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# Strategies to Prevent Transmission of *Candida auris* in Healthcare Settings

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## Abstract

**Purpose of Review** *Candida auris*, a recently recognized yeast pathogen, has become a major public health threat due to the problems associated with its accurate identification, intrinsic and acquired resistance to antifungal drugs, and its potential to easily contaminate the environment causing clonal outbreaks in healthcare facilities. These outbreaks are associated with high mortality rates particularly among older patients with multiple comorbidities under intensive care settings. The purpose of this review is to highlight strategies that are being adapted to prevent transmission of *C. auris* in healthcare settings.

**Recent Findings** Colonized patients shed *C. auris* into their environment which contaminates surrounding equipment. It resists elimination even by robust decontamination procedures and is easily transmitted to new patients during close contact resulting in outbreaks. Efforts are being made to rapidly identify *C. auris*-infected/*C. auris*-colonized patients, to determine its susceptibility to antifungals, and to perform effective cleaning and decontamination of the environment and isolation of colonized patients to prevent further transmission.

**Summary** Rapid and accurate identification of hospitalized patients infected/colonized with *C. auris*, rapid detection of its susceptibility patterns, and appropriate use of infection control measures can help to contain the spread of this highly pathogenic yeast in healthcare settings and prevent/control outbreaks.

**Keywords** *Candida auris* · Global epidemiology · Diagnosis · Antifungal drug susceptibility · Environmental decontamination · Infection control

## Introduction

Invasive fungal infections (IFIs) are regarded as the diseases of medical progress, and invasive candidiasis, particularly candidemia, is the most common manifestation of IFIs [1•, 2••]. The incidence of candidemia/invasive candidiasis has been consistently rising globally, and *Candida* spp. are the causative agent in nearly 25% of all bloodstream infections among hospitalized patients [1•, 2••, 3]. Important risk factors for invasive candidiasis include extremes of age; admission into intensive care units (ICUs); total parenteral nutrition; multiple comorbidities such as diabetes mellitus, chronic pulmonary, cardiovascular, or kidney disease, neutropenia, and malignancy; presence of central venous/urinary catheters; and prior use of broad-spectrum antibiotics/antifungal agents [3–6]. Invasive *Candida* infections have an attributable mortality of nearly 30% in adults and nearly 15% in neonates [7, 8]. With rapid changes in clinical practice, the spectrum of *Candida* and other yeast species capable of causing IFIs is also changing [9•, 10].

*Candida albicans* is usually the most common cause of invasive candidiasis; however, majority (> 50%) of *Candida* infections are now caused by non-*albicans Candida* species (NACS) [10–14]. The NACS usually exhibit reduced susceptibility/resistance to one or more antifungal drugs [10, 15•, 16–18]. The incidence of NACS-invasive infections has increased due to their selection as a result of increasing use of fluconazole/other antifungal drugs for prophylaxis or therapy for IFIs [10, 12–14, 15•, 16–18]. The emerging multidrug-resistant *Candida* spp. include *C. glabrata*, *C. krusei*, *C. lusitaniae*, *C. guilliermondii* complex members, *C. kefyr*, *C. haemulonii* complex members, and *C. auris* [10, 12–14, 15•, 16–18, 19••]. Of these, *C. auris* is now recognized as a threat to global public health due to its ability to cause outbreaks of invasive infections in healthcare facilities

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which have been difficult to control and treat [19••, 20•, 21]. In this article, the current epidemiology of *C. auris* infections, its rapid detection from infected/colonized patients, and strategies to control its spread in healthcare facilities by infection prevention are described.

## Global Epidemiology of *C. auris* Infections

*Candida auris*, isolated from the external ear canal of a Japanese patient, was first described as a novel *Candida* species in 2009 [22]. However, a subsequent retrospective study from South Korea revealed that the earliest *C. auris*, a bloodstream isolate initially misidentified as *C. haemulonii*, dates back to 1996 [23]. Fifteen other *C. auris* isolates, misidentified earlier as *C. haemulonii*, were also identified among archived cultures collected from ear samples during 2004–2006 [24]. Soon afterwards, several invasive isolates were identified in India [25], and the first outbreak was reported from the UK [26•]. The epidemiology of *C. auris* infections has witnessed dramatic changes over the past 10 years as several thousand sporadic or outbreak isolates have been recovered from blood and other specimens mostly from hospitalized patients in > 50 countries/territories from Asia (Japan, South Korea, India, Kuwait, Israel, Oman, Pakistan, United Arab Emirates, China, Malaysia, Saudi Arabia, Iran, Thailand, Singapore, Bangladesh, Lebanon, Qatar, Taiwan, and Vietnam), Europe (Great Britain, Spain, Norway, France, Belgium, Germany, Russia, Austria, Switzerland, Italy, Greece, Netherlands, Poland, and Denmark), North/South Americas (USA, Venezuela, Canada, Colombia, Panama, Chile, Costa Rica, Brazil, Guatemala, Mexico, and Peru), Africa (South Africa, Kenya, Egypt, Sudan, Algeria, and Nigeria), and the Oceania (Australia) [19••, 20•, 21, 27–29].

Whole genome sequencing of clinical *C. auris* isolates has identified five distinct clades which exhibit large sequence differences (> 200,000 single nucleotide polymorphisms, SNPs) and likely originated simultaneously. *C. auris* isolates within the same clade usually show minor sequence differences [30••, 31, 32]. The five clades include South Asian Clade (clade I), East Asian Clade (clade II), African Clade (clade III), South American Clade (clade IV), and Iranian Clade (clade V) [30••, 31, 32]. *C. auris* isolates exhibit clade-specific resistance patterns to antifungal drugs, and invasive infections/outbreaks are mostly caused by clade I, clade III, and clade IV isolates, while clade II and clade V isolates mainly cause ear infections and are usually susceptible to antifungal drugs [30••, 33, 34]. Genomic analyses and in vitro/in vivo evolution of resistance studies have shown that clade I and clade IV isolates develop resistance to fluconazole rather easily which is not lost even after drug removal during growth of *C. auris* indicating that no fitness cost is associated with resistance [35•]. Resistance development likely occurred due to deletion of multiple genes near subtelomeric regions, and a mutator phenotype was also identified exhibiting elevated mutation rates and high level of resistance during in vitro and in vivo passages [35•]. A fluconazole-resistant *C. auris* belonging to clade V and isolated from fungal otitis has also been described recently [36].

The impact of coronavirus disease (COVID-19) epidemic has also been investigated as ICU admissions, a major risk factor for acquiring invasive *C. auris* infections, dramatically increased at times during this period [37–39]. Based on the meta-analysis of 10 studies, Vaseghi et al. [38] reported an overall pooled prevalence of 5.7% for COVID-19-associated *C. auris* infections, and male gender was a major risk factor for acquiring *C. auris* infection. The authors concluded that the prevalence of *C. auris* infections decreased during the COVID-19 pandemic. On the contrary, Vinayagamoorthy et al. [39] reported a prevalence of 14% for COVID-19-associated *C. auris* infections and concluded that the prevalence of *C. auris* infections remained unchanged during the COVID-19 pandemic. Both studies reported the same common risk factors (hypertension, diabetes mellitus, placement of a central venous catheter, ICU stay, and treatment with broad-spectrum antibiotics) for *C. auris* infection among COVID-19-infected patients [38, 39].

In recent years, *C. auris* has caused invasive infections/outbreaks with increasing frequency which have been associated with high mortality rates among hospitalized patients [19••, 20•, 21, 40–43]. The increasing incidence of *C. auris* infections has also caused major shift in the epidemiology of invasive *Candida* infections at many geographical locations with *C. auris* becoming a major bloodstream pathogen, even surpassing *C. glabrata* or *C. tropicalis* in some settings [19••, 44–47].

Although *C. auris* isolates described until 2020 were obtained from clinical specimens, environmental isolation of *C. auris* has also been described recently, first from the tropical marine ecosystems in the Indian Ocean and subsequently from a coastal habitat in Colombia [48•, 49]. These findings have supported climate change as the main driving force for the recent emergence of *C. auris* as a novel human fungal pathogen. Climate change has likely resulted in stress adaptation (thermotolerance and halotolerance) and biotic predation allowing adaptation to diverse environmental niches [19••, 48•]. Furthermore, *C. auris* has been isolated from apples previously treated with fungicidal agents, and this practice in food industry may have been responsible for the selection of drug-resistant *C. auris* [50•, 51].

## Identification of *C. auris* in Yeast Cultures and Clinical Specimens

Until recently, *C. auris* was usually misidentified as *Candida haemulonii/duobushaemulonii*, *Candida sake*, *Rhodotorula glutinis*, or other *Candida* species by biochemical substrate utilization-based systems such as VITEK2, API 20C AUX, Phenix YIS, RapID Yeast Plus, or MicroScan [19••, 52]. These automated systems now identify *C. auris* accurately with updated databases; however, they are time-consuming as they require yeast culture [19••, 52].

Like *C. glabrata*, *C. haemulonii* complex members, *C. kefyr*, *Candida guilliermondii*, *Candida famata*, *Candida conglobata*, and *Candida utilis*, *C. auris* also forms pink-colored colonies on CHROMagar Candida [53]. However, on CHROMagar™ Candida Plus, *C. auris* forms cream-colored colonies with a blue halo which differentiates it from other closely related species [54, 55]. Other low-cost phenotypic methods are not completely specific for *C. auris* [19••, 52]. Phenotypic methods are slow as they require yeast culture, and to avoid misidentification, clinical isolates are usually subjected to analysis by matrix assisted laser desorption ionization time-of-flight mass spectrometry (MALDI-TOF MS) by using Bruker-Daltonics MALDI Biotyper or VITEK MS with their updated databases which consume additional cost and time [52, 56].

Rapid and definitive identification is usually achieved by PCR amplification and/or PCR sequencing of rDNA-based methods, and both in-house and commercial tests have yielded ≥ 90% clinical sensitivities and specificities with yeast cultures/clinical specimens [19••, 52, 57]. Implementation of *C. auris* real-time PCR for surveillance in the UK was recently shown to reduce the risk of invasive infections [58]. Since clinical *C. auris* strains exhibit clade-specific virulence and resistance to antifungal drugs, PCR-based clade-identification methods have also been developed [59].

## Susceptibility of C. auris and Molecular Basis of Resistance to Antifungal Drugs

Although there are no established susceptibility breakpoints for *C. auris*, tentative breakpoints have been suggested by expert opinion and by the Centers for Disease Control and Prevention (CDC) of the USA and are as follows: fluconazole, ≥ 32 µg/mL; amphotericin B, 2 µg/mL; caspofungin, 2 µg/mL; micafungin, 4 µg/mL; and anidulafungin, 4 µg/mL [30••, 60–62].

Worldwide, nearly 90% of clinical *C. auris* isolates are resistant to fluconazole, and susceptibility to voriconazole and other triazoles varies widely even among isolates belonging to the same clade [19••, 21]. Nearly 4% isolates are pan-resistant; however, resistance rates in different countries/healthcare settings vary considerably [19••, 21]. Thus, nearly 90%, 30%, and ~ 5% of *C. auris* isolates from the USA were resistant to fluconazole, amphotericin B, and echinocandins, respectively, while in the New York-New Jersey area where 55% of all US isolates occur, 99.8% of the isolates were fluconazole-resistant, and 50% isolates were amphotericin B-resistant [63]. The resistance rates of 90–95%, 7–37%, and < 2% and 90%, 5.5%, and 0.25% have been reported for fluconazole, amphotericin B, and echinocandins among *C. auris* from India and South Africa, respectively [44, 60, 64, 65]. These differences are mainly due to the occurrence of different percentages of *C. auris* isolates belonging to different clades in different settings [35•, 63–65].

The reference broth microdilution-based antifungal susceptibility testing (AST) protocols recommended by the Clinical and Laboratory Standard Institute (CLSI) and European Committee on Antimicrobial Susceptibility Testing (EUCAST) are the methods of choice for *C. auris* [60–63]. Other broth microdilution-based methods (Sensititre® YeastOne, MICRONAUT) have also yielded comparable results [40, 43, 66]. Rapid methods such as MALDI TOF MS, Etest, Liofilchem MIC Test Strip, and VITEK2 have also been used; however, VITEK2 results for fluconazole and amphotericin B may not be suitable to guide therapeutic decisions [53, 56, 66–68].

The molecular mechanisms of resistance to antifungal drugs in *C. auris* have been elucidated in the past few years (Table 1). The molecular basis of resistance to different antifungal drugs in *C. auris* has also been reviewed recently [69]. The *ERG11* encoding cytochrome P450-dependent lanosterol demethylase, involved in ergosterol biosynthesis, is the main target conferring resistance to fluconazole, and VF125AL, Y132F, or K143R are the most common genetic alterations [60, 69–72]. However, these mutations alone are not sufficient to confer high-level fluconazole resistance commonly observed among clinical isolates as replacement of wild-type *C. auris* allele with mutant alleles increased fluconazole and voriconazole minimum inhibitory concentrations (MICs) by only 8–16 fold. Similarly, replacement of K143R mutation with wild-type allele led to a 16-fold decrease in fluconazole MIC [72]. Other studies have shown the involvement of an ATP-binding cassette (ABC) transporter (*CDR1*) and a major facilitator superfamily (MFS) member (*MDR1*) in conferring resistance of *C. auris* to fluconazole (Table 1) [69, 73, 74].

Studies have shown that *CDR1* homologs are upregulated in triazole-resistant *C. auris* and deletion of *CDR1* gene in a triazole-resistant strain caused nearly 100-fold decrease in the MIC for fluconazole [73]. Furthermore,

**Table 1** Genes and their encoded products involved in conferring resistance to antifungal drugs in *C. auris*

| Antifungal drug | Resistance gene | Encoded product | Genetic alterations | Main reference(s) |
|---|---|---|---|---|
| Fluconazole | *ERG11* | Lanosterol demethylase | VF125AL, Y132F, K143R | [60, 70–72] |
| | | | Upregulation | [60] |
| | *CDR1* | ATP-binding cassette transporter | Upregulation | [73] |
| | *TAC1B* | Transcription factor | Gain-of-function mutations | [74] |
| | *MDR1* | Major facilitator superfamily member | Upregulation | [73, 75] |
| | *MRR1* | Transcription factor | Gain-of-function mutations | [75] |
| | *YMC1* | Transmembrane transporter | Upregulation | [64] |
| Amphotericin B | *ERG6* | C-24 sterol methyltransferase | Frame shift deletion mutation | [76, 77] |
| | *ERG2* | C-8 sterol isomerase | G145D | [64] |
| Echinocandins | *FKS1* | 1,3-β-D-glucan synthase-Hotspot-1 | Δ635F, F635L/Y, S639F/Y/P/T, D642Y | [40, 43, 60, 71, 78, 79] |
| | | 1,3-β-D-glucan synthase-Hotspot-2 | R1354S/H | [43, 79] |

fluconazole-resistant *C. auris* belonging to clades I and IV contain missense mutations in *TAC1B* transcription factor which caused increased expression of *CDR1* [74]. Gene replacement studies involving a common *TAC1B* mutation (A640V) have confirmed the role of this gene in fluconazole resistance [74]. *MDR1* homologs are also upregulated in triazole-resistant *C. auris*. The *MDR1* is upregulated by *MRR1*, another transcription factor. A gain-of-function mutation (N647T) has been described in *MRR1* which causes upregulation of *MDR1*, and introduction of mutant *MRR1* allele in a fluconazole-susceptible *C. auris* isolate caused significant increase in the MIC for triazoles [69, 75]. Another *C. auris* gene implicated in fluconazole resistance is *YMC1* that encodes transmembrane transporter activities important for mitochondrial function, and few fluconazole-resistant *C. auris* isolates lacking K143R mutation in *ERG11* contain a nonsynonymous (G145D) mutation in *YMC1* (Table 1) [64].

Unlike *C. glabrata* or *C. albicans*, gene targets conferring amphotericin B resistance in *C. auris* are poorly defined [18, 19••, 69]. The role of a nonsynonymous (G145D) mutation in *ERG2*, detected in some amphotericin B-resistant *C. auris* isolates, is not well established [64]. The first molecular mechanism conferring high level of resistance to amphotericin B (MIC of 32 µg/mL) in *C. auris* identified a novel deletion (frame shift) mutation in *ERG6* which was supported by sterol analyses of mutant cells and by Cas-9-mediated genetic manipulations [76]. Another *C. auris* isolate carrying a large deletion of 164 amino acids in *ERG6* and exhibiting high-level of resistance to amphotericin B has also been described. The mutant allele was confirmed to confer resistance to amphotericin B when it was introduced into a susceptible strain [77]. However, mutations in *ERG6* do not appear to be the main mechanism of resistance to amphotericin B in *C. auris*, particularly for isolates with low level of drug resistance [19••, 69, 76].

Echinocandin resistance in *C. auris* mainly involves nonsynonymous mutations in the hotspot-1 (HS-1) and HS-2 regions of *FKS1* encoding 1,3 β-D-glucan synthase. Most genetic alterations occur at codon 639 in HS-1 of *FKS1* gene (Table 1) [43, 60, 71, 78, 79]. Two nonsynonymous mutations (F635L and F635Y) as well as deletion of codon F635 and D642Y mutation within HS-1 of *FKS1* have been detected in some echinocandin-resistant *C. auris* [40, 43, 78, 79]. Two nonsynonymous mutations (R1354S and R1354H) have also been found within HS-2 of *FKS1* (Table 1) [43, 79]. Clinical *C. auris* isolates with identical *FKS1* mutations exhibit variable susceptibility to echinocandins (different MIC values) likely due to differences in their genetic background [35•, 43, 78, 79]. Also, patients infected with *C. auris* strains carrying different *FKS1* mutations show variable in vivo response to treatment with antifungal drugs suggesting differences in fitness cost associated with these mutations [43, 78, 80]. This is also supported by the gradual reversal of echinocandin resistance after removal of antifungal pressure [80]. Echinocandin-treated *C. auris* cells exhibit slower growth, cell–cell adhesion, biofilm formation, elevated chitin content, and cross resistance to fluconazole [80]. These characteristics likely aid in the survival and persistence of *C. auris* in the environment and promote reservoirs that may subsequently cause outbreaks in healthcare settings.

## Strategies to Prevent Transmission of *C. auris* in Healthcare Settings

There are several reasons why *C. auris* is able to cause outbreaks of invasive infections in healthcare facilities that have been difficult to treat. These include its overlapping phenotypic characteristics with other closely related species compromising its rapid identification, its ability to resist killing by common disinfectants, persist and remain viable for weeks to months, mostly due to biofilm formation, in the hospital environment, and its intrinsic resistance to some

drugs and ability to rapidly acquire resistance to other antifungals, often resulting in a multidrug-/pan-resistant phenotype [19••, 43, 52, 78, 81–83]. *C. auris* frequently colonizes the skin, respiratory tract, and urinary tract and is shed from the skin into the environment contaminating surfaces/equipment. This causes person-to-person transmission of infection through direct/indirect contact in hospital settings [19••, 26•, 64, 84•, 85].

Risk factors for invasive *C. auris* infections are common with other pathogenic *Candida* species described above, and nearly 10% of *C. auris*-colonized patients develop invasive infections, particularly those with mechanical ventilation and placement of invasive devices in ICU settings [26•, 40, 46, 64, 84•, 85–87]. Crude mortality rates of 0 to 72% have been reported for *C. auris* infections [20•, 26•, 40, 44, 88]. Due to these reasons, specific guidelines/recommendations have been published by the CDC and other leading international health agencies for controlling *C. auris* outbreaks in healthcare facilities [88–91]. A brief account of the current recommendations is described below, and the main points are summarized in Table 2.

## Identification of Cases of C. auris-Invasive Infections and Colonization

Rapid and accurate detection of *C. auris* in yeast cultures and more importantly in clinical specimens is vital to identify infected/colonized patients. Recommendations from leading experts and international health agencies advocate that detection of even a single case of *C. auris* should start an epidemiological investigation and implementation of infection control measures and contact precautions to prevent further transmission [19••, 84•, 85, 89–92]. Research has shown that delayed recognition of infection/colonization and delayed implementation of infection control practices causes rapid transmission of *C. auris* to other hospitalized patients sharing space and/or common facilities and equipment [26•, 84•, 85, 93, 94]. Although culture is considered the gold standard for definitive diagnosis of *Candida* infection, it is slow and also lacks sensitivity as nearly 50% cases of candidemia/invasive candidiasis remain culture-negative [95, 96]. Furthermore, species-specific identification of *C. auris* in all cultures from invasive samples consumes additional time and resources [52, 56, 97].

Recent developments in molecular diagnostic procedures now allow rapid identification of invasive *C. auris* infections within a few hours with high sensitivity and specificity [52, 57, 97]. Quantitative real-time PCR assays have been developed for cost-effective and rapid detection of live *C. auris* cells from the hospital environment and from skin and other patient swab samples for the detection of colonized patients [98–100]. A portable quantitative real-time PCR-based point-of-care test for *C. auris* detection in clinical samples, reporting results in ≤ 30 min, has also been developed recently [101].

Once a *C. auris*-positive case has been identified, the hospital infection control team should be informed immediately to implement transmission-based precautions (TBPs) so that other patients in the facility are not affected [19••, 84•, 85, 89]. The treating clinicians/infectious disease specialists should be alerted for proper patient management and the microbiology laboratory staff for diagnostic capacity building to efficiently and correctly identify *C. auris*. One study has shown that hospitalized patients on ventilator or those who received systemic fluconazole or carbapenem antibiotics in the prior 90 days or had ≥ 1 visit to the hospital for acute care in the previous 6 months are more likely to be colonized with *C. auris* [102]. Pre-emptive screening of new patients suspected to be colonized, particularly those with international exposure or history of previous stay in a hospital with *C. auris* infections or with risk factors listed above, should be carried out for axilla, groin, and other relevant (urine, throat, wounds, catheter) sites [19••, 64, 84•, 85, 89]. Considering the high frequency of skin and rectal colonization and shedding into the environment [19••, 84•, 85, 94, 102, 103], *C. auris*-positive patients should be placed in single occupancy rooms with attached toilet facilities. If this is not feasible, all *C. auris*-positive patients should be cohorted and cared for by a dedicated healthcare workers (HCWs) team familiar with the management of patients infected with multidrug-resistant organisms [19••, 84•, 85].

## Hand Hygiene and Other Transmission-Based Precautions (TBPs)

Transmission of *C. auris* to other patients in hospital settings is largely facilitated by its ability to persist in a viable form on various environmental surfaces/equipment within the patient's room such as walls/floors, mattresses/pillows/bed sheets, bed side trolleys, sinks, door and faucet handles, disposable/reusable equipment (oxygen mask, temperature/blood pressure monitors), and other objects (intravenous pole, personal mobile phones, cloth lanyards, etc.) 19••, 84•, 85, 89, 94, 102. *C. auris* also survives for weeks on different environmental surfaces due to the formation of biofilms and has also been isolated from the hands/nares/groin of HCWs which could also serve as the source of its transmission to other hospitalized patients [19••, 26•, 64, 83, 84•, 85, 104].

Since new patients are colonized with this yeast with a contact time of just 4 h with *C. auris*-positive patients and invasive infections have occurred in patients within 48 h of admission in ICU settings [26•, 64], efforts should be made to minimize transmission of *C. auris* to other patients in hospital settings. All HCWs attending *C. auris*-infected patients should frequently use alcohol-based hand rubs, and soiled hands should be thoroughly cleaned with soap and

**Table 2** Strategies to prevent transmission of *C. auris* in healthcare facilities

| Key intervention steps | Specific aim(s) and/or actions | Infection control measures |
|---|---|---|
| Identification of *C. auris*-infected/*C. auris*-colonized patients | - Species-specific identification of *Candida* in sterile body fluids from all suspected cases of invasive infections | - Alert infection control team, treating clinicians and microbiologists |
| | - Pre-emptive isolation and screening of patients with international exposure or from facilities with existing *C. auris* cases and their close contacts or those suspected to be colonized | - Cohorting or isolation of *C. auris*-positive patients in single rooms with attached toilet facilities |
| | - Since culture-based methods are slow and lack sensitivity, rapid quantitative real-time PCR-based automated methods, reporting results in hours, should be preferred | - Periodic assessment of the persistence of colonization and deisolation of negative patients |
| Hand hygiene and other transmission-based precautions (TBPs) | - Frequent use of alcohol-based hand rubs by healthcare workers (HCWs) and washing of soiled hands with soap and water followed by alcohol-based hand rubs | - Strict adherence to hand hygiene and PPE by HCWs |
| | - Proper use of personal protective equipment (PPE) by HCWs and usage of disposable items/equipment whenever possible | - Restricted visitors entry and strict adherence to PPE and TBPs |
| | - Restricted movement of *C. auris*-positive patients and they are to be scheduled last for medical procedures or surgery | - TBPs to be followed till *C. auris*-positive cases are detected |
| Environmental/equipment cleaning and disinfection | - Two or 3 times daily cleaning of patients' rooms/toilets with chlorine-based or hospital grade sporicidal disinfectants | - Discard less-expensive items which cannot be easily cleaned |
| | - Single-patient use items (pillows, bedding material, wipes for cleaning) and equipment (thermometers, blood pressure cuffs, etc.) are preferable | - Thorough monitoring of the environment and equipment cleaning procedures by regular sampling for *C. auris* growth |
| | - Common equipment should be thoroughly cleaned and disinfected as per manufacturer's recommendations | |
| | - Terminal cleaning of patient's room/equipment on discharge with agents with certified antifungal activity | |
| | - Hydrogen peroxide vapor/ozone/UV-C disinfection as an additional safety measure | |
| Decolonization of *C. auris*-positive patients | - No specific protocols or recommendations are advocated by any leading health organization | - Adherence to central, peripheral, and urinary catheter care bundles |
| | - Skin decontamination with chlorhexidine washes/wipes, mouth gargles for patients on ventilators and disinfectant-soaked pads for catheter exit sites may be helpful | |

water followed by application of alcohol-based hand rub, don personal protective equipment (PPE) while attending the patients and use disposable items/equipment whenever it is feasible to do so [89–91, 94, 104–106]. Minimum number of HCWs should be designated for the care of *C. auris*-infected patients. The infection control team of the hospital should ensure strict adherence to hand hygiene and proper use of PPE (gloves and a long-sleeved gown) by HCWs while attending *C. auris*-infected patients. Wearing of a face mask by HCWs may also be helpful in preventing their own colonization with *C. auris* [89–91, 94, 104–106].

Rooms housing *C. auris*-infected patients should be clearly marked, and limited entry by visitors should be allowed only after adherence to PPE and TBPs. *C. auris*-positive patients should be moved only when it is absolutely necessary, and they should be placed last on the list for non-emergency imaging, medical procedures, or surgery to avoid contact with other patients and to allow thorough cleaning of the equipment/environment afterwards [19••, 84•, 85, 89]. Colonized patients should be followed until discharge from the facility or when they have turned culture-negative during regular screening, and TBPs should be enforced until *C. auris* cases are detected in the facility [19••, 84•, 85].

## Cleaning and Disinfection of Environment and Reusable Equipment

International health agencies and expert opinion have recommended disinfection of high touch areas and reusable equipment in rooms housing *C. auris*-infected patients with hospital-grade agents effective against *Clostridium difficile* spores to minimize cross-transmission of infection to other patients [19••, 84•, 85, 89]. Cleaning surfaces twice or three times daily in rooms with *C. auris*-positive patients with chlorine-based or other sporicidal disinfectants is highly effective in controlling cross-transmission of infection [19••, 84•, 85]. To avoid laborious cleaning procedures, single-use items (pillows, bedding material, and fiber cloth wipes for cleaning), and equipment (thermometers, blood pressure cuffs, etc.) should be preferred for *C. auris*-positive patients. Less expensive items which cannot be easily cleaned should be discarded [19••, 84•, 85]. Considering that biocidal agents effective against *C. auris* should be fast-acting as real-world contact times for disinfectants usually do not exceed 1 to 2 min, commonly used hospital agents (such as chlorhexidine and benzalkonium chloride) have limited activity against *C. auris* [107–110]. The efficacy and minimum contact time for different formulations of disinfectants and antiseptics effective against *C. auris* planktonic cells and biofilms are listed in Table 3.

Chlorine-based products such as sodium hypochlorite (≥ 1000 parts per million, ppm) are effective against planktonic cells and, at pH of 13.13, against *C. auris* biofilms during environmental decontamination. However, very high concentrations (≥ 6000 PPM) are irritating to some patients/HCWs and corrosive for medical/dental devices [105, 109–111]. Peracetic acid at 2000 ppm and sodium dichloroisocyanurate at 4000 ppm are also effective against planktonic cells of *C. auris* (Table 3) [104, 109, 111]. For biofilms, peracetic acid (3500 ppm, pH 8.82) and sodium dichloroisocyanurate (1000 ppm, pH 13.13) are also effective as they prevented the transfer and regrowth of *C. auris* [111]. Chlorhexidine gluconate (2%) in 70% isopropanol and povidone-iodine (10%) are yeasticidal for planktonic cells of *C. auris* [112].

Hydrogen peroxide (> 1%) or vaporized hydrogen peroxide, ozone, and ultraviolet subtype-C (UV-C) light are also yeasticidal for *C. auris* [82, 112–115]. The UV-C light also prevents biofilm formation [116]. The UV-C light was more effective in non-shaded areas than in shaded areas [115]. Flushing of sinks in patient's room with ozonated water (2.5 ppm) for 30 s every 4 h resulted in complete elimination of *C. auris* within 2 days [117]. Silver nanoparticles have also been recently recognized as promising antifungal agents against growth and biofilm formation of *C. auris* on medical and environmental surfaces [118].

Common equipment serves as a source of *C. auris* spread in healthcare facilities and should be thoroughly disinfected after every use as per the manufacturer's instructions and its compatibility with the disinfectant [19••, 84•, 85, 119]. Glutaraldehyde and peracetic acid preparations, though expensive and/or corrosive for some metals, have also been used for cleaning of medical/dental devices to prevent cross-transmission of *C. auris* [108, 113]. Ethanol (70%), isopropyl alcohol (70%), and other products containing ethanol or phenols are suitable for cleaning small spills [105, 108].

Terminal cleaning and disinfection of everything in the patient's room on discharge are mandatory with agents of certified antifungal activity. In addition to regular cleaning with disinfectants, fogging with hydrogen peroxide vapor, ozone, and UV-C disinfection should also be performed as an additional safety measure [19••, 84•, 85, 94]. Regular sampling for *C. auris* growth should be done to ensure that the environment and reusable equipment are being disinfected adequately [19••, 84•, 85, 94].

## Decolonization of C. auris-Positive Patients

Once *C. auris* is acquired, patients usually remain colonized with this yeast. One hospitalized patient in Kuwait yielded more than 17 isolates from five (urine, tracheal secretion, vagina, catheter tip) different sites over a span of nearly 10 months [71]. Strict adherence to central and peripheral catheter care bundles, urinary catheter care

**Table 3** Efficacy of common disinfectants and antiseptics against planktonic cells and biofilms of *C. auris*

| Disinfectants and antiseptics | Concentration | CFU reduction or % killing | Minimum contact time (min) | Main reference(s) |
|---|---|---|---|---|
| For planktonic cells | | | | |
| Sodium hypochlorite | 1000 ppm | > 6 $Log_{10}$ CFU reduction | 5 | [82, 109] |
| Sodium hypochlorite | 4000 ppm | > 3 $Log_{10}$ CFU reduction | 1 | [109] |
| Sodium dichloroisocyanurate | 1000 ppm | > 6 $Log_{10}$ CFU reduction | 4 | [109] |
| Sodium dichloroisocyanurate | 4000 ppm | > 3 $Log_{10}$ CFU reduction | 1 | [109] |
| Peracetic acid | 2000 ppm | 100% | 5 to 10 | [104] |
| Chlorhexidine gluconate in 70% IPA | 2% | > 5 $Log_{10}$ CFU reduction | 2 | [112] |
| Isopropyl alcohol | 70% | > 3 $Log_{10}$ CFU reduction | 1 | [108] |
| Povidone-iodine | 10% | > 4 $Log_{10}$ CFU reduction | 2 | [112] |
| Hydrogen peroxide | 1.4% | > 5 $Log_{10}$ CFU reduction | 1 | [113] |
| Hydrogen peroxide (vaporized) | 8 $g/m^3$ | 96.6 to 100% | 3 to 5 | [82] |
| Ozone | 300 $mg/m^3$ | > 3 $Log_{10}$ CFU reduction | 40 | [110] |
| Ozonated water for bathroom sinks | 2.5 ppm | Undetectable level | 30 s/4 h, 2 days | [117] |
| Ultraviolet (UV-C) light | 254 nm | > 6 $Log_{10}$ CFU reduction | 30 | [114, 115] |
| For biofilms | | | | |
| Sodium hypochlorite, pH 13.13 | 1000 ppm | > 7 $Log_{10}$ CFU reduction | 2 | [104] |
| Hydrogen peroxide | 3% | 90% | 5 | [104] |
| Peracetic acid, pH 8.82 | 3500 ppm | > 7 $Log_{10}$ CFU reduction | 2.2 | [111] |
| Sodium dichloroisocyanurate, pH 5.64 | 1000 ppm | > 7 $Log_{10}$ CFU reduction | 2.2 | [111] |
| Ultraviolet (UV-C) light | 267 nm | 99.90% | 0.4 | [116] |
| Silver nanoparticles | 2.3 ppm | > 80% | 24 h | [118] |
| For medical/dental devices | | | | |
| Glutaraldehyde | 2.4% | > 4 $Log_{10}$ CFU reduction | 1 | [108] |
| Peracetic acid | 3500 ppm | > 7 $Log_{10}$ CFU reduction | 5 to 10 | [113] |

*CFU*, colony-forming units; *ppm*, parts per million; *s*, seconds; *h*, hours

bundle, and proper care of the tracheostomy site are measures that are more likely to prevent *C. auris*-invasive infections [89]. Although there are no specific guidelines for the decolonization of *C. auris*-positive patients from CDC or other international health agencies, some centers have attempted to eliminate this organism from colonized patients. One study reported only partial success, with twice daily skin decontamination with disposable wash cloths (wipes) soaked in 2% chlorhexidine gluconate or 4% chlorhexidine solution, mouth washing of patients on ventilator support with 0.2% chlorhexidine and chlorhexidine-soaked disks for central vascular catheter exit sites to minimize seeding of blood with *C. auris*, as new cases continued to occur in the hospital [26•]. Isopropanol augments the activity of chlorhexidine for decolonization of *C. auris* from skin, and both tea tree and lemongrass oil further enhanced the decolonization by chlorhexidine/isopropanol combination [120]. However, even if decolonization is transiently achieved in some patients, recolonization may occur soon afterwards from the bedding material, pillows, or other personal items where *C. auris* can survive for several days [19••, 26•, 105].

## Future Perspectives

New rapid, sensitive, and more specific point-of-care tests are being developed for rapid identification of *C. auris* in yeast cultures and also directly in clinical specimens [52, 98–101]. These tests will help in rapid identification of *C. auris*-infected/*C. auris*-colonized patients for early implementation of strategies to prevent further transmission of infection to other patients in hospital settings. Advances are also being made in *C. auris* eradication from patients' rooms. In addition to silver nanoparticles, silver functionalized nanostructured titanium has recently been recognized as a promising antifungal agent against growth and biofilm formation of *C. auris* on medical and environmental surfaces [121]. Far ultraviolet subtype C (222 nm) (Far-UVC) has recently been shown to destroy airborne pathogens nearly instantly in room-sized chambers [122]. Other novel antifungal agents and disinfectants are also being discovered with potent activity against *C. auris* [123, 124].

Major developments are also underway in the discovery of new drugs/drug combinations to improve treatment of *C. auris* infections [125, 126•]. Emerging antifungal compounds being investigated include natural compounds, antimicrobial

peptides, immunotherapy, metals and nano particles, photodynamic and combinational therapy, and repurposed drugs [118, 125, 126•, 127]. Colistin showed synergistic activity with amphotericin B against *C. auris* [128], while farnesol boosted the antifungal effect of fluconazole [129]. Fluconazole-resistant *C. auris* isolates have higher levels of chitin in their cell wall and increased susceptibility to a glucosamine-6-phosphate synthase inhibitor [130]. Ibrexafungerp, a member of the triterpenoids, inhibits the production of (1,3)-β-D-glucan and has shown good in vivo activity against fluconazole-resistant *C. auris* in an experimental mouse model of invasive candidiasis [131]. Combination therapy with a lower dose of amphotericin B with anidulafungin/caspofungin provided greater killing with synergistic and/or fungicidal outcomes against *C. auris* [132]. Major advances in the above areas will be greatly beneficial in controlling *C. auris* infections and outbreaks.

Recent description of *Candida khanbhai*, another novel yeast species [133] closely related to *C. haemulonii* species complex and its colony characteristics on CHROMagar Candida Plus diagnostic test, similar to *C. auris*, have compromised the utility of this simple test for specific identification of *C. auris* among clinical yeast isolates.

## Conclusions

*C. auris* has now become a major threat to global public health as sporadic cases detected in some countries soon after its identification as a human fungal pathogen have given way to major outbreaks in healthcare facilities in many countries with unfavorable outcomes. The patients most commonly affected include elderly subjects with multiple comorbidities, exposure to broad-spectrum antibiotics/antifungal drugs, arterial or central venous catheters, major surgery, and prolonged stay in the ICU. Major problems associated with inadequate management of *C. auris*-infected patients include faulty routine diagnostic methods yielding inaccurate identification in yeast cultures and clinical specimens, its intrinsic or acquired resistance to one or more antifungal drugs limiting treatment options, its resistance to killing by hospital disinfectants, and its rapid transmission to other susceptible patients during routine contact or shared equipment in healthcare facilities. However, recent advances towards rapid, sensitive, and more specific point-of-care tests for identification of *C. auris* in yeast cultures and clinical specimens, susceptibility testing to guide treatment, and its eradication from the patients' environment by using novel disinfectants and infection control measures offer hope that *C. auris* infections/outbreaks can be controlled or even prevented in the near future.

## Declarations

**Conflict of Interest** The authors declare no competing interests.

**Human and Animal Rights and Informed Consent** This article does not contain any studies with human or animal subjects performed by any of the authors.

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