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Narrative review

Resistance of *Candida* to azoles and echinocandins worldwide

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ABSTRACT

Background: Recently there has been an increase in *Candida* infections worldwide. A handful of species in the genus *Candida* are opportunistic pathogens and have been known to cause infections in immunocompromised or otherwise impaired hosts. These infections can be superficial, affecting the skin or mucous membrane, or invasive, which can be life-threatening. Azoles and echinocandins are antifungal drugs used globally to treat *Candida* infections. However, resistance to these antifungal drugs has increased in many of the *Candida* species, and the effects this has in the clinical setting can be seen.
Objectives: Here, we discuss the mechanisms that *Candida albicans*, *Candida dubliniensis*, *Candida glabrata*, *Candida parapsilosis*, *Candida tropicalis* and *Candida auris* are implementing to increase resistance to azoles and echinocandins, and how they are affecting clinical, or hospital, settings worldwide.
Sources: Different studies and papers describing the mechanisms of antifungal drugs and *Candida* species evolution to becoming resistant to these drugs were looked at for this review.
Content: We discuss the mechanisms that azoles and echinocandins use against *Candida* species to treat infections, as well as the evolution of these fungi to become resistant to these drugs, and the effect this has in the clinical settings around the globe.
Implications: Increased resistance to azoles and echinocandins by *Candida* species is an increasingly serious problem in clinical settings worldwide. Understanding the mechanisms used against antifungal drugs is imperative for patient treatment. **K.E. Pristov, Clin Microbiol Infect 2019;25:792**

Introduction

Fungal infections caused by *Candida* species are emerging as a major problem in the healthcare field, leading to high mortality rates and expensive medical costs for governments and hospitalized patients [1,2]. High mortality rates can be attributed to the increasing occurrence of invasive systemic infections and cases of septicaemia, especially in immunocompromised patients [1–3]. Currently, *Candida* systemic diseases are the fourth leading cause of nosocomial bloodstream infections [3,4]. Of all invasive infections, 90% are caused by opportunistic *Candida* [1,5]. Opportunistic *Candida* species that reside in healthy hosts include *Candida albicans*, *Candida glabrata*, *Candida tropicalis*, *Candida parapsilosis* and *Candida krusei* [5]. When an individual becomes immunocompromised these species can cause invasive infections that may disseminate to the internal organs. Increased development of new treatments for diseases has caused an increase in the number of immunosuppressed patients along with surgery, long-term stays in intensive care units and previous administration of broad-spectrum antibiotics, all of which increase the risk of disseminated candidiasis [1,2,5].

Though antifungal drugs are available for *Candida* infections, mortality rates continue to be high. Estimated mortality rates from these infections may be up to 45% [6]. The use of new classes of antifungal drugs has not significantly improved the prognosis for infected patients [7]. Classes of drugs—such as azoles—have seen an increase in *Candida* resistance due to general and long-term use [4,8]. In this regard, resistance can be described as clinical or mycological. Monitoring resistance trends based on the resistance mechanism of *Candida* is key to predicting the response in a clinical setting, where actual patients are treated and observed, as opposed to working in a laboratory setting [9].

Clinical resistance is the failure to eradicate a fungal infection from a patient even though an antifungal drug with *in vitro* activity against the fungus has been administered. Mycological resistance is

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the ability of fungus to grow in the presence of antifungal drugs that would otherwise kill them or limit their growth *in vitro*. *In vitro* testing of the activity of an antifungal drug against a fungus is performed outside a living organism (i.e. in a Petri dish or test tube). The CLSI defines standard breakpoints for the MIC, which is used to measure the susceptibility of an antifungal drug against certain fungal species *in vitro* (Table 1).

In this review we discuss the mechanisms used by azoles and echinocandins to fight *Candida* infections, and also the mechanisms that *Candida* species are using to increase resistance to azoles and echinocandins. We will also discuss how increased resistance to these antifungal drugs in *Candida* species is affecting clinical and hospital settings worldwide. It is important to have antifungal drugs that will treat these infections without leading to increased resistance, though the use of azoles and echinocandin antifungal drugs against *Candida* species has seen this happen. As changes are seen in the resistance of fungi to antifungal drugs, CLSI breakpoints must evolve as well.

Candida species increased resistance to azoles and echinocandins

The presence of *Candida* species does not always signify that an individual has a fungal infection. The pathogenesis of candidiasis depends on the health of the host as well as on virulence factors expressed by the yeast. These factors include germ-tube formation, adhesions, phenotypic switching, biofilm formation and the production of hydrolytic enzymes [4]. The majority of diseases caused by *Candida* species are due to biofilm formation. A biofilm is a group of microorganisms embedded in an extracellular matrix, forming a three-dimensional structure on biotic and antibiotic surfaces (such as mucosal surfaces) [10]. Biofilms are genetically resistant to amphotericin B and fluconazole, both clinically and *in vitro*, providing the microorganisms with shelter and the opportunity to withstand high concentrations of antifungal agents [10–12]. Biofilms are formed by a number of *Candida* species [3], but pathogenic effects caused by biofilm formation are seen most frequently in *C. albicans* [8].

Table 1
Overview of CLSI susceptible and resistant breakpoints for various *Candida* species *in vitro*

Antifungal	*Candida* species	MIC breakpoints (mg/L)	
		S	R
Anidulafungin	*C. albicans*	≤0.25	≥1
	C. glabrata	≤0.12	≥0.5
	C. parapsilosis	≤2	≥8
	C. tropicalis	≤0.25	≥1
Caspofungin	*C. albicans*	≤0.25	≥1
	C. glabrata	≤0.12	≥0.5
	C. parapsilosis	≤2	≥8
	C. tropicalis	≤0.25	≥1
Micafungin	*C. albicans*	≤0.25	≥1
	C. glabrata	≤0.06	≥0.25
	C. parapsilosis	≤2	≥8
	C. tropicalis	≤0.25	≥1
Voriconazole	*C. albicans*	≤0.12	≥1
	C. glabrata	—	—
	C. parapsilosis	≤0.12	≥1
	C. tropicalis	≤0.12	≥1
Fluconazole	*C. albicans*	≤2	≥8
	C. glabrata	—	≥64
	C. parapsilosis	≤2	≥8
	C. tropicalis	≤2	≥8

Abbreviations: R, resistant; S, susceptible.
NOTE: CLSI has not determined breakpoints for *C. dubliniensis* and *C. auris;* any MIC of ≥4 mg/L is considered resistant.

For many years, infections caused by *Candida* species have been treated with azoles, the largest family of antifungal drugs. Recently, resistance to azoles has increased in *Candida* species, both in clinical settings and *in vitro*. Azoles are able to treat fungal infections by interfering with the enzyme lanosterol 14-α-sterol demethylase (Fig. 1) [5]. This enzyme is involved in ergosterol biosynthesis, which is a large component of the fungal cell wall, and is a promising antifungal target [1,13]. Inhibition of lanosterol 14-α-sterol demethylases by azoles leads to inhibition of fungal growth by altering the structure and function of the cell membrane [1,13]. Azoles do not interfere with host cell walls because the major target components—chitin, glucan and mannan—are absent from the human body, and because of the difference in structures between ergosterol and cholesterol (which is the main component in the host cell walls) [1,13].

There are three main ways in which *Candida* species may become resistant to azoles (Table 2). The first mechanism is the introduction of multidrug pumps in the fungal cell wall, which allow the cell to pump out the drug, decreasing the inhibition of enzymes and alteration of the fungal cell wall [1,2,5]. The pumps are the result of the up-regulation of genes through point mutations (*CDR1*/*CDR2* and *MDR1*) and transcription factors (TAC1 and MDR1), encoding for efflux pumps, which has been seen in *C. glabrata* strains that are resistant to azoles [1,5]. The second mechanism that can lead to azole resistance is through the alteration or up-regulation of the gene encoding for the enzyme being targeted, *ERG11*. If *ERG11* is mutated, the result is an alteration in the binding site of the enzyme, preventing the binding of azoles [1,5]. However, this mechanism seems to play a minimal role in the development of resistance to azoles in *Candida* species. The final mechanism is for the fungal cell to develop bypass pathways as a result of mutations. To prevent the alteration of the cell membrane and the accumulation of toxic products, another pathway that is not interrupted by azoles is formed that allows the fungus to maintain functional cell membranes [5].

As *Candida* species have become more resistant to azoles, a development shown in MICs and in clinical infections that do not respond to antifungal treatment, the use of echinocandins to treat *Candida* infections has increased. Echinocandins (lipopeptidic antifungals) interfere with glucan synthesis [1,14]. The drug inhibits the synthesis of β-(1,3) D-glucan (a critical cell wall polysaccharide) by non-competitive inhibition of the enzyme β-(1,3) D-glucan synthase (Fig. 1) [5,14]. All fungi have β-(1,3) D-glucan in their cell walls, making it the ideal target for broad-spectrum antifungal drugs [13,14]. The end result is impaired fungal cell wall formation that can result in osmotic lysis, causing cell death [1,5,13,14]. The fungicidal activity of echinocandins against most *Candida* species is concentration-dependent [5].

Echinocandins looked to be the answer for yeasts that were resistant to azoles, but recently there has been an emergence of *Candida* species that are resistant to echinocandins in both laboratory and clinical settings [2]. A link has been found between reduced susceptibility of *Candida* isolates and mutations in *FKS1* and *FKS2* genes (Table 2) [2,7]. The mutation of two regions of the *FKS1p* subunit of β-(1,3) D-glucan synthase leads to the substitution of serine 645 for proline, phenylalanine and tyrosine [2]. This changes the target site, therefore inhibiting echinocandins.

Prolonged drug exposure to *Candida* isolates seems to have led to reduced echinocandin susceptibility, especially in immunocompromised patients with recurrent candidaemia [4]. The emergence of multidrug-resistant *Candida* species and strains is spreading globally, affecting hospital settings and patients, as well as the treatments implemented for infections [15].

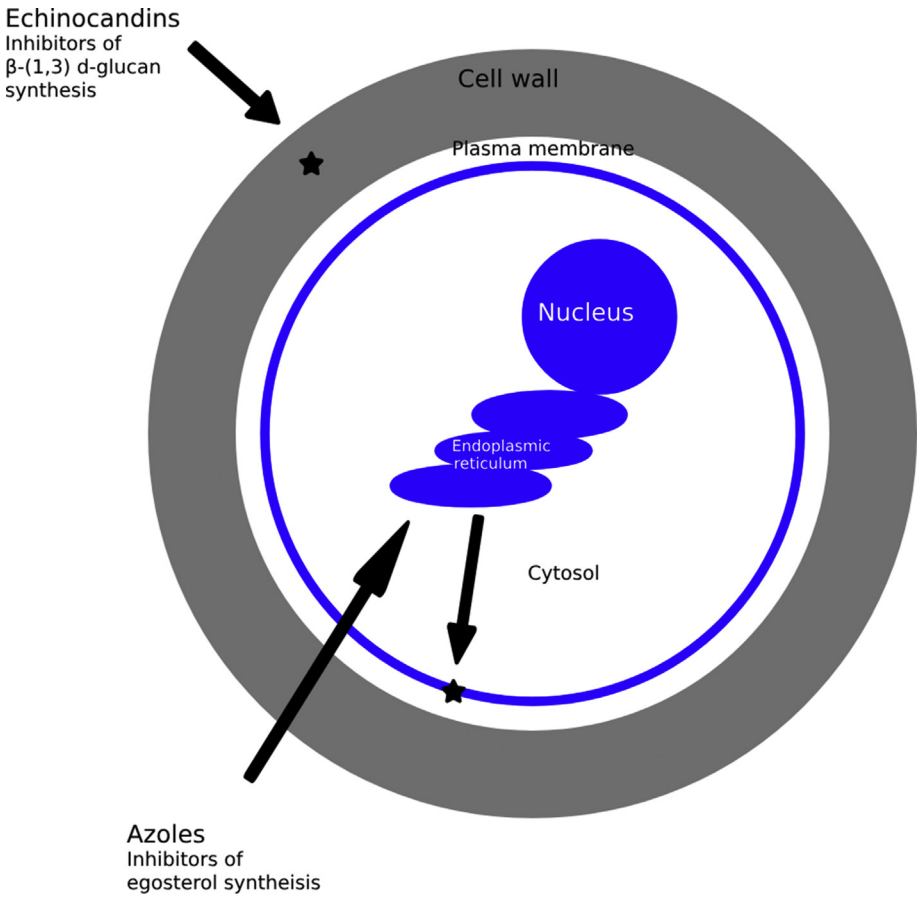

Fig. 1. Primary targets and mode of action by azoles and echinocandins [5].

Candida albicans

Candida albicans is the main cause of candidiasis in most clinical settings [7]. It is the third most commonly isolated microbe of bloodstream infections in hospitalized patients in the USA, according to the CDC [16]. It is an opportunistic pathogen residing in the oral and conjunctival flora, as well as in the gastrointestinal and genitourinary tracts [1]. When the host becomes immunocompromised, *C. albicans* can cause infection either superficially or internal dissemination, as well as septicaemia [17,18]. *Candida albicans* has the ability to switch morphology, existing in yeast, pseudohyphal and hyphal forms depending on the environment [18]. Virulence factors such as evasion of the host immune system and the ability to switch morphology combined with its prominence in the hospital setting makes *C. albicans* a high threat to patients [14,18].

Biofilms allow the cells to adhere to and proliferate on medically implanted devices as well as host tissue, causing infections [10,18,19]. Biofilm production by *C. albicans* is important to its resistance, with multiple studies reporting up to a 1000-fold greater drug resistance in biofilm-forming cells compared with non-biofilm cells *in vitro* [18].

Candida albicans can become resistant to azoles by increasing the number of efflux pumps in the cell, as described above [5,20,21]. Efflux pumps are membrane-associated transporters that work by preventing the intracellular accumulation of drug, thereby avoiding toxic levels that would kill the cell [1,5,20,21]. Due to this overexpression of efflux pumps, cross-resistance between azoles is often seen in *C. albicans*, both *in vitro* and clinically.

Candida albicans has also shown a high degree of cross-resistance to echinocandins. Unlike azole resistance, mutations in the amino acid positions in the *FKS1* gene have been linked to echinocandin resistance [1,20,21]. Elevated MICs, reduced β-(1,3) D-glucan synthase sensitivity and cross-resistance among echinocandins result from these mutations in the *FKS1* gene [20]. The development of *Candida* species resistance to antifungal drugs seems to be due to the genomic plasticity of the fungus [22].

Table 2
Overview of resistance mechanisms of azoles and echinocandins by Spampinato et al. [5]

Antifungal class	Genetic basis for resistance	Functional basis for resistance
Azoles	Up-regulation of *CDR1*/*CDR2* and *MDR1* by point mutations in *TAC1* and *MRR1* transcription factors	Up-regulation of drug transporters
	Point mutations in *ERG11*	Decreased lanosterol 14-α-demethylase binding affinity for the drug
	Up-regulation of *ERG11* by gene duplication and transcription factor regulation	Increased concentration of lanosterol 14-α-demethylase
	Point mutations in *ERG3*	Inactivation of C5 sterol desaturase leading to alterations in the ergosterol synthetic pathway
Echinocandins	Point mutations in *FKS1* and *FKS2*	Decreased glucan synthase processing for the drug

Candida dubliniensis

Candida dubliniensis is a species of *Candida* that was recognized in 1995 [23]. It shares many phenotypic characteristics with *C. albicans*, but it is much rarer in the normal human microflora [23,24]. This is reflected in the low prevalence of *C. dubliniensis* invasive infections. Moreover, the incidence of infection by this species has declined due, most probably, to the effectiveness of the antiretroviral therapies. *Candida dubliniensis* is highly prevalent in the oral cavities of individuals infected with human immunodeficiency virus or who have acquired immune deficiency syndrome, though the underlying reason is unclear [23,24].

Unlike *C. albicans* and other species of *Candida*, *C. dubliniensis* isolates are not currently showing drastic increased resistance to azoles and echinocandins [24]. Fluconazole is the one drug that *C. dubliniensis* has shown increased resistance to [23,24]. In one study, it was shown that fluconazole-susceptible isolates will go on to develop resistant derivatives once exposed to the drug *in vitro* [23,24]. The main mechanism for fluconazole resistance is similar to those of *C. albicans*, an overexpression of major facilitator efflux pump *MDR1* and *CDR1* [24].

Candida glabrata

Candida glabrata is the species most often responsible for resistance in hospitals, and is the second most frequently isolated from *Candida* infections [14,23,25,26]. *Candida glabrata*, along with *C. tropicalis* and *C. parapsilosis*, are the three most frequent causes of oral candidosis [27]. *Candida glabrata* has a higher incidence in adults than children and neonates [27]. Despite its inability to switch from yeast to hyphae or secrete protease enzymes, *C. glabrata* has many virulence factors, including thick biofilms that contribute to its pathogenicity [26,28]. It evades the host immune system, but persists without causing severe damage [14].

Many *C. glabrata* strains that cause septicaemia are resistant to fluconazole, an azole commonly used in the treatment of fungal infections [9,29]. *Candida glabrata* has a reduced susceptibility to azoles from an overexpression of efflux pumps, as seen in *C. albicans*, as well as cross-resistance to other azoles [29,30]. Decreased susceptibility to one or more echinocandins is seen in clinical isolates of *C. glabrata* [30,33]. Fluconazole-resistant *C. glabrata* strains isolated from the bloodstream of infected patients show co-resistance to echinocandins. It is believed that the increased use of azoles and echinocandins has caused selection pressure on *C. glabrata*, resulting in multidrug-resistant strains, as well as co-resistance [30].

In many cases, echinocandins are used for *C. glabrata* infections that have been previously treated with azoles. It has been discovered that *C. glabrata* isolates that have increased resistance to echinocandins have mutations in the *FKS1* or *FKS2* gene, or both [5,17,25,31]. This change substitutes subunits of β-(1,3) D-glucan synthase, the targets of echinocandins [1,32]. This leads to concerns of mutations in the *FKS* gene that may cause fluconazole-resistant *C. glabrata* strains to independently acquire resistance to echinocandins [9,25]. It has been seen that *C. glabrata* isolates recovered from patients who were previously treated with caspofungin for candidaemia showed high caspofungin MICs and mutations in the *FKS1* gene [23,26]. The greatest risk factor for developing breakthrough infections caused by echinocandin-resistant *C. glabrata* strains with *FKS* mutations is due to exposure within the preceding month [33].

Candida glabrata is a unique species that has the ability to acquire and then express resistance mutations in the presence of selection pressure brought on by the increased use of both azoles and echinocandins in the clinical setting.

Candida parapsilosis

Candida parapsilosis infections have increased recently, becoming the second or third leading cause of candidaemia, after *C. albicans*, in some European, Asian and Latin American medical centres [27,34,35]. Infections caused by *C. parapsilosis* are a significant problem among neonates, transplant recipients and patients receiving parenteral nutrition [27]. *Candida parapsilosis* has also been frequently isolated from human hands; it is suggested that colonization on healthcare workers hands leads to infection [27,35]. Its ability to form biofilm on medical devices, colonize intravascular devices and prosthetic materials, grow within parenteral nutrition, undergo phenotypic switching and secrete hydrolytic enzymes has led to the occurrence of nosocomial outbreaks and a high mortality rate [35–37]. Although *C. parapsilosis* has a lower mortality rate (4%) compared with *C. albicans*, it ranks second in producing biofilm among *Candida* species [27,35].

As is seen with other *Candida* species, certain *C. parapsilosis* isolates have been found to be increasingly resistant to azoles [37,38]. Rates of fluconazole resistance in *C. parapsilosis* isolates were found to be five times higher than those in *C. albicans* [36]. The mechanism for resistance is similar to that of *C. albicans* and *C. glabrata*, discussed above [35,37].

When it comes to echinocandin resistance, *C. parapsilosis* has a unique intrinsic resistance to these drugs, with MIC values, according to CLSI, for echinocandins being naturally higher than other common *Candida* species (2 mg/L vs 0.25 mg/L for *C. parapsilosis* and *C. albicans*, respectively) [27,34,36]. Though patients with systemic infections respond well to echinocandin treatments, even with the high MIC values, repeated exposure to echinocandins is a risk factor for *C. parapsilosis* developing resistance [34]. The echinocandin resistance mechanism in *C. parapsilosis* differs from the phenotypic changes seen in other *Candida* species. *Candida parapsilosis* has a natural polymorphism in *FKS1* gene, leading to reduced *in vitro* echinocandin susceptibility [34,36].

Candida tropicalis

Candida tropicalis is considered by many the second most virulent *Candida* species, behind *C. albicans* [39]. In recent years, there has been an increase in infections caused by *C. glabrata*, *C. tropicalis* and *C. parapsilosis* [27]. *Candida tropicalis* is seen most commonly in patients with neutropenia and malignancy [27]. The virulence factors of *C. tropicalis* include adhesion to buccal epithelial and endothelial cells, secretion of lytic enzymes (proteinases, phospholipase, haemolysins) and phenotypic switching; it is a strong biofilm producer [39].

Candida tropicalis shows resistance to azoles, and shows high resistance to fluconazole specifically [39]. Its mechanism for azole resistance is similar to those of the other *Candida* species [38,39].

Unlike other *Candida* species, *C. tropicalis* shows low resistance to echinocandins [39]. Any decrease in susceptibility to echinocandins by *C. tropicalis* would be a result of adaptive stress or mutations in the *FKS* genes, which is the resistance mechanism used by other species of *Candida* [2,7,39]. Currently, echinocandins show excellent activity against *C. tropicalis* and are a good option for treating infections [39].

Candida auris

Candida auris is a more recently discovered species of *Candida*, with the earliest isolate being discovered in 1996 [40,41]. It has emerged as a nosocomial pathogen globally and has proven difficult to treat. This yeast has become widespread across several countries due to its high clonal inter- and intra-hospital

transmission, and can be grouped into unique clades depending on geographical region [42–46]. *Candida auris* affects patients rapidly and colonizes the skin persistently, though the precise mode of transmission is unclear [44–46]. Infections with *C. auris* usually occur several weeks after admission; they are invasive infections that are a therapeutic challenge with no optimal treatment [40].

Like the other species of *Candida*, *C. auris* can cause superficial and invasive candidiasis, as well as bloodstream infections [40,41]; however, isolation of *C. auris* from non-sterile body sites are more likely colonization than infections [41]. *Candida auris* shares many virulence factors with *C. albicans*, such as genes and pathways involved in remodelling the cell wall, acquisition of nutrients, enzyme secretions and multidrug efflux pumps. It has also been discovered that a large percentage of *C. auris* genes are devoted to metabolism, which is a common occurrence in pathogenic *Candida* species and an adaptation to changing environments [40]. *Candida auris* is unique in that it is multidrug resistant, exhibiting resistance to fluconazole and variable susceptibility to other azoles, amphotericin B and echinocandins [40].

The only species that has isolates shown to be resistant to all four classes of human antifungal drugs is *C. auris* [20,21,40]. It has been found that almost half of *C. auris* isolates are multidrug-resistant, showing resistance to two or more classes of drugs, and a low number (about 4%) show resistance to all classes of antifungals [20,21,40]. The multidrug-resistant nature of *C. auris* may be explained by the genome encoding ATP-binding cassette and major facilitator superfamily transporter families along with drug transporters [40]. The *C. auris* isolates show mutations at azole-resistance codons similar to *C. albicans*, which results in azole resistance [3,5,20,21]. *Candida auris* infections are commonly treated with echinocandins. Although caspofungin is usually effective against biofilms formed by other *Candida* species, it has proved to be ineffective against *C. auris* biofilms [8,10,40].The full mechanism of *C. auris* antifungal resistance is still unclear. A few studies have reported breakthrough fungaemia while on fluconazole, suggesting an intrinsic resistance against this drug [40]. Although clinical breakpoints have yet to be defined for *C. auris*, newer azoles such as posaconazole (range 0.06–1 mg/L) and isavuconazole (range <0.015 to 0.5 mg/L) show excellent *in vitro* activity against *C. auris* [40]. As for treatment of *C. auris* infections in patients, the CDC recommends initial therapy with an echinocandin [47]. If the patient is clinically unresponsive to this treatment or has persistent fungaemia for >5 days, then switching to a liposomal amphotericin B (5 mg/kg daily) is recommended [47].

The multidrug resistance seen in *C. auris* is why it is such a formidable yeast.

Clinical impact

The emergence of drug-resistant isolates of *Candida* species has created a higher risk for clinical infections. The impact that these strains may have in the clinical setting is an ever growing concern. This could be associated with poorer clinical outcomes for patients and breakthrough infections during antifungal treatment and prophylaxis, and increased healthcare costs [20,48].

Candida auris has emerged as a major threat in the healthcare setting, having caused outbreaks in hospitals, and proved difficult to treat due to its multidrug-resistant nature [45,46,49,50]. The CDC states that *C. auris* is difficult to identify and may be misidentified in laboratories without specific technology, leading to inappropriate management and outbreaks [49]. It is speculated that the hands of healthcare workers, as well as medical devices, can become contaminated and lead to cross-contamination between patients if cleaning is inadequate [16,45]. Biswal et al. performed as study in a hospital, where samples taken from the environment and from healthcare workers' hands showed the presence *C. auris* [51]. Current infection-control procedures for outbreaks include patient contact isolation, cleaning environmental surfaces with chlorine-based products, reducing bedside equipment, and adequate hand hygiene by healthcare workers [43,44,46,48–50,52].

Other studies have recovered *C. auris*, as well as other *Candida* species, from environmental surfaces and reusable equipment in healthcare facilities, implying that contaminated surfaces may be the source of transmission [45,53]. Transference of *C. auris* from surfaces to hands has been successfully demonstrated in a study by Schelenz et al. [46]. It has been shown to colonize and infect patients, and they can contaminate their immediate environment because *C. auris* has been recovered from infusion pumps, chairs, countertops and windowsills [12,34]. Many of the *Candida* species can survive for prolonged periods on surfaces, whether moist or dry, for up to 7 days [49,53]. It is recommended by the CDC that surfaces be disinfected daily and after discharge in the rooms of patients with *C. auris* [49].

However, the Environmental Protection Agency does not have any registered hospital disinfectants for use against *C. auris* specifically [53]. It is also unknown whether *C. auris* is less susceptible to disinfectants than other *Candida* species [46,54]. There is limited information regarding the eradication of *C. auris* from hand transmission or the efficacy of skin decolonization regimens [46]. Quaternary ammonium wipes are typically used for cleaning; however, a study showed relatively poor activity of the cleaner against all *Candida* species [55]. *Candida auris* in particular seems to be resistant to quaternary compounds and cationic surface-active disinfectants [41]. The CDC has recommended that Environmental Protection Agency-registered hospital-grade disinfectants effective against *Clostridium difficile* spores be used against *C. auris*. One study showed support for this recommendation, although, they were also able to demonstrate that non-sporicidal improved hydrogen peroxide disinfectants showed high activity against *Candida* species, including *C. auris* [44]. Supporting evidence of this came from another study that used disinfectants with sporicidal activity and hydrogen peroxide-based products to clean surfaces and healthcare facilities, which resulted in the highest reduction of *C. auris* CFU [41].

Another problem presented by *C. auris* is colonization of non-sterile body sites [41,44,55]. These sites include the urinary tract, external ear canals, wounds and lungs, which will not cause an active infection [41,55,56]. The CDC recommends the same infection control for both infection and colonization with *C. auris* [56]. Colonization has been found on patients several months after an active infection has been resolved, although the maximum amount of time a patient can be colonized is unknown [56]. The CDC states that currently there are no data on the efficacy of decolonization of patients with *C. auris*, such as using chlorhexidine or topical antifungals [46,56]. Further research of *C. auris* colonization using animal skin models (similar to those used for bacterial colonization) in the hope of finding an optimal treatment for *C. auris* colonization is crucial.

Conclusion

Our review demonstrates that although azoles and echinocandins are effective against *Candida* species, many species have developed resistance to them. Drug-resistant *Candida* strains pose a threat to infected patients and have clinical impacts worldwide. Being able to identify and treat invasive infections caused by *Candida* is important to the health of patients and in preventing clinical outbreaks.

Additionally, we discuss the critical impact that *C. auris* has had in hospitals worldwide. Its multidrug-resistance, as well as its

ability to survive on surfaces, dry or moist, for multiple days, emphasizes the importance of disinfecting hospital surfaces in patient rooms. Colonization of *C. auris* is also an increasing issue as it can eventually cause invasive infections and outbreaks. Currently, there is no recommended action for decolonization of *C. auris*, and this paired with its multidrug resistance makes it an difficult yeast to manage.

Future recommendations for expanding knowledge, as well as effective treatment, for *C. auris* colonization is through the development of an animal skin model. Bacterial colonization has been tested on such models and results have provided useful compounds for decolonization [57]. Demonstrating an effective way to decolonize *C. auris* could help prevent infections and outbreaks in the clinical setting and warrants further exploration.

Transparency declaration

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