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Candida auris—the growing menace to global health

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Summary

A paradigm shift of candidiasis from *Candida albicans* to non-albicans *Candida* species has fundamentally increased with the advent of *C. auris*. *C. auris*, despite being a newly emerged multidrug-resistant fungal pathogen, is associated with severe invasive infections and outbreaks with high mortality rates. Initially reported from Japan in 2009, *C. auris* have now been found in different countries on all the continents except Antarctica. Due to its capability of nosocomial transmission and forming adherent biofilms on clinically important substrates, a high number of related hospital outbreaks have been reported worldwide. As *C. auris* is a multidrug-resistant pathogen and is prone to misidentification by available conventional methods, it becomes difficult to detect and manage *C. auris* infection and also limits the therapeutic options against this deadly pathogen. The emergence of multidrug-resistant *C. auris* advocates and amplifies the vigilance of early diagnosis and appropriate treatment of fungal infections. In this review, we discussed the nine-year-old history of *C. auris*—its trends in global emergence, epidemiological relatedness, isolation, mortality, associated risk factors, virulence factors, drug resistance and susceptibility testing, diagnostic challenges, microbiological characteristics, therapeutic options and infection prevention and control associated with this pathogen.

KEYWORDS
Candida auris, candidemia, epidemiology, multidrug resistance

1 | INTRODUCTION

With ever increasing microbial drug resistance and emergence of new multidrug-resistant (MDR) species, clinicians and microbiologists are battling to control the associated morbidity and mortality rates. Among new MDR species, *C. auris* is an emerging fungal pathogen that causes severe invasive infections, with a crude mortality ranging from 30% to 72%.[1-5] *C. auris* is first isolated and described from an ear canal discharge of a patient in Japan in year 2009[6], and since then it was isolated from the 6 continents of the world.[7] After its description in 2009, first associated invasive infection was recognised from three patients in South Korea in 2011.[8] In comparison with other *Candida* species, which are thought to cause sporadic infection, *C. auris* exhibit a capability for nosocomial transmission.[9] As a result, significant clonal hospital outbreaks were reported from India, Pakistan, Colombia, Panama, Venezuela, United States, South Africa, Spain and United Kingdom.[10,50]

By 2018, cases of *C. auris* infections become widespread across the globe and had been reported from South Korea[8,11], India[12,13], Pakistan[3], Bangladesh[9], Israel[14], Kuwait[15], Oman[16,17], Malaysia[18], China[19], United Arab Emirates[20], Saudi Arabia[21], Iran[22], Singapore[23], Thailand[7], South Africa[3,24], Kenya[25], Spain[26,27], Germany[27], France[27], Austria[28], Norway[27], Belgium[29], United Kingdom[30,31], Switzerland[32], Netherlands[7], Russia[33], USA[34,35], Canada[36], Panama[37], Colombia[38], Venezuela[39] and Australia.[40] It is anticipated that *C. auris* has emerged in other countries also but has remained undetected due to its phenotypical resemblance with *Candida haemulonii*, *Candida famata*, *Candida sake*, *Saccharomyces cerevisiae* and *Rhodotorula glutinis* and is frequently misidentified by commercially available identification systems, such as Vitek-2,

API20 C-AUX and Auxacolor.[41-43] To avoid misidentification of *C. auris* more sophisticated methods, such as Matrix-assisted laser desorption/ionisation-time-of-flight mass spectrometry (MALDI-TOF MS) or molecular identification based on sequencing the internal transcribed spacer (ITS) or D1/D2 region of the 28s ribosomal DNA are used.[41-46] Recently, T2 Biosystems (Lexington, MA) developed a new rapid diagnostic T2 assay specific for the detection of *C. auris*.[47] In addition, early diagnosis of *C. auris* can initiate early and appropriate treatment therapy, which can significantly reduce the mortality rates associated with this pathogen.

The prevalence of *C. auris* and other non-albicans MDR *Candida* species was thought to be over increasing due to the misuse of currently available antifungal drugs with special emphasis on fungistatic drugs, such as fluconazole. On these basis, Antimicrobial Stewardship has been employed which clearly determines the MIC breakpoints to distinguish susceptible and resistant isolates. Despite there is lack of concrete guidelines for these MIC breakpoints in *C. auris* isolates, current distribution is based on previously used Clinical and Laboratory Standards Institute (CLSI) and/or European Committee for Antimicrobial Susceptibility Testing (EUCAST) guidelines set for other *Candida* species. The Centers for Disease Control and Prevention (CDC) and other research groups have already stated high resistance of *C. auris* against fluconazole and variable susceptibility to other azoles.[3,41,48] In addition, *C. auris* has been reported to be resistant to polyenes (approximately 50%), echinocandins (5%-10%) and nearly 50% exhibited simultaneous resistance to two classes of antifungals (azoles and polyenes).[3,41,48] Some strains of *C. auris*, unlike other species of *Candida*, demonstrated higher MICs to all three major classes of antifungal drugs (azoles, echinocandins and polyenes)[3,41,48], and thereby indicating limited treatment options against these multidrug-resistant strains.

Candida auris has been recognised as globally emerging multidrug-resistant fungal pathogen. In June 2016, CDC issued clinical alert to healthcare facilities and provided interim guidelines for clinical management, laboratory testing and infection control. Similarly, World Health Organization (WHO), Pan American Health Organization (PAHO) and South African National Institute of Communicable Diseases (NICD) also issued similar epidemiological alert in 2016.[49,50]

1.1 | Aim of the review article

Given several uncertainties related to *C. auris*, we aim to summarise and provide comprehensive update of *C. auris* published reports available to date. The review covers all important aspects of the pathogen including epidemiology, epidemiological relatedness, healthcare-associated outbreaks, clinical presentation, mortality, risk factors, pathophysiology, drug resistance and susceptibility testing, identification, microbiological characteristics, therapeutic options and infection prevention and control. Therefore, it is anticipated that this review is an excellent critique of all reported findings on this newly emerged fungal pathogen available to date.

1.2 | Study selection

We comprehensively searched and reviewed published work on *C. auris* between January 2009 to November 2018 using the most popular scientific search engines such as PubMed, Scopus and ScienceDirect. Besides these searches, we also consider the reports and updates on *C. auris* from CDC, WHO, Public Health England (PHE), NICD and the European Centres for Disease Control and Prevention (ECDC). The search words "*C. auris*" and "*Candida auris*" were used and all the publications in non-English languages and non- *C. auris* were excluded. The search was performed in duplicate by different individuals for the reproducibility. After deduplication and exclusion, 182 peer-reviewed published articles, case studies, reports and updates from CDC, PHE, WHO, NICD and ECDC up to November 2018 were included. The results were systematically grouped and presented in this review.

2 | GLOBAL EPIDEMIOLOGY AND HEALTHCARE-ASSOCIATED OUTBREAKS

The global prevalence of *C. auris* and the actual frequency of its infection are obscure. This uncertainty is related to its phenotypical resemblance with other *Candida* species and the failure of commercially available diagnostic methods for its early detection, which results in misidentification and that would underestimate the number of *C. auris* cases.[51] In a recent survey conducted by International Antifungal Surveillance Program SENTRY (JMI Laboratories), 15,271 *Candida* isolates collected from 2004 to 2015 in 152 international medical centres in different countries (Asia 41, Europe 50, Latin America 15 and North America 46) were re-tested using DNA sequencing and/or MALDI-TOF. Of all the tested isolates, only 4 isolates were re-identified as *C. auris* (2009, 2013, 2014 and 2015); however, no *C. auris* isolate was detected before 2009. Therefore, it is believed that the prevalence of *C. auris* was very rare before 2009.[3,52] In contradiction, one of the reports by Lee et al[8] a misidentified *Candida* species recovered in 1996 in South Korea was later identified as *C. auris* by molecular identification and this is so far the earliest known *C. auris* strain. In different surveillance studies in five hospitals of South Korea for the *Candida* isolates recovered between 2004 and 2006 and from Pakistan in 2008; misidentified and undetected *Candida* species were later detected as *C. auris*.[3,11] These historical isolates suggest the emergence of *C. auris* before 2009; however, rapid global emergence of *C. auris* has only been reported since 2009.

Candida auris infections are mostly involved in hospitalised patients, which depicts its emergence as an important nosocomial pathogen with significant potential of colonel transmission within hospitals.[42,53,54] The infection usually occurs few weeks posthospital admission with high mortality rates.[55] So far, healthcare-associated outbreaks of *C. auris* have been reported in numerous countries involving six of seven continents, which are briefly described below:

2.1 | Asia

Asia, being the mother of *C. auris*, has been detected in as many as 15 countries in this continent. After confirmation of *C. auris* invasive infection from South Korea in 2011[8], an outbreak from a hospital in India was reported with 15 *C. auris* isolates recovered from 15 different patients. Among these 15 isolates, 13 were earlier reported as *C. haemulonii* but were re-confirmed as *C. auris* by sequencing.[12,13,56] Subsequently, cases of *C. auris* infection from North and South Indian healthcare centres have been reported.[12,13,44,56,57] According to the national survey of ICUs in India, *C. auris* accounted for > 5% of candidemia; however, these figures go up to 30% at individual hospitals.[12,58] In a recent study on 114 *Candida* isolates collected from 2012 to 2017 from the candidemia patients in 165—bedded trauma centre in Delhi, India, 20 isolates (17.5%) were re-identified as *C. auris*. Of these 20 isolates, 15 were misidentified as *C. haemulonii* and 5 as other species. With these figures, *C. auris* was reported as the second most dominant species causing candidemia in these patients.[59]

In 2015, an outbreak in a hospital in Pakistan has been reported where the causative organism was initially reported as *Saccharomyces cerevisiae*; however, later CDC re-confirmed these isolates as *C. auris*.[3] This was the first reporting of *C. auris* cases from Pakistan and after that increased number of cases were reported from this country.

In China, the first reported case of *C. auris* infection is in 2018, isolated from the bronchoalveolar lavage fluid of a 76-year-old hospitalised women with hypertension and nephritic syndrome.[19] Simultaneously, another study reported 35 *C. auris* isolates from 15 patients from a hospital in Shenyang, China. These isolates were collected between January 2011 to October 2017 and were initially misidentified as *C. haemulonii* by Vitek but were later confirmed as *C. auris*.[60] In a recent study by Yong and his co-workers, two new cases of *C. auris* fungemia with different antifungal resistance profiles were detected from a neonatal ICU in Beijing.[61]

Although *C. auris* has been previously identified in Korea, a new case study has reported the role of *C. auris* in causing otomastoiditis.[62] In Singapore, identification of first 3 cases of *C. auris* infection in three different patients from a tertiary care hospital is recently reported.[23]

The first report of *C. auris* involved in mixed candidemia with *C. tropicalis* have been reported from Malaysia in 2018 from the blood of 63-year-old neutropenic patient.[18]

In Israel, six patients suffering from candidemia caused by *C. auris* have been reported from two hospitals in Tel Aviv.[14] These isolates were collected in a gape of one year between May 2014 and April 2015. Phylogenetic analysis based on ITS and LSU sequences showed that these collected isolates are distinct from *C. auris* isolates of East Asia, Africa and Middle East. However, in a different report travel-associated infection of *C. auris* has also been reported from Israel, where *C. auris* was isolated from a 25-year-old man transferred from South Africa with some medical conditions. Upon phylogenetic analysis, the isolate exhibits similitude to South African clade and not with Israeli clade of *C. auris*.[63]

In Kuwait, first case of *C. auris* candidemia was reported in 27-year-old women in May 2014 who was admitted to ICU for chronic renal failure.[15] A comprehensive study on emergence of *C. auris* from Kuwait on 280 clinical yeast isolates (based on the formation of pink-coloured colonies on CHROMagar *Candida*), collected between May 2014 and September 2017, reported that 158 isolates were identified and confirmed as *C. auris* from 56 patients of different clinical specimen.[64] All 158 isolates were initially misidentified as *C. haemulonii* by Vitek-2, but were re-confirmed as *C. auris* by species-specific PCR and PCR sequencing of ITS region of rDNA. In another report by Khan et al[65] invasive cases of *C. auris* including 13 cases of candidemia and four cases of other invasive infections in six different hospitals across Kuwait were reported during 2015 to 2017.

In Oman, two different studies concurrently reported separate *C. auris* fungemia cases from two different hospitals in the year 2017.[16,17] One study reported two cases of *C. auris* candidemia from two patients in a tertiary care hospital in the city of Muscat.[16] In another study, five cases of candidemia caused by *C. auris* at Sultan Qaboos University Hospital Oman, have been reported.[17] All the isolates were detected between August 2015 to February 2017 and were initially misidentified as *C. haemulonii*, but were later confirmed as *C. auris*.[1]

The first case of *C. auris* from United Arab Emirates has been recently reported in 2018 from its capital city Abu Dhabi, when this pathogen was isolated from the blood of an 84-year-old female patient with persistent candidemia.[20]

In Saudi Arabia, first three cases of *C. auris* infection have also been recently reported from two hospitals between December 2017 and February 2018. Initially, these isolates were misidentified as *C. haemulonii*, but later with the help of MALDI-TOF MS all the three isolates were confirmed as *C. auris*. Whole genome sequencing of these isolates revealed that these strains belong to the South Asian Clade.[21]

A case report recently published in Mycoses reported the first case of *C. auris* from Iran isolated from a 14-year-old female with otomycosis.[22]

2.2 | Africa

With the tropical climate of African continent and due to global warming, increasing number of immunocompromised patients and haphazard development, Africa is known as Infectious Disease continent. Surprisingly, so far *C. auris* infections have only been reported from 2 countries in the whole continent. In a recent South Africa national laboratory-based surveillance programme, the earliest confirmed case of *C. auris* infection from South Africa was in 2009.[50] This isolate was initially misidentified as *C. haemulonii*, but later in 2014 was confirmed as *C. auris*. According to this surveillance report, 1692 confirmed or probable cases of *C. auris* have been identified during a period of October 2012 to November 2016 at both public and private hospitals countrywide; however, most of the cases are in private

hospitals in Gauteng Province. Magobo et al[24] detected 4 cases of *C. auris* candidemia in South Africa between October 2012 through October 2013. Subsequently, 10 more isolates were reported in 2017 which were collected between 2012 and 2014.[3] South Africa also witnessed the outbreaks of *C. auris* infections in 2016 from different hospitals, with most cases reported in Johannesburg and Pretoria hospitals. In the same year, *C. auris* was reported as second and fourth most common cause of candidemia in South African private and public-sector hospitals, respectively. By now, *C. auris* accounts for ≈ 1 of every 10 cases of candidemia in South Africa and has now been isolated from ≥ 94 hospitals across the country.[50]

In Kenya, from a single-centre study between September 2010 and June 2013, candidemia attributed to 39% of nosocomial infections, and the most common cause was *C. haemulonii* later reidentified as *C. auris* accounting for 45 (38%) episodes followed by *C. albicans* (27%).[25]

2.3 | Europe

With the global spread of *C. auris* infection, ECDC conducted a survey in the European Union and European Economic Area countries (EU/EEA) on reported cases of *C. auris* and laboratory capacity for *C. auris* detection. This study reported a total of 620 cases of *C. auris* from six different countries [Spain (n = 388), UK (n = 221), Germany (n = 7), France (n = 2), Belgium (n = 1) and Norway (n = 1)] in a period from 2013 to 2017, including four nosocomial outbreaks in Spain and UK.[27] The first case of fungemia by *C. auris* in continental Europe occurred in Spain among four patients, hospitalised in the surgical intensive care unit between April and June 2016.[26] The same group in a separate study reported an outbreak in a Spanish National Public Health Service Hospital during April 2016-January 2017, where all the isolates were reported to have a genotypical connection with South African clade.[5] In another recent study, a single case of *C. auris* was reported from Austria in January 2018, from a 22-year-old man with an infection of external auditory canal.[28] In Switzerland, the first case of *C. auris* has been isolated from tracheal aspirates in a 74-year-old female patient with acute respiratory distress syndrome repatriated from a Spanish hospital.[32] A female patient referred from Kuwait developed a catheter-related fungemia with *C. auris* and was reported as the first case of *C. auris* infection from Belgium.[29]

In England, sporadic cases of *C. auris* infection have been identified since August 2013. The first outbreak of *C. auris* infection in England was reported in Royal Brompton Hospital, a London cardiothoracic centre, between April 2015 and July 2016. In this outbreak, fifty cases of *C. auris* infection were identified.[66] Another outbreak of *C. auris* has been reported from the United Kingdom in neurosciences intensive care unit of the Oxford University Hospitals between February 2015 and August 2017.[67] In this outbreak, a total of 70 patients have been identified as coloniser or infected with the *C. auris*. The whole genome sequencing analysis of these strains confirmed that all these isolates formed a single genetic cluster related to the *C. auris* South African clade.[67] The results from this study also concluded that reusable patient equipment including multiple axillary skin-surface temperature probes may serve as a source of hospital outbreaks.

2.4 | South America

Between March 2012 and July 2013, first *C. auris* outbreak in South America was reported in an ICU of tertiary care hospital in Maracaibo, Venezuela.[39] All these isolates were only confirmed as *C. auris* by sequencing after being initially misidentified as *C. haemulonii*. During this period, *C. auris* were reported as the sixth most common cause of fungemia in tertiary medical centre in Venezuela.[39]

Since 2012, sporadic cases of *C. auris* infection have been reported from various cities of Colombia.[38,68,69] In 2016, an outbreak by *C. auris* was reported in a paediatric intensive care unit in Cartagena, and five cases of disseminated *C. auris* infection were reported. These isolates were previously identified as *C. albicans*, *C. guillermondii* and *Rhodotorula rubra*.[49] Colombian Instituto Nacional de Salud (INS) Surveillance Programme for *C. auris*, recently confirmed and reported 123 *C. auris* cases in Colombia, during February 2015-May 2017. Most of these isolates were previously misidentified and reported as *C. haemulonii* while as confirmed as *C. auris* upon reidentification by MALDI-TOF.[69]

2.5 | North America

In North America, the first seven cases of *C. auris* infection were detected in USA occurring during May 2013-August 2016 (one in 2013, one in 2015 and five in 2016). Six of seven cases were identified through retrospective review of microbiology records from reporting hospitals and reference laboratories.[34] As of 30 November 2018, 493 confirmed and 30 probable cases of *C. auris* infection in the USA have been reported by CDC (CDC 2018). Most of the *C. auris* cases in USA have been reported from the New York City (n = 265), New Jersey (n = 99) and Chicago (n = 108). In a separate report, it has been observed that most of the *C. auris* strains in the USA have been linked to other countries of the world.[70] A molecular epidemiological survey used WGS on 133 *C. auris* cases (73 clinical and 60 screening cases) collected from the ten US states between May 2013 and August 2017. In this survey, it has been reported that all the isolates from the USA were genetically related to one of the four major clades (South America, Africa, East Asian and South Asian), suggesting *C. auris* have been introduced several times in to the USA.[71]

In May 2017, first case of multidrug-resistant *C. auris* has been reported in Canada.[36] In Central America, 14 isolates of *C. auris* from nine hospitalised patients were reported in a hospital in Panama City, Panama.[37] These isolates initially identified as *C. haemulonii* by Vitek-2 automated system were later confirmed as *C. auris* by molecular methods.

2.6 | Australia

Australian continent is the latest to join the list of other continents where *C. auris* infections have been detected. Until the end of 2018, no published data of *C. auris* infection in this continent were

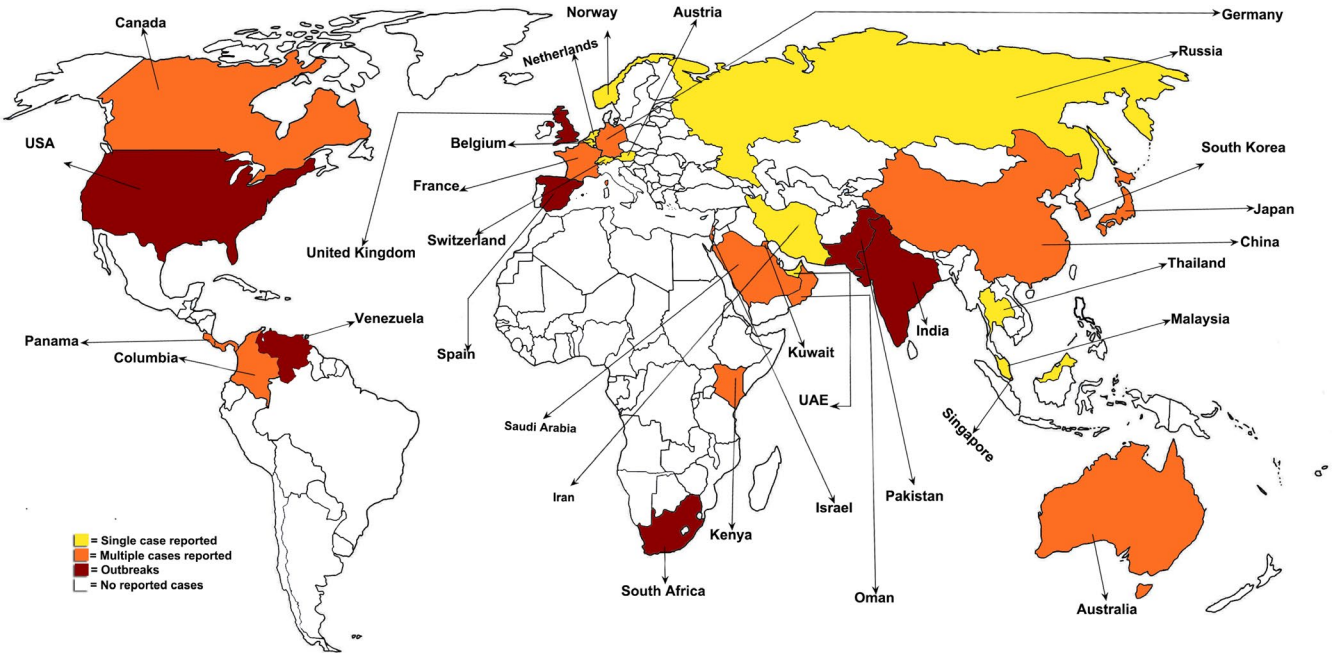

FIGURE 1 Global distribution of *Candida auris* from 2009 to 2018 in 6 continents. Different colour coding highlights single case, multiple cases and outbreaks

reported. However, in a recent report by Heath et al, travel-associated case of *C. auris* infection has been reported from Australia in a 65-year-old male patient with a history of ICU treatment in Kenya in 2012. The patient was diagnosed with chronic *C. auris* sternal osteomyelitis in 2015 in Australia, and the *C. auris* isolate was related to South African clade III.[40]

It is possible that *C. auris* has emerged in other countries also but remain undetected due to lack of special modern laboratory identification techniques, especially in the developing countries. Figure 1 outlines the global prevalence of multidrug-resistant *C. auris* from 2009 to 2018. In this figure, we also highlighted the outbreaks as well as single and multiple cases reported from these countries so far (Figure 1).

3 | EPIDEMIOLOGICAL RELATEDNESS

To determine the genetic relatedness of *C. auris* isolates, whole genome sequencing of 47 *C. auris* isolates comprised exclusively from Pakistan (16), India (15), South Africa (10), Venezuela (5), and Japan (1) during 2012-2015 was performed.[3] The estimated genome size of *C. auris* isolates is 12.3-12.5 Mb like other *Candida* species with a G+C content of 44.53%-44.8%.[72-74] Phylogenetic analysis of isolates recognises four distinct *C. auris* clades that cluster geographically.[3] These clades are East Asia, South Asia, South America and South Africa and differ by tens of thousands of single-nucleotide polymorphisms (SNPs) between the geographic regions. However, within the clades, high degree of relatedness was observed. With different clades from different geographical areas, it is suggested that emergence of *C. auris* in each geographical region is independent and not spread from a single source.[3] A very small percentage of SNPs differences were identified within clusters, for example < 70 SNPs differentiated any two isolates from the South Africa clade while as < 16 SNPs differentiated from South American clade. From South Asian clade, <60 SNPs differentiated 34 of 36 isolates. The only big difference was identified in two isolates from Pakistan, which vary from the rest of the South Asian clades by > 600 SNPs. Furthermore, from a single hospital in Pakistan, two smaller clusters were identified consisted of nearly identical strains (<2 SNPs difference).[3] However, the data also indicate that clonal isolates of *C. auris* are spread over large distance within countries and continents.

In an another study conducted on 104 isolates of *C. auris* collected from there different countries: India (n = 90), South Africa (N = 6) and Brazil (n = 5) along with control strains from Japan (n = 1) and Korea (n = 2) reported the population structure and genetic diversity in *C. auris* using multilocus sequence typing (MLST), MALDI-TOF MS and amplified fragment length polymorphism (AFLP) fingerprinting.[75] M13 PCR fingerprinting and AFLP were identified as the most accurate analytical methods for strain typing and geographical clustering.[44,75] AFLP grouped *C. auris* isolates in to Indian and Latin American cluster. South African isolates were randomly distributed among the clusters.[75] In United Kingdom, rDNA sequencing of 24 *C. auris* isolates from 14 different hospitals, separated the isolates in three different clades belonging to India/Malaysia/Kuwait, Japan/Korea and South Africa.[31]

4 | MICROBIOLOGICAL AND BIOCHEMICAL CHARACTERISTICS

Candida auris is phylogenetically related to *C. haemulonii* in the Metschnikowiaceae clade of *Candida* family.[6] *C. auris* as other

TABLE 1 Misidentification of *Candida auris* by different traditional biochemical yeast identification methods

Identification method	Misidentify *Candida auris* as
API 20C AUX	*Rhodotorula glutinis*
	Candida sake
	Saccharomyces cerevisiae
BD Phoenix	*Candida haemulonii*
	Candida catenulata
Vitek- 2[a]	*Candida haemulonii*
	Candida duobushaemulonii
	Candida famata
	Candida lusitaniae
MicroScan	*Candida famata*
	Candida guilliermondii
	Candida lusitaniae
	Candida parapsilosis
	Candida catenulata
	Candida albicans
	Candida tropicalis
RapID Yeast Plus	*Candida parapsilosis*

Note: This table is based on data from various publications [2,8,12,26,37,38,42,45,57,60,64,77,114].

[a]Update Vitek-2 software (version 8.01) should be able to accurately identify *C. auris* from the rest of the closely related species.

Candida species can grow in different culture media. Up on microscopic examination, the cells are ovoid, ellipsoidal to elongate in shape with a size of 2.0-3.0 × 2.5-5.0 μm and appears in single, pairs or in aggregates.[6,14,30] Unlike other *Candida* species, *C. auris* does not form hyphae, chlamydospore and are germ tube negative.[8,12,76] However, occasional pseudohyphae formation has been found in *C. auris*, suggesting it might be strain or condition specific.[30] It develops pale purple to pink colonies on CHROMagar and grows at 37-42°C, whereas *C. haemulonii* isolates do not grow at 42°C.[14] On Sabouraud dextrose agar (SDA), *C. auris* forms dull white to cream coloured smooth colonies, and on malt extract agar, it grows as butyrous to viscous, white to grey, smooth and glistening colonies.[6,8] *C. auris* cells treated by Gram stain appears as single or paired ovoid to elongated budding yeast cells.[77]

Biochemical features of *C. auris* for the utilisation of nitrogen and carbon sources are distinct from other *Candida* species. It ferments glucose, trehalose (weak), sucrose (weak), but does not ferment maltose, lactose, galactose or raffinose.[6] It assimilates glucose, maltose, D-trehalose, sucrose, D-melezitose, D-raffinase, soluble starch, galactitol, D-mannitol, citrate and sorbitol for carbon source.[1,6] It has been reported that some strains are also able to assimilate N-acetyl-D-glucosamine for carbon source.[12,13,75] The non-assimilated carbon sources are D-galactose, L-sorbose, D-arabinose, D-xylose, melibiose, ribose, lactose, D-cellobiose, L-arabinose, L-rhamnose, D-glucosamine, methanol, glycerol, ethanol, erythritol, salicin, succinate, inositol, α-methyl-D-glucoside, xylitol, hexadecane, DL-lactate, D-gluconate, 2-keto-D-gluconate and N-acetyl-D-glucosamine.[1,6] For the nitrogen sources, ammonium sulphate, cadaverine and L-lysine are utilised but does not utilise sodium nitrate, potassium nitrate and ethylamine.[1,6] *C. auris* does not grow in medium containing 0.1%-0.01% cycloheximide.[6,13,56,58]

These distinct microbiological and biochemical features are important as they can play an important role to develop new media, methods and/or kits for the early and accurate identification of this pathogen.

5 | IDENTIFICATION

For appropriate treatment of any infectious disease, rapid and correct identification of the causing pathogen is important. Same is true for *C. auris*, where timely diagnosis can lead to appropriate antifungal treatment and thereby can help in preventing healthcare-associated outbreaks. Species level identification of *Candida* can help in the appropriate treatment and implementation of effective infection control measures.[78] However, in *C. auris* diagnosis correct identification is a major challenge, as most of the laboratories worldwide use commercially available biochemical-based yeast identification systems such as API- 20C AUX, VITEK-2 YST, BD-Phoenix, MicroScan and Auxacolor (Table 1). These identification systems frequently misidentify *C. auris* with other closely related *Candida* species, because of lack of *C. auris* in their databases.[12,41,42] Depending upon the method used for identification, *C. auris* is frequently misidentify as *Rhodotorula glutinis*, *Candida sake* or *Saccharomyces cerevisiae* by API-20C AUX (BioMeÂrieux), as *C. haemulonii* or *C. famata* by VITEK-2YST VITEK (BioMeÂrieux), as *C. haemulonii* (except for one as *C. catenulata*) by BD-Phoenix (BD Diagnostics), as *C. famata*, *C. lusitaniae* and *C. guilliermondii* or *C. parapsilosis* by MicroScan (Beckman Coulter), and as *Saccharomyces cerevisiae* by Auxacolor (Bio-Rad).[12,42,45] However, an updated Vitek-2 software (version 8.01) should be able to accurately identify *C. auris* from the rest of the closely related species[10] (Table 1).

To facilitate reliable and accurate identification of *C. auris* with 100% sensitivity and specificity VITEK MS (BioMeÂrieux) and Bruker Biotyper (Bruker-Daltonics), MALDI-TOF MS devices using an updated "research-use only" databases can be used.[41,44,75] Molecular methods, such as sequencing of the ITS and D1/D2 regions of the 28S ribosomal DNA, PCR, real-time PCR and AFLP, can also reliably identify and confirm *C. auris*.[41,51,75] PCR assays based on the unique GPI protein encoding and *ITS2* genes have claimed accurate identification of *C. auris*.[79,80] Recently, GPS MONODOSE dtec-qPCR kit (Alicante, Spain) for the detection of *C. auris* have been introduced with many advantages compared to other PCR methods. This kit is user friendly and detects the target in less than an hour.[81]

5.1 | Clinical symptoms and course of infections

Candida auris infection has almost similar clinical presentation as that of the other *Candida* infections.[82] It has been reported to be isolated from multiple body sites with associated clinical conditions,

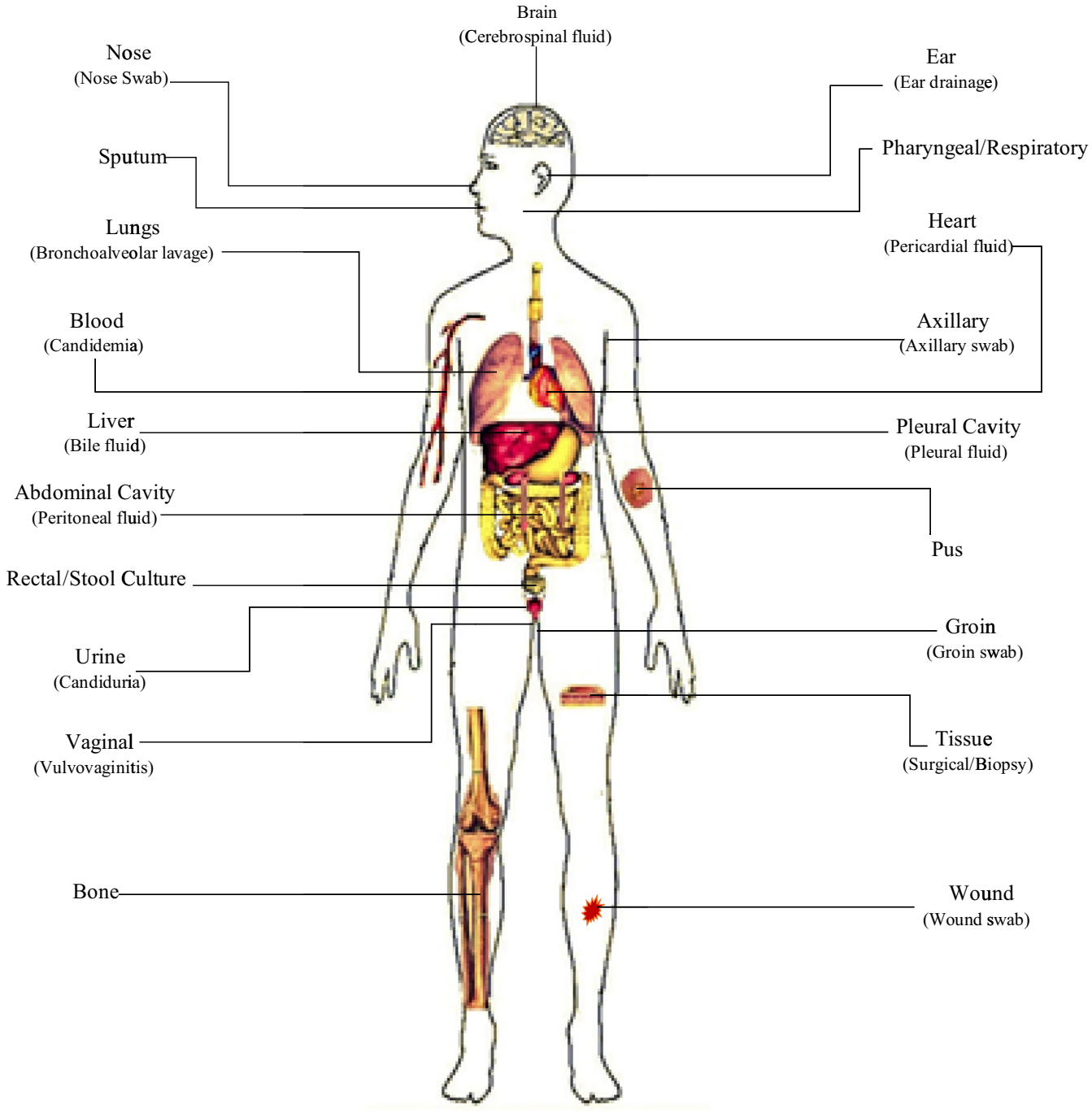

FIGURE 2 Schematic highlighting areas of the human body with distinct anatomical sites of *Candida auris* infection and colonisation

as shown in Figure 2.[56] It was first isolated from the external ear canal of a patient in Japan in 2009, followed by the first report of *C. auris* invasive infection in South Korea in 2011.[6,8] Blood stream infection (fungemia) caused by *C. auris* has been reported almost from all the continents except Antarctica. *C. auris* has been identified and reported as a cause of vulvovaginitis (from vaginal sample) and pericarditis (from last stage liver disease patient) and both these cases were reported from India.[57,83] In another recent study from India, *C. auris* nosocomial cerebrospinal fluid shunt infection was reported in a 58-year-old patient.[84] First donor-derived *C. auris* infection in a lung transplant recipient was also reported in USA in 2017.[76] In Cardio-thoracic Center outbreak in London, persistent presence of *C. auris* has been reported around patient bed-space areas, also a nose swab sample from a healthcare worker was reported positive for *C. auris*.[66] Isolation of *C. auris* has also been reported from urinary tract infections, surgical and burn wound infections, skin abscesses related to insertion catheter, bone infections, meningitis and has been isolated from respiratory tract samples.[13,38,42,56,58] The isolation of *C. auris* from urine, respiratory tract samples, wound and external ear is difficult to differentiate weather these are clinically

invasive disease or just colonisation at those sites.[56] It has been reported that *C. auris* infected patients can be colonised at multiple anatomic sites which includes the groin, axilla, rectum, nose and oropharynx[85] (Figure 2). It has also been documented that colonisation by *C. auris* persists for 1 to 3 months after initial infection.[34]

In addition, *C. auris* were also isolated from samples collected from the bed rails, bedside tables, chairs, mattress, floor around bed sites, windowsills, radiators, equipment monitors and keypads.[34,66] The reason for the survival of *C. auris* on abiotic surfaces is related to the characteristic of this pathogen to survive on plastic surfaces for 14 days, on steel surfaces and contaminated bedding for up to one week.[86-88]

6 | MORTALITY

Invasive infections caused by any species of *Candida* can be fatal; however, the mortality rate associated with *C. auris* infections is comparatively higher than other species. The crude mortality rate from *C. auris* infections has been documented ranging from 30% to 72%.[1-5] Better survival likelihood was seen in the paediatric population and in patients with immediate source control, although majority of infections affect adults.[8,39] Despite these figures, it has not yet been proven whether patients with invasive *C. auris* infections are more likely to die than patients infected with other *Candida* species.[56] An investigation, conducted by CDC on 54 *C. auris* infection cases in five countries, has reported 59% mortality rate, while as only 28% fatality has been reported from *C. auris* outbreak in a Venezuelan hospital involving 18 patients. However, in an outbreak in UK, no death case was reported from 22 involved *C. auris* infection patients. The variation in mortality data is due to the other several underlying medical conditions in these patients, confounding the attributable mortality due to *C. auris*.[12]

6.1 | Risk factors

There are no marked differences between the reported risk factors associated with *C. auris* and other *Candida* species infections.[56] The major *C. auris*-associated risk factors are prolonged hospitalisation, abdominal surgery, diabetes mellitus, admission to intensive care units, severe underlying disease and immunosuppression (such as haematological malignancy, solid tumours, bone marrow transplantation, HIV), chronic kidney disease, use of central venous and urinary catheters, recent surgery, corticosteroid therapy, parenteral nutrition, neutropenia, prior exposure to broad spectrum antibiotics and antifungal therapy.[3,8,13,14,16-18,26,34,38,39,58,66,70,76] *C. auris* has also been reported to cause infections in patients of all ages, from infants to the elderly people.[89]

6.2 | Pathophysiology

The pathogenicity of *C. albicans* and other *Candida* species is well studied; however, the exact cause of pathogenicity in *C. auris* is still being investigated. Pathogenicity of *C. auris* was compared with the other important *Candida* species such as *C. haemulonii*, *C. glabrata* and *C. albicans* in a murine model. The highest pathogenic potential was found with *C. albicans* followed by *C. auris*, *C. glabrata* and *C. haemulonii*.[90] Numerous virulence attributes of *C. auris* resemble with *C. albicans* which includes enzyme secretion, tissue invasion, nutrient acquisition, iron acquisition, histidine kinase—2 component system, multidrug efflux, genes and pathways involved in cell wall modelling and nutrient acquisition.[72-74] Study performed on an isolate of *C. auris* from a case of vulvoginitis showed phospholipase, proteinase and haemolysin activity.[83] In another study, conducted on 16 different *C. auris* isolates collected from different geographical regions showed that phospholipases and proteinases production are strain dependent.[91] Most strains of *C. auris* form biofilms, but lack of biofilm formation in some strains has also been reported.[12,72,91-93]

In vitro studies of *C. auris* isolates showed that isolates can be phenotypically divided into aggregating and non-aggregating strains.[14,30,93] The aggregative strain has the capability to form large aggregates of cells and cannot be physically disrupted, even by vortexing or by detergent treatment.[30] This property of aggregating strain may also promote the survival of *C. auris* isolates in hospital environments. In a study using *Galleria mellonella* infection model, the non-aggregating isolates exhibited more pathogenicity than aggregating isolates and have comparable pathogenicity to *C. albicans*.[30] It has also been reported that non-aggregating strains can be more pathogenic than *C. albicans*.[93] Moreover, non-aggregating isolates formed large number of individual budding yeast cells which exhibited strong biofilm forming ability in comparison with aggregating isolates of *C. auris*.[30,92] Unlike *C. albicans*, where morphological transition from non-pathogenic yeast form to pathogenic hyphae form has been identified as initial step of pathogenesis, no morphological transition has been observed in *C. auris* isolates. In different studies, it has been reported that *C. auris* isolates do not produce hyphae or only produce pseudohyphae under certain conditions.[30,76] However, in a recent study by Yue and his coworkers, a novel phenotypic switching system in *C. auris* has been reported which transits cells in three different cell types—typical yeast, filamentation-competent (FC) yeast and filamentous cells.[94]

C. auris exhibited high thermotolerance (up to 42°C) and has salt tolerant properties, which can promote its survival and pathogenicity.[6,30] A study reported that *C. auris* biofilms were thinner showing only 50% thickness compared to *C. albicans* biofilm, however, and had strong biofilm forming capacity than *C. glabrata*.[2,91] Caspofungin showed no inhibitory activity against biofilms formed by *C. auris*.[91] To fully understand the pathophysiology of *C. auris*, further research is needed to identify other virulence factors and their role in the pathogenesis of *C. auris*.

7 | DRUG RESISTANCE AND SUSCEPTIBILITY TESTING

C. auris isolates has demonstrated multidrug-resistant properties worldwide, which has not been seen in other *Candida* species

before.[56] A collaborative study undertaken by the CDC released a clinical report based on 54 *C. auris* isolates collected from five different countries, which showed that 50 (93%) isolates were resistant to fluconazole, 19 (35%) to amphotericin B and 4 (7%) isolates to echinocandins. Overall, 22 (41%) isolates were resistant to two antifungal classes (MDR), and two (4%) isolates were resistant to three antifungal classes (azoles, echinocandins and polyenes) which make them XDR.[3] A comprehensive study from Kuwait on 56 *C. auris* isolates showed 100% resistance to fluconazole, 72% to voriconazole, 23% to amphotericin B and 20% were resistant to fluconazole, voriconazole, amphotericin and only one isolate was resistant to caspofungin and micafungin.[65] It has been reported from US, that 86% of the first 35 *C. auris* cases were resistant to fluconazole, 43% and 3% were resistant to amphotericin B and echinocandins, respectively.[70] Another study reported drug resistance profiles of London outbreak isolates, which showed high level resistance to fluconazole (MIC ≥ 256 mg/L), variable susceptibility to amphotericin B (MIC = 0.5-2 mg/L) and majority of the isolates showed susceptibility to echinocandins (MIC = 0.06-0.25 mg/L) and 5-flucytosine (MIC < 0.06-0.12 mg/L).[66] Recently, antifungal susceptibility testing was performed on 350 isolates of *C. auris* from 10 hospitals in India over a period of 8 years (2009-2017) exhibited 90% of *C. auris* isolates were resistant to fluconazole (MIC 32-≥64 mg/L), 2.3% to voriconazole (MIC 16 mg/L), 8% to amphotericin B (MIC ≥ 2 mg/L) and 2% to echinocandins (MIC ≥ 8 mg/L).[95] A mouse model testing of all the three antifungal classes against nine *C. auris* strains showed that micafungin had higher fungicidal potential and is more effective than other antifungals.[96] A detailed MIC ranges of different *C. auris* isolates from different countries against all the major classes of antifungal drugs are summarised in Table 2.

Drug resistance mechanisms in *C. auris* are not clear yet; however, some studies reported that these mechanisms resemble with other resistant species of *Candida*.[53,77] Resistance of *C. auris* to azoles is assumed to occur due to upregulation of efflux pumps as that in *C. haemulonii* and *C. glabrata*[14,72]; however, it has been reported that *C. auris* in comparison *C. haemulonii* and *C. glabrata* demonstrates higher ABC-type efflux pump activity.[14] In another study, it has also been reported that the efflux pump-related genes including ATP-binding cassette (ABC) and major facilitator superfamily (MFS) transporters were upregulated in *C. auris* biofilm formation, which played a major role in azole drug resistance in this pathogen.[97] The draft genome of *C. auris* divulged that *C. auris* possess single copies of ERG3, ERG11, FKS1, FKS2 and FKS3 genes, and these genes in *C. auris* showed 78% to 85% similarity with *C. albicans* and *C. glabrata* genes.[73,74] It is also reported that a significant portion of *C. auris* genome encodes ABC and MFS transporter families along with drug transporters that could be the reason of multidrug resistance in this pathogen.[72,74] Upon comparison of *C. auris* and *C. albicans* ERG11 amino acid sequences, for the detection of azole-resistant mutations, it has been reported that the alterations in codons responsible for azole resistance in *C. albicans* are also present in *C. auris*.[3] In a recent study, it was reported that mutations in *ERG11* of *C. auris* leading to Y123F and K143R substitutions result in reduced azole susceptibility.[98] However, these substitutions are specific to geographic clades.[3] Besides role of gene mutations in azole resistance, it is evident that mutations in some genes lead to amphotericin B resistance in *C. auris*. In Colombia, four novel nonsynonymous mutations associated significantly with amphotericin B resistance were found in isolates of *C. auris*.[99] There are also reports associated with the misuse and overuse of antifungal drugs resulting in mutation of genes in *C. auris*, inducing multidrug resistance (MDR). However, there is still scope of further studies on complete genomic analysis to identify other mechanisms of multidrug resistance in this pathogen.

To better understand the drug resistance patterns and for effective patient therapy against different pathogenic microorganisms, antimicrobial susceptibility testing is an essential guide. Two major institutes, CLSI and EUCAST, have established MIC breakpoints for most of the antifungal drugs used to treat candidiasis. However, to date no such data have been reported for *C. auris* and thereby susceptibility testing for *C. auris* isolates is highly recommended by CDC. By then, for the case of clinicians to treat this pathogen, CDC provided provisional MIC breakpoints which are based on breakpoints used in other *Candida* species and on the expert opinions. CDC interim MIC breakpoints (in μg/ml) for *C. auris* include—fluconazole (≥32), amphotericin B (≥2), echinocandins (≥4 for anidulafungin and micafungin; ≥2 for caspofungin), for voriconazole and other second-generation trizoles, fluconazole resistance can be considered surrogate marker.[85]

For antifungal susceptibility testing, most commonly used methods are CLSI-BMD, VITEK-2 and Etest method.[56] The other frequently used method to check antifungal susceptibility of *C. auris* is Sensititre YeastOne™.[5] Comparison of these commonly used antifungal susceptibility methods against *C. auris* has shown differences in MIC interpretations.[75] All the methods uniformly shown higher MICs for fluconazole. There are variations in MICs of amphotericin B, which are reported high with Vitek-2 and low with Sensititre YeastOne method. The reports of antifungal susceptibility by Sensititre YeastOne method revealed high MIC values for fluconazole, however, and very low MIC values for other azoles.[5] Falsely elevated MIC of caspofungin was reported by CLSI-BMD method, reduced to 12% using Etest. Several reports also showed inter-laboratory variation in caspofungin susceptibility with both CLSI-BMD and EUCAST methods.[41,73] Several authors recommend CLSI-BMD and Etest method for antifungal susceptibility testing of *C. auris*.[56,100] To prevent fatal consequences and inappropriate treatments due to false susceptibility testing, use of more than one method to check resistance profiles of *C. auris* is highly suggested.[13,26,34,38,41,83]

8 | THERAPEUTIC OPTIONS

With an increasing case of *C. auris* infections, it becomes essential to have a broad range of therapeutic strategies against these infections. Unlike other *Candida* species, there are no concrete documented therapeutic options for *C. auris* infections and therefore it is advised that case-by-case treatment options should be followed.

In addition, CDC highly recommended the consultation of infectious disease specialist when clinicians are treating *C. auris* patients. Although *C. auris* exhibit multidrug resistance, most of the isolates are responding to echinocandins. Therefore, echinocandins are recommended initial treatment of invasive *C. auris* infections; however, prior susceptibility testing is still required.[42] A collective first- and second-line recommendations were issued by CDC with different drug dosages for adults and infants.[85]

For neonates, the initial therapy for treatment is 1 mg/kg/day of amphotericin B deoxycholate; however, if the patient is unresponsive to this initial therapy, 5 mg/kg/day of liposomal amphotericin B could be considered. Use of echinocandins for this age group could be considered only in exceptional circumstances, where central nervous system is involved. Echinocandin drugs are recommended as per dosage as first-line treatment for *C. auris* infections in adults and children ≥ 2 months of age (except anidulafungin which is not approved for use in children). Switching to a liposomal amphotericin B (5 mg/kg/day) in adults and children ≥ 2 months of age could be considered if the patient is clinically unresponsive to echinocandin therapy or has persistent fungemia for more than 5 days. However, liposomal amphotericin B has also been reported effective against *C. auris* and is used in combination therapies with an echinocandin drug.[15,26,34,76,93] An *in vitro* combinations of azoles and echinocandins drugs have also been found effective treatment against *C. auris* infections.[101] In an another study by Eldesouky, a synergistic combination of sulfamethoxazole with voriconazole and itraconazole against azole-resistant *C. auris* infections was reported.[102] Antifungal treatment is not recommended for *C. auris* cultures from non-invasive sites, when the evidence suggests colonisation rather than infection.[103,104] Despite the management of *C. auris* infection is similar to other *Candida* infections, the choice of antifungal drug treatment varies to larger extend. Importantly, it has been documented that *C. auris* rapidly develop antifungal resistance and therefore patients on treatment should be carefully monitored with follow-up cultures and susceptibility testing.

There are numerous studies reporting the efficacy of natural products, semi-synthetic and synthetic compounds, nanoparticles and peptides against *C. albicans* and other non-albicans *Candida* species; however, very limited or nothing is reported against *C. auris*. Recent studies reported SCY-078 and VT-1598 are novel antifungal compounds and are currently in the pipeline for drug development, which exhibit potent antifungal activity against *C. auris* and other pathogenic fungal species.[91,103,105] SCY-078 is the first orally bioavailable 1,3-β-D-glucan synthesis inhibitor, which demonstrated potent antifungal and antibiofilm activity against *C. auris* via growth inhibition.[91] Fungal Cyp51 (lanosterol 14α-demethylase) inhibitor VT-1598 is a tetrazole-based drug, that prevents the conversion of lanosterol to ergosterol results in disruption of ergosterol biosynthetic pathway.[103] A novel antifungal agent APX001 (formerly E1211) exhibited potent antifungal activity against *C. auris* and other drug resistant fungal species by targeting fungal enzyme *Gwt1* which catalyses the glycosylphosphatidylinositol anchored wall transfer protein 1 (GPI) biosynthesis pathway.[106] CD101 is a novel echinocandin with enhanced safety and stability, allowing intravenous administration once weekly, furthermore CD101 possesses potent antifungal activity against *C. auris*.[107,108] All these novel compounds could be an important antifungal drug for the treatment of MDR species, such as *C. auris*. The other for granted approach to test against *C. auris* is the drug combinations. Drug combinations have gained a lot of interest among microbiologists and clinicians to treat several communicable as well as non-communicable diseases, including that caused by MDR pathogens. There are several evidences which can warrant to study the combination of different antifungal drugs as well as the combination of antifungal drugs with natural products, peptides and nanoparticles to test against *C. auris* infections. From our laboratory results, we combined different antifungal drugs with different monoterpene phenols and observed that MICs of these antifungals decreased by several folds (unpublished data). These preliminary results will lead a foundation to study natural products as a chemosensitising agents to combat *C. auris* infections.

9 | INFECTION PREVENTION AND CONTROL

Candida auris, being a multidrug-resistant pathogen, is associated with nosocomial transmission and clonal hospital outbreaks. Therefore, above and over treatment options, infection prevention and control (IPC) measures are very important in limiting the spread of *C. auris*. The initial IPC measure is to isolate patients infected, colonised or suspected with *C. auris* in private single-patient rooms and while handling these patients follow both Standard Precautions and Contact Precautions as recommended by CDC, ECDC, PHE and COTHI—South Africa.[40,85] Healthcare personnel should strictly follow Contact Precautions when caring patients infected or colonised with *C. auris* to reduce the spread of infection, which includes strict adherence to hand hygiene following standard hand hygiene practices and proper use of Personal Protective Equipment (PPE).[42,85] So far, it has been reported that 3% (4/45) healthcare workers are colonised with *C. auris* on their hands.[88] Therefore, it is highly suggested to strictly follow PHE recommendations of handwashing with soap and alcohol sanitisers before and after caring patients with *C. auris* infection.[1] More care is required when healthcare personnel handle patients with high risks such as wound dressing, assisting patients with bathing, toileting, etc.[85] In addition, there are strict guidelines suggesting that any equipment used in sharing should be cleaned and disinfected after every single use. When transferring patients to other healthcare facilities, the staff at the receiving facility should be notified about the patient's *C. auris* infection or colonisation status and the level of precautions recommended.

The CDC guidelines recommended that residents in nursing homes must also be put on Standard and Contact Precautions. The CDC guidelines recommend continued infection control precautions for as long as the patient is infected or colonised with *C. auris*.

TABLE 2 Summarised antifungal resistance profile data of *Candida auris* isolates based on various susceptibility methods from different countries between 2009 and 2018

Country	No. of isolates tested/ years	Method of susceptibility	MIC range (μg/mL)	
			FLU	ITC
South Africa	4 (2012-13)	CLSI BMD (M27- A3)	64->256	0.06-0.25
India	90 (2010-14)	CLSI BMD (M27- A3)	4->64	<0.03-2
	74 (2011-12)	CLSI BMD (M27- A3)	43	3
	15 (2011-13)	CLSI BMD (M27- A3)	64	0.06-0.25
	12 (2009-11)	CLSI BMD (M27- A3)	16-64	0.125-0.25
	5 (2012-14)	CLSI BMD (M27- A3)	16-64	_
	4 (2013)	CLSI BMD (M27- A3)	>64	0.03-0.125
	2 (2011)	Not mentioned	64	_
	1(NS)	CLSI BMD (M27- A2)	≤16	≥2
	350 (2009-17)	CLSI BMD (M27- A3/S4	1-≥64	0.03-16
	123 (2010-15)	CLSI BMD M27- A3/S4)(India)	4->64	0.032-2
		EUCAST (E. Def 7.3)(Denmark)	0.05–>64	≤0.008-1
	20 (2012-17)	CLSI BMD (M27- A3/S4) (India)	0.125-32	0.03-0.125
Pakistan (19) India (19) South Africa (10) Venezuela (5) Japan (1)	54 (2012-15)	CLSI BMD (M27- S4)	4-256	0.125-2
Kuwait	1 (2014)	E-test (BioMérieux, Marcy l'Etoile, France)	>256	_
	56 (2014-17)	E-test (bioMérieux, Marcy l'Etoile, France)	128-≥256	_
	17 (2015-17)	E-test (bioMérieux, Marcy l'Etoile, France)	≥256	_
Oman	5 (2016-17)	Colorimetric microdilution Panel (YeastOne® Se-nsititre® TREK Diagnostic Systems Ltd., East Grinstead, UK)	128->256	0.12-0.25
	2	CLSI BMD (M27- A3)	≥64	0.125-0.031
	1 (2016)			
	1 (2017)			
Israel	6	CLSI BMD (M27 - A3)	32-64	0.5
	4 (2014)			
	1 (2015)			
	1 (2014-15)			
Saudi Arabia	3 (2017-18)	YeastOne microdilution broth method (TREK Diagnostics, OH, USA)	64-256	0.03-0.25
Singapore	F 3 (2018)	Sensititre™ YeastOne®microdilution panel (TREK Diagnostic Systems Ltd, Thermo Scientific)	≥256	0.12-0.25
Malaysia	1 (2018)	E-test(AB Biodisk, Solna, Sweden)	>256	4
South Korea	20	CLSI BMD, except AMB by E-test, (AB BIODISK)	2-128	0.125-4
	15 (2006)			
	5 (2007-10)			
	3	CLSI BMD (M27- A3)	2-128	0.125-2
	1 (1999)			
	2 (2009)			
Japan	1 (2009)	Not mentioned	2	0.063
China	1 (2018)	Sensititre YeastOneTM methodology (Thermo Scientific, Inc., Cleveland, OH, USA)	2	0.03
	15 (2011- 17)	Sensititre YeastOne colorimetric microdilution method(Thermo Fisher scientific, Oxoid, USA)	32	0.12
Canada	5 (2017)	CLSI BMD (M27- A3)	128	_

VRC	ISA	POS	AMB	CAS	MFG	AFG	FC	References
0.25-2	_	0.015-0.06	0.5-1	0.03-0.25	0.06-0.12	0.06-0.25	0.06-0.12	26
<0.03-16	<0.015-4	<0.015-8	0.125-8	0.125-8	<0.015-8	<0.015-8	<0.125->64	41,42
2	_	_	10	7	_	_	_	4,61
0.5-4	0.06-0.5	0.015-0.125	0.25-1	0.25-1	0.06-0.125	0.125-0.25	0.25-64	14
0.125-1	<0.015-0.25	0.06-0.25	0.25-1	0.125-0.25	0.06-0.125	0.125-0.5	0.125	13
_	_	_	Apr-16	0.25	_	_	1	74
0.06-0.125	_	≤0.015	0.125- 0.5	1	0.06	0.125-0.25	0.125-4	82
2	_	_	16	_	_	_	1	109
≤0.5	_	_	≤0.5	_	_	_	_	81
0.03-16	≤0.016-4	≤0.016-8	0.125-8	0.125-16	≤0.016-16	≤0.016-8	0.125-≥ 64	56
0.032-16	0.015-4	0.015-8	0.015-8	_	0.015-8	0.015-8	_	97
≤0.008-4	≤0.008-2	≤0.008 -0.5	0.25-1	_	0.002-4	0.002-2	_	
0.03-0.5	_	0.03-0.02	0.06-0.5	0.06-1	0.015	0.015-0.03	0.125-8	62
0.03-16	_	0.06-1	0.38-4	0.03-16	0.06-4	0.125-16	0.125-128	3
0.38	_	_	0.064	0.064	_	_	_	17
0.064-6	_	_	0.047-3	0.012-4	0.006-4	_	_	65
0.064-6	_	_	0.064-3	0.012-1	0.006-0.5	_	0.002-0.016	65
0.15-2	_	0.06-0.12	1-2	0.08-0.12	0.06-0.12	0.12	0.06-8	19
0.125-1	<0.016 -0.125	<0.016 -0.063	1-2	_	0.063 -0.125	0.031 -0.125	_	18
0.5-1	_	0.12-0.5	1-2	0.5	0.12-0.25	0.03	0.25-1	16
0.12-1	_	0.016-0.25	0.5-2	0.12	0.12	_	≤ 0.06-0.25	23
1-2	_	0.06	1-2	0.12-≥8	0.06-0.25	0.12-0.5	≤0.06-0.25	24
>32	_	_	3	>32	_	0.75	_	20
0.03-2	_	_	0.38-1.5	0.125-0.25	0.03	_	_	12,90,110
0.03-1	_	_	0.5-1	0.06	0.03	_	_	8
0.031	_	_	_	_	_	_	0.5	6
0.02	_	0.02	0.25	0.06	0.06	0.12	<0.06	21
0.25	_	0.25	0.5	0.25	0.12	0.03	4	63
_	_	_	2	_	0.5	_	_	37

(Continues)

TABLE 2 (Continued)

Country	No. of isolates tested/ years	Method of susceptibility	MIC range (μg/mL)	
			FLU	ITC
Colombia	17 (2016)	VITEK cards	16->64	_
United Kingdom	53	CLSI BMD (M27- A3)	8-> 64	_
	3 (2013)			
	1 (2014)			
	7 (2015)			
	4 (2016)			
	7 (2014 –16)			
	50 (2015-16)	Colorimetric microdilution Panel (YeastOne® Sensititre® TREK Diagnostic Systems Ltd., East Grinstead, UK)	>256	_
	4	CLSI BMD (M27- A3)	>32	_
Germany	2 (NS)	CLSI BMD (M27- A3)	> 64	0.5
Spain	8 (2016)	Colorimetric microdilution Panel (YeastOne®Sensititre® TREK Diagnostic Systems, USA)	>256	S
Austria	1 (2018)	EUCAST (microdilution method), Micronaut (Merlin Diagnostica, Bornheim, Germany).Etest (bioMérieux)	0.25-0.5	≤ 0.03
United States(US, tested strains collected from Japan (1) India (11) South Korea (2) Germany (2)	224 (2016-17)		>32 = 30	_
	Clinical-104Colonised-120			
	7		R = 5	_
	1 (2013)			
	1 (2015)			
	5 (2016)			
	16	CLSI BMD (M27- A3)	1->64	<0.063-1
	1 (2017)	Colorimetric microdilution Panel (YeastOne®Se-nsitire® TREK Diagnostic Systems, Cleveland, Ohio)	4	_
United Arab Emirates	1 (2017)	_	_	_
Venezuela	18 (2012-13)	CLSI BMD (M27- A3/S4)	>64	_

Note: AFG, anidulafungin; AMB, amphotericin B; CAS, caspofungin; CLSI-BMD, clinical and laboratory standards institute broth microdilution method; eucast, european Committee on Antimicrobial Susceptibility Testing; FC, flucytosine; FLU, fluconazole; ISA, isavuconazole; ITC, itraconazole; MFG, micafungin; MIC, minimum inhibition concentration; POS, posaconazole; VRC, voriconazole.

As the colonisation period of *C. auris* is unclear, periodic reassessment (every 1-3 months, depending upon the patient symptoms) for the existence of colonisation by *C. auris* can assist to notify the period of infection control measures. In addition, weekly testing of axilla and groin swabs, along with sites which were reported positive for *C. auris* on previous cultures, is used for the assessment of colonisation.[85] It is recommended at least two negative assessments should be performed one week apart to discontinue infection control precautions. While reassessing these patients, it should be noted that patient must not use any antifungal active against *C. auris*. Rigorous daily and terminal cleaning of patient rooms are also recommended, as patients may shed *C. auris* from their skin and other body sites for which can survive from weeks to months.[66,85,88]

Although there are no concrete evidences of any disinfectant killing *C. auris*, CDC guidelines recommend the disinfectant should be effective against *Clostridium difficile* spores. Several studies suggested use of high strength chlorine-based agents (Chlorohexidine 0.2% to 4%), hydrogen peroxide vapour, ultra violet light and phenol are effective for environmental cleaning.[34,66,88,109,110] *C. auris*, however, exhibit the tolerance against sodium hypochlorite and peracetic acid in a surface depend manner.[111] For decolonisation of skin, 2% chlorhexidine gluconate containing wipes or aqueous 4% chlorhexidine can be used.[66] Oral nystatin is effective in decolonising oropharynx.[66] In an *in vitro* study, efficacy of chlorhexidine, iodine povidone, chlorine and vaporised hydrogen peroxide exhibits effective killing of *C. auris* isolates. Inhibition of isolates was seen by chlorhexidine gluconate, iodine povidone and chlorine at a concentration of 0.125%-1.5%, 0.07%-1.25% and 1000 ppm, respectively. H_2O_2 vapour demonstrates 96.6%-100% effective killing of *C. auris*.[112] For oral decolonisation, 0.2% chlorhexidine mouthwash has been used, also chlorhexidine-impregnated protective discs

VRC	ISA	POS	AMB	CAS	MFG	AFG	FC	References
< 0.12-2	_	_	8-> 16	< 0.25-0.5	< 0.06 -0.25	_	_	[39]
0.06-2	_	< 0.03-1	0.5 -1	_	_	0.03-0.5	< 0.125-0.25	[30,31]
_	_	_	0.5-2	0.06-0.25	0.06-0.25	0.06-0.25	< 0.06-0.12	[9]
Jan-32	_	_	0.25-0.5	2-> 32	0.06-0.5	_	_	[111]
0.125-0.5	0.031	0.25-0.5	4	0.5	0.25	0.25	0.5	[89]
2	S	S	S	S	_	S	_	[28]
≤0.008 -0.016	0.002	≤0.008 -0.032	0.5-1.0	0.032 -0.125	0.064 -0.125	0.012-0.125	≤ 0.064	[68]
_	_	_	>2 = 15	>4 = 1	>4 = 1	>4 = 1	_	CDC 2017, [72]
_	_	_	R = 1	R = 1	R = 1	R = 1	_	[84]
0.063-2	0.004-0.25	0.25-1	0.5-8	_	_	_	0.5-1	[89]
0.03	_	_	2	0.12	0.12	_	0.12	[77]
0.016-1	_	_	0.02-1	0.016-0.25	_	_	_	[22]
4	_	_	01-Feb	_	_	0.125	0.5	[10]

for central vascular catheter exit sites have been found effective to reduce line-associated *C. auris* bloodstream infections.[48,50,66] For decolonisation of *C. auris* in sink drainage systems, ozonated water has been effectively used.[113] Compared to planktonic cells, *C. auris* biofilms showed reduced sensitivity to commonly used disinfectants such as povidone iodine, chlorhexidine and hydrogen peroxide.[97]

Prompt initiation of infection control interventions to control nosocomial *C. auris* outbreaks is essential to establish the source of the outbreak and to prevent further transmission of infection. Although there are limited data regarding the effectiveness of infection control interventions to control nosocomial *C. auris* outbreaks, control measures such as rapid identification of carriers, isolation of infected patients and use of recommended disinfectants for decolonisation of positive patients and their indwelling device sites should be considered.

10 | CONCLUSION AND FUTURE PROSPECTIVE

Epidemiological studies have already confirmed that *C. auris* infections are spread all around the globe. *C. auris* infections are more prevalent in developed and developing countries than under developed countries, and the underlying reason is that the efficient diagnostic tools are still beyond the reach of many microbiology laboratories in these countries. The initial requirement to deal with this pathogen is to urgently initiate consistent, sensitive and precise detection regimes. Such regimes will allow us to detect these infections at large scale and routine use and continue to build upon the fundamental knowledge of effective and well in time therapeutic treatments of *C. auris* infections in critically ill and high-risk patients. Despite the introduction of several high throughput techniques such as MALDI-TOF MS, PCR and WGS,

these techniques are expensive and time-consuming. Therefore, there is an urgent need to develop new, cost-effective and easily accessible technique or kit for early detection of this pathogen. With these features, it can be easily accessible to the different mycology laboratories worldwide. Treatment options for drug resistant *Candida* species were already limited and the increasing prevalence of *C. auris* enhances the challenges to deal with this deadly fungal pathogen. It is worth to mention that there are no or poorly defined treatment guidelines to treat *C. auris* patients. Despite the epidemiology of this pathogen gained a lot of attention for past few years, there is a greater need to develop and test new antifungals against *C. auris*. Immediate action of testing natural compounds, semi-synthetic compounds, synthetic compounds, nanoparticles, peptides against *C. auris* is a prompt requirement. These compounds have already been reported to possess antifungal activities against *Candida* and other fungal pathogens. In conclusion, it is becoming necessary to understand and recognise the *C. auris* associated problems and to implement the infection control measures, early detection and appropriate therapy for the spread and cure of the *C. auris* infections.

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COMPETING INTERESTS

We declare no competing interests.

AUTHOR CONTRIBUTIONS

AA conceived the idea; SAL collected the data; SAL and AA analysed the data; SAL led the writing.

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