–	–	Topical nystatin	survived

Ampho B, conventional amphotericin B; BS-abx, broad- spectrum antibiotics; DM, diabetes mellitus; GIT, gastrointestinal tract; CVC, central venous catheter; VAP, ventilator assonated pneumonia; IHD, ischemic heart disease; PVD, peripheral vascular disease; ARDS, adult respiratory distress syndrome; CVA, cerebrovascular accident; CMV, cytomegalovirus, SLE, Systemic lupus erythematosus; CKD, Chronic kidney disease; CRF, chronic renal failure; RF, Renal failure LAMB, liposomal amphotericin B.

lonii using Yeast ID panels of the automated identification system (Phoenix, BD Diagnostics, USA). However, all five strains were confirmed to be *C. auris* by MALDI-TOF at a reference laboratory in Bristol, UK [45]. All five patients had serious underlying comorbidities including prolonged hospital stay, extensive and prolonged antimicrobial exposure and invasive interventions predisposing them to healthcare associated infections. Patient's characteristics and susceptibility profile are in Tables 1 and 2. In these cases *C. auris* added a new dimension to the already existent MDR pathogens acquired in the hospital. The mortality rate in these cases was alarmingly high, with 30-day all- cause mortality reported to be 60%. Since genomic studies were not conducted, it was not possible to describe the virulence of the *C. auris* isolates or any specific clades these strains belonged to. The time from hospital admission to onset of *C. auris* candidemia was 4–9 weeks, with a median of approximately 6 weeks, highlighting the likelihood of *C. auris* as a true opportunistic healthcare associated pathogen. AST revealed high MICs to fluconazole (128 ≥ 256 mg/L) and voriconazole (0.5–2 mg/L) while MICs to other azoles, posaconazole and itraconazole were low (0.06–0.25 mg/L) as also to amphotericin B (1–2 mg/L) and echinocandins (anidulafungin, caspofungin, and micafungin) (0.06–0.12 mg/L) [45].

Saudi Arabia

The first report of *C. auris* infections from Saudi Arabia appeared in 2018 [46]. The 3 cases were admitted to adult ICU at two different city hospitals (Dammam and Riyadh) during a period between December 2017 and February 2018. There was no history of travel in the preceding 6 months in any of the patients. Contrary to the observation in other countries, all the 3 patients were of female gender. Nevertheless, they presented with multiple co-morbidities including diabetes mellitus, hypertension, chronic heart failure, acute pancreatitis, empyema, and lupus nephritis. Also, they had surgical procedures done, central venous catheters in situ and were on antibacterial coverage at the time of *C. auris* isolation. The blood cultures from 2 patients in Dammam and pleural tissue from patient in Riyadh yielded growth of a yeast, which was identified as *C. haemulonii* by Vitek 2 System. However, the ability of these isolates to grow at 42 °C and confirmation of the identification by MALDI-TOF (Bruker Inc., MA, USA) revealed these isolates to be *C. auris*. Furthermore, WGS performed at the CDC, USA, identified these isolates to belong to the South Asian clade. Using YeastOne microdilution broth method (TREK Diagnostica, OH, USA), AST showed that while all 3 strains were resistant to fluconazole with MIC ≥ 64 mg/L, only two had elevated MIC to amphotericin B (MIC = 2 mg/L). However, MICs against other antifungal agents were low, with anidulafungin, micafungin and caspofungin exhibiting MICs of 0.25 mg/L, 0.12 mg/L and 0.12 mg/L, respectively. Other azoles (itraconazole, posaconazole and voriconazole) also showed low MICs, varying from 0.016 to 1 mg/L. All 3 strains were also inhibited by 5-flucytosine at low MICs (≤0.06–0.25 mg/L) [46].

Combination therapy with liposomal amphotericin B plus micafungin was used for patients in Dammam, one of whom died within

Table 2
Antifungal susceptibility results of *C. auris* isolate.46

Country	Report reference	No. of isolate/s	AFST (method)	MIC mg/L (range)									
				FLU	VOR	POS	ISA	ITR	CAS	MYC	ANI	AMB	FLC
Kuwait	Emara et al. [40]	1	E-Test	≥256	0.38				0.064			0.064	
	Khan et al. [41]	56	E-Test	(128–≥256)	(0.064–6)				(0.012–4)	(0.006–4)		(0.047–3)	
	Khan et al. [41]	15	E-Test	>256	0.064–6				0.012–1	0.06–0.5		0.064–3	0.002–0.016
Israel	Ben-Ami et al. [13]	5	MBD	(32–64)	0.5	(0.012–0.5)		0.5	0.5	(0.12–0.25)	0.03	(1–2)	(0. 25–1)
	Belkin et al. [43]	1		R	≥8							≤2	
Oman	Al-Siyabi et al. [45]	5	Yeast One sensititer	(128–>256)	(0.5–2)	(0.06–0.12)		(0.12–0.25)	(0.08-0.12)	(0.06–0.12)			
	Mohsen et al. 2017	2	MBD	≥64	(0.125–1)	(≤0.016–0.063)	(≤0.016–0.125)	(0.031–0.125)		(0.063–0.125)	(0.31–0.125)	(1–2)	
Saudi Arabia	Abdulhamid et al. 2018	3	Yeast One MBD	(64–256)	(0.12–1)	(0.16–0.25)		(0.03–0.25)	0.12	0.12	0.25	(0.5–2)	(≤0.06–0.25)
United Arab Emirates	Alatoon et al. 2018	1			(0.016–1)[a]				(0.016-0.25)[a]			(0.25–1)[a]	
Iran	Abastabar et al. [48]	1	E-test	16	0.125	0.016	0.063	0.063		0.031	0.016	0.5	

AST, antifungal susceptibility test; FLU, fluconazole; VOR, voriconazole; POS, posaconazole; ISA, isavuconazole; ITR, itraconazole; CAS, caspofungin; MYC, micafungin; ANI, Anidulafungin; AMB, amphotericin B; FLC, flucytosine; MBD, microbroth dilution.

[a] Increase in MIC during therapy.

a month of being diagnosed with *C. auris* candidemia. The patient in Riyadh received treatment with anidulafungin and survived yielding a crude mortality rate of 33.33% [46]. Summary of the cases presented in Tables 1 and 2

United Arab Emirates

Persistent candidemia due to *C. auris* in a patient admitted to Cleveland Clinic Abu Dhabi Hospital was reported earlier this year (2018) [47]. The patient, an 84-year-old female, had a protracted hospital stay over 1 year with several co-morbid conditions, such as, chronic renal failure on hemodialysis, severe psoriasis, chronic atrial fibrillation and hypertension. During her hospitalization she was admitted to ICU repeatedly and developed multiple infections (BSIs, pneumonia, UTIs due to several bacterial and fungal pathogens. In June 2017, 3 months into her hospital stay, her blood culture was positive for *C. haemulonii*, identified by Vitek 2 (software version 7.1, BioMerieux, France). However, the isolate was identified as *C. auris* by MALDI-TOF at the reference laboratory in the USA. During the repeated isolation of the organism from blood the AST showed rising MICs to amphotericin B (from 0.25 mg/L to 1 mg/L), caspofungin (from 0.016 mg/L to 0.25 mg/L) and voriconazole (from 0.016 mg/L to 1 mg/L). After an initial unsuccessful attempt to treat candidemia with caspofungin, therapy was switched to amphotericin B. Although a repeat blood culture after 48 h of therapy was sterile, patient deteriorated over the next month and died 3 months after the first isolation of *C. auris* from blood. The death was attributed to ring-enhancing lesions in the brain. No data on genomic studies were available [47]. Case summary in Table 1 and 2.

Iran

A case of otomycosis due to *C. auris* in a 14-year-old girl was recently reported from Iran [48]. The patient was previously healthy and used to swim regularly in a swimming pool four months prior to the development of her ear complaints. Culture of ear swabs yielded growth of *Candida* species on SDA and CHROMagar Candida, which was later identified as *C. auris* by sequencing the ITS rDNA and MALDI-TOF (score 2.4). However, *C. auris* was not isolated from any other body sites and environmental samples from patient contact areas in the hospital room. AST of the isolate revealed MICs to be: fluconazole, 16 μg/mL; itraconazole 0.063 μg/mL; voriconazole, 0.125 μg/mL; micafungin, 0.031 μg/mL; amphotericin B 0.5 μg/mL; anidulafungin and posaconazole 0.016 μg/mL and isavuconazole 0.063 μg/mL. Treatment with topical nystatin (100,000 units/g) t.i.d and terbinafine 250 mg t.i.d was initiated. With the ongoing therapy patient had failed to show any improvement until her last follow-up. Review of the literature published from 2009 to 2016 showed that otomycosis due to *C. auris* was uncommon with only one case from Japan and 15 cases from Korea reported during that period [54]. However, since 2017, in addition to the case from Iran, several reports of otomycosis due to *C. auris* have appeared from Canada [55], USA [56,57], Switzerland [58], and Austria [59]. *C. auris* isolate from Iran was nested and was found to be closely related to *C. auris* isolates originating from ear samples. The strain was found to be related to Japanese and Korean ear isolates and distinct from isolates of invasive infections and clonal outbreaks.

Management and clinical outcomes

There are no official guidelines for management of *C. auris* infection in terms of an optimal antifungal agent(s) with dosing and duration regimen since CLSI/EUCAST breakpoints for this pathogen are yet to be defined [5,37,60]. Echinocandins remain the first line therapy for *C. auris* infection although resistance to all three main classes of antifungal agents has been reported. However, patients need to be monitored closely for microbiological culture-based reassessment to detect therapeutic failure or development of resistance during therapy [60]. In case of unresponsiveness to echinocandins, liposomal amphotericin B (as single or combination therapy with an echinocandin) is recommended [6,12,24,29,40]. Since good in vitro activity has been reported against itraconazole, posaconazole and isavuconazole these agents may be prescribed in refractory cases. Combination therapy has also been used with success as synergistic interactions have been demonstrated for micafungin and voriconazole.MICs should ideally be measured using the CLSI microbroth dilution protocol to ensure accurate susceptibility results, which can inform correct therapeutic choices [60]. Clinicians should also consider removing CVCs and other catheters where possible as certain studies have found such options useful in resolving persistent candidaemia [2,16,24].

There is an urgent need to expand the antifungal armamentarium, especially in the face of rising incidence and continuous spread of multidrug resistant isolates of *C. auris*. Among some newly investigated compounds SCY-078, a novel triterpene glucan synthase inhibitor, has shown promising in vitro results against *C. auris* [20,61]. It acts by growth inhibition and anti-biofilm activity against *C. auris* isolates being effective against echinocandin-resistant strains. Also, this drug is not affected by common mutations in protein targets and is orally bioavailable. Recently, antifungal properties of theta-defensins, 18-aminoacid macrocyclic peptides have been described with potential for therapeutic treatment for systemic MDR infections [62]. Another compound, APX001 is a broad-spectrum antifungal agent, which is being considered for the treatment of invasive fungal infections caused by species resistant to other antifungal classes. It acts by inhibiting an enzyme (*Gwt 1*), which plays a role in the glycosyl-phosphatidylinositol (GPI) biosynthesis pathway [62]. A novel echinocandin, CD 101 has a prolonged half-life and an improved safety profile, allowing once weekly intravenous administration [63]. In a recent study, encouraging in vitro activity was demonstrated against most *C. auris* isolates, including strains resistant to echinocandins although antifungal therapy is not advisable for colonized patients [64].

Infection control and prevention

Higher rates of treatment failure in patients infected with *C. auris* and persistence of the organism on inanimate objects and the hospital environment is posing a challenge for infection control personnel in all healthcare centers. The major hurdle is the inability to identify *C. auris* accurately by most of the microbiology laboratories all over the world. While in suspected cases the patient must be isolated, contact precautions endorsed and empirical echinocandin therapy initiated while awaiting culture results [12,36,60,64] confirmed cases of *C. auris* infections should be isolated or cohorted under strict contact precautions as recommended by the CDC [36], ECDC [65] and PHE [66]. However, as part of antimicrobial stewardship program unwarranted prophylactic use of broad-spectrum antibiotics and antifungal drugs should be discouraged [13,65]. Patients or healthcare workers coming in close contact with infected persons should also be placed under strict contact precautions until they consistently provide negative cultures over 3 weeks [7]. The wards of patients found to be colonized or infected with *C. auris* should be thoroughly disinfected as described [7]. Besides culture-based methods in surveillance studies, esterase activity as measured by a solid-phase cytometer should be considered to enhance the detection of viable but non-culturable strains [11]. Hospital wards, bedding materials, beds, invasive and noninvasive medical devices, clothing of patients, skin and surface wounds etc. should be decontaminated, using chlorine-based

detergents such as chlorhexidine (0.2%–4%) and hydrogen peroxide vapor [7,29]. As well, chlorhexidine-impregnated protective discs for all CVC exit sites can aid reduce line-associated *C. auris* BSIs [7]. Chlorhexidine washes, oral nystatin and nasal ointments for 5 days have proved effective in decolonizing healthy nasal carriers [7]. Soap and hand washing followed by alcohol-based hand sanitizer is recommended by PHE [66]. Admission screening of patients from infected sites or areas, active surveillance to identify carriers and prompt notification of the clinical infection control team are important [65].

Conclusions

Unless efficient identification tools such as MALDI-TOF, PCR and WGS are made available in diagnostic laboratories, especially in low resource countries, it would be impossible to determine the true prevalence of *C. auris* infections occurring worldwide. In the Mid-East, *C. auris* has been reported from only six countries. Since genomic studies were lacking from some countries it was not possible to ascertain their similarity with *C. auris* clades from other geographic areas. Resistance to several antifungal agents and persistence in the hospital environment make this organism a potential menace for the treating physician and the infection control personnel. Discovery of a few novel compounds with robust antifungal activity, especially against *C. auris* may help in controlling the infections due to this organism.

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