



Review on Antifungal Resistance Mechanisms in the Emerging Pathogen *Candida auris*

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Candida auris is an emerging multi-drug resistant yeast, that causes major issues regarding patient treatment and surface disinfection in hospitals. Indeed, an important proportion of *C. auris* strains isolated worldwide present a decreased sensitivity to multiple and sometimes even all available antifungals. Based on recent tentative breakpoints by the CDC, it appears that in the USA about 90, 30, and < 5% of isolates have been resistant to fluconazole, amphotericin B, and echinocandins, respectively. To date, this has led to a low therapeutic success. Furthermore, *C. auris* is prone to cause outbreaks, especially since it can persist for weeks in a nosocomial environment and survive high-end disinfection procedures. In this review, we describe the molecular resistance mechanisms to antifungal drugs identified so far in *C. auris* and compare them to those previously discovered in other *Candida* species. Additionally, we examine the role that biofilm formation plays in the reduced antifungal sensitivity of this organism. Finally, we summarize the few insights on how this yeast survives on hospital surfaces and discuss the challenge it presents regarding nosocomial environment disinfection.

Keywords: *Candida auris*, antifungal resistance, biofilm, emerging pathogen, MIC, outbreaks

1. INTRODUCTION

In the last decade, an emerging nosocomial *Candida* species has been causing severe cases of candidemia and other types of fungal infections. Outbreaks of the responsible pathogen, namely *Candida auris*, have been observed all around the world (see **Figure 1A**) (Lockhart et al., 2017).

Whole genome sequencing determined the presence of four specific clades within the *C. auris* species: East Asia, South Asia, South Africa, and South America. All clades are characterized by distinct single nucleotide polymorphisms (SNPs), which highlights the independent and worldwide emergence of this pathogen (Lockhart et al., 2017).

Comparative studies in different animal models (murine and *Galleria mellonella* larvae) showed strain-dependant virulence levels for *C. auris*. In most cases, *C. auris* strains proved to be less virulent than *C. albicans* (Borman et al., 2016; Ben-Ami et al., 2017; Fakhim et al., 2018; Wang et al., 2018). However, reported cases of *C. auris* outbreaks were linked with a high mortality rate, primarily in immunocompromised patients. Other conditions such as diabetes, cardiovascular and/or pulmonary diseases, sepsis or a prior treatment with antibiotics seemed also to be important risk factors (Osei Sekyere, 2018).

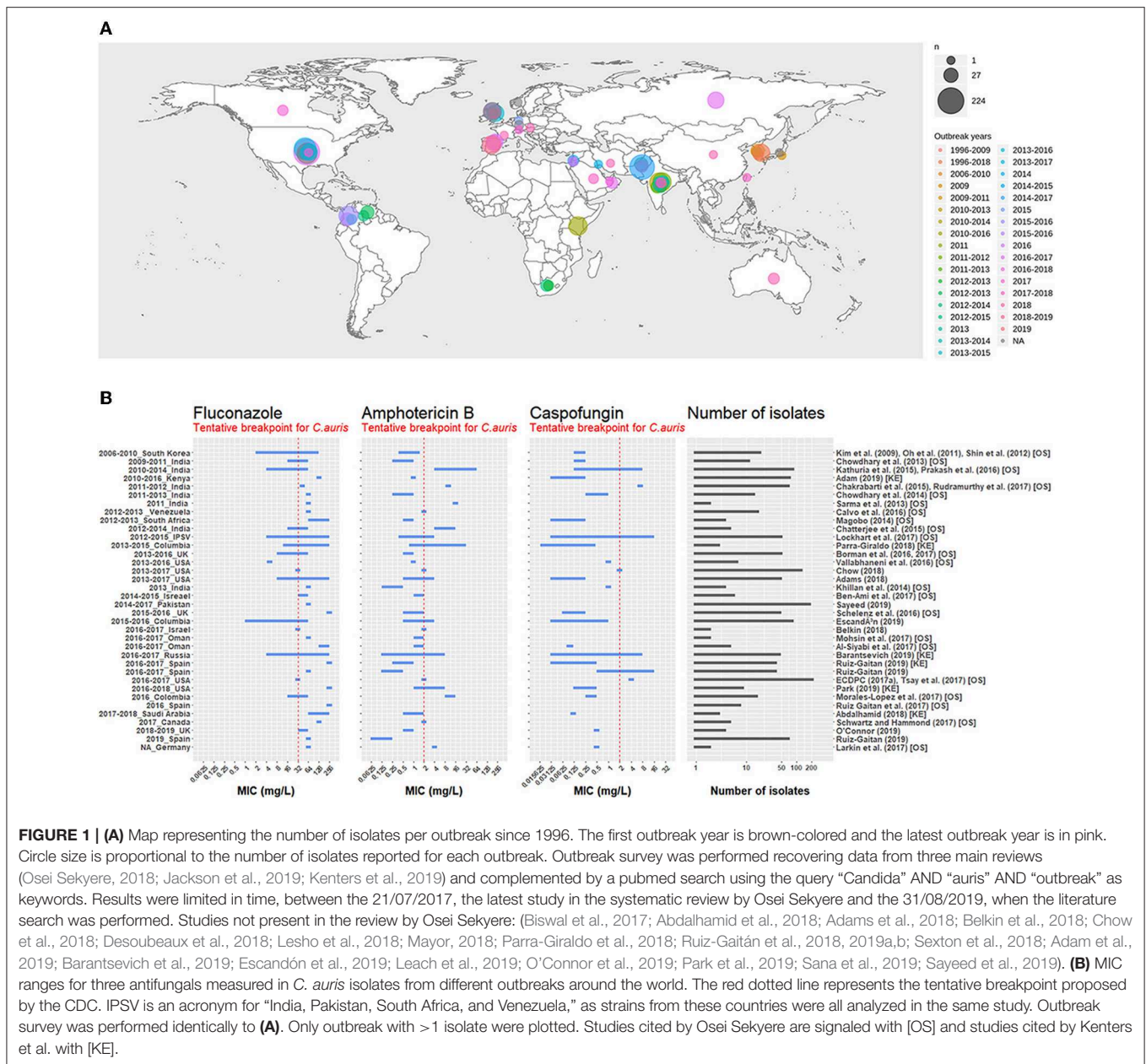


FIGURE 1 | (A) Map representing the number of isolates per outbreak since 1996. The first outbreak year is brown-colored and the latest outbreak year is in pink. Circle size is proportional to the number of isolates reported for each outbreak. Outbreak survey was performed recovering data from three main reviews (Osei Sekyere, 2018; Jackson et al., 2019; Kenters et al., 2019) and complemented by a pubmed search using the query “*Candida*” AND “*auris*” AND “outbreak” as keywords. Results were limited in time, between the 21/07/2017, the latest study in the systematic review by Osei Sekyere and the 31/08/2019, when the literature search was performed. Studies not present in the review by Osei Sekyere: (Biswal et al., 2017; Abdalhamid et al., 2018; Adams et al., 2018; Belkin et al., 2018; Chow et al., 2018; Desoubreaux et al., 2018; Lesho et al., 2018; Mayor, 2018; Parra-Giraldo et al., 2018; Ruiz-Gaitán et al., 2018, 2019a,b; Sexton et al., 2018; Adam et al., 2019; Barantsevich et al., 2019; Escandón et al., 2019; Leach et al., 2019; O’Connor et al., 2019; Park et al., 2019; Sana et al., 2019; Sayeed et al., 2019). **(B)** MIC ranges for three antifungals measured in *C. auris* isolates from different outbreaks around the world. The red dotted line represents the tentative breakpoint proposed by the CDC. IPSV is an acronym for “India, Pakistan, South Africa, and Venezuela,” as strains from these countries were all analyzed in the same study. Outbreak survey was performed identically to **(A)**. Only outbreak with >1 isolate were plotted. Studies cited by Osei Sekyere are signaled with [OS] and studies cited by Kenters et al. with [KE].

Exceptionally for a yeast, *C. auris* has successfully spread in nosocomial environments. For example, in a UK hospital, a single patient colonized with *C. auris* led to subsequent identifications of other cases among other hospitalized patients. The pathogen was also detected on the healthcare staff even several months after its first isolation, suggesting an efficient human to human transmission. Additionally, traces of *C. auris* had been found on bed sides, windowsills, monitors, and other equipment throughout the hospital, showing that *C. auris* is capable to persist on nosocomial surfaces (Schelenz et al., 2016), in contrast to other *Candida* species. Investigation into an outbreak in another UK hospital reported that the use of reusable equipment such as axillary temperature probes was the primary cause of transmission to patients (Eyre et al., 2018), further illustrating its capability to survive on surfaces.

The capacity to survive in nosocomial environments could be due to the ability of *C. auris* to form biofilms; a growth form in which cells are arranged together in microcolonies protected by a matrix of glucan. By convention, cells enclosed in the matrix are called sessile, and cells outside of it are called planktonic. *C. auris* cells protected by this structure were proven to be difficult to eliminate, even with high-levels of disinfection procedures (Kean et al., 2018b).

In addition to potentially allowing an increased survival on inert surfaces, the ability of *C. auris* to form biofilms may also be an important factor of its resistance to systemic antifungals used in patient treatment. Indeed, the fact that biofilm forming cells were isolated from wounds and catheter tips indicates that some *C. auris* cells could survive in biofilm-form in patients (Borman et al., 2016) and it was shown that sessile cells presented

reduced susceptibility for several antifungals. (Sherry et al., 2017). Finally, biofilm has also been shown to be an important virulence factor, as biofilm forming *C. auris* strains are linked to increased morbidity and mortality (Borman et al., 2016).

With this review we aim to highlight molecular resistance mechanisms acquired by *C. auris*, which led to its extraordinary survival in nosocomial environment and in hospitalized patients.

2. C. AURIS ANTIFUNGAL SUSCEPTIBILITY

After 10 years of recording minimum inhibitory concentration (MIC) for available antifungals, the CDC recently published a tentative of breakpoints to better define *C. auris* antifungal susceptibility¹. It clearly appeared that *C. auris* has exceptionally high MICs for the four main classes of antifungal drugs: azoles, echinocandins, polyenes (Figure 1B), and nucleoside analogs. In this chapter, we will examine in detail two factors that proved to play a role in this decreased susceptibility to antifungal treatments: molecular resistance mechanisms and biofilm-associated resistance mechanisms.

2.1. Molecular Resistance Mechanisms

We define here molecular resistance as the ways individual cells can decrease their sensitivity to antifungals due to genetic modifications leading to drug target modification, efflux pumps overexpression, or metabolism modifications (see for review: Pemán et al., 2009; Sanglard et al., 2009; Krishnasamy et al., 2018). This section compiles, for each class of antifungal, the main molecular resistance mechanisms found in *C. auris* up to now. Additionally, Table 1 summarizes for each drug, the mode of action, the related resistance mechanisms described in non-*auris Candida* and the resistance mechanisms discovered in *C. auris*, as of yet.

2.1.1. Mechanisms of Resistance to Azoles

2.1.1.1. MFS and ABC efflux pumps overexpression

Efflux pumps are proteins that transport components across the cell membrane. Some of them can pump drugs outside of the cell, lowering their concentration and effect on the cell. There are two major families of efflux pumps involved in antifungal resistance: ATP Binding Cassette (ABC) and Major Facilitator Superfamily (MFS) transporters. Enhanced overexpression of efflux pumps is one of the major resistance mechanism to azoles in pathogenic *Candida* species (Schuetzer-Muehlbauer et al., 2003; Morschhäuser et al., 2007).

Indian strains of *C. auris* sequenced in two different studies exhibit numerous genes orthologous to ABC and MFS transporters of *C. albicans* (Chatterjee et al., 2015; Sharma et al., 2016). Interestingly, *C. auris* strains that were isolated in Israel showed an intrinsically high ABC transporter activity compared to *C. glabrata* and *C. haemulonii*, by measuring efflux of a fluorescent substrate (Rhodamine 6G) (Ben-Ami et al., 2017).

¹CDC (2019). Antifungal Susceptibility Testing and Interpretation. Available online at: <https://www.cdc.gov/fungal/candida-auris/c-auris-antifungal.html> (accessed April 29, 2019).

In *C. albicans*, *CDR1* is a gene encoding for an ABC efflux pump, known for its role in azole resistance (Sanglard et al., 1995). A gene homologous to *CDR1* was found in *C. auris*. (Rybak et al., 2019). The same study also showed that the deletion of this gene could increase susceptibility of resistant strains from 64- to 128-fold (Rybak et al., 2019).

2.1.1.2. Point mutations in ERG11

Ergosterol is a key membrane component in fungi. In *Candida* spp., its biosynthesis is mediated, among others, by the enzyme Lanosterol 14- α -demethylase (LD), encoded by the gene *ERG11* which converts lanosterol to ergosterol. The LD is the primary target of azoles, antifungals that inhibit the function of the enzyme and effectively shut down ergosterol biosynthesis, thus impairing membrane integrity (Sanglard et al., 1998).

Point mutations in *ERG11* have been shown to reduce azole sensitivity in *Candida* spp., particularly in three “hot-spot” regions located between amino-acids 105–165, 266–287, and 405–488 (Vandeputte et al., 2012).

Interestingly, after having retrieved the amino acid sequences of 44 *C. auris* isolates from India, 15 missense mutations were found when aligned to the *C. albicans* wild-type *ERG11* sequence (Chowdhary et al., 2018). Five of these mutations were already associated with azole resistance in *C. albicans*. Among these variants two were found in every resistant strain tested in this study, namely Y132F or K143R (Chowdhary et al., 2018). It can also be noted that these mutations are in the first “hot spot” discussed earlier.

A screen for variants in the *ERG11* gene of *C. auris* strains from Columbia identified the same Y132F and K143R substitutions. Upon heterologous expression of these two mutations in *S. cerevisiae*, MICs for azoles presented a two-fold increase as compared to *S. cerevisiae* strains expressing the wild-type *C. auris ERG11* gene (Healey et al., 2018).

2.1.1.3. ERG11 overexpression

In *C. albicans*, an overexpression of *ERG11* has been linked to a resistance to azole treatment as well. The increased production of LD overwhelms the capacity of the antifungal to inhibit the activity of the protein, resulting in an active protein despite drug treatment (Lopez-Ribot et al., 1998).

In *C. auris*, real time PCR experiments showed that in absence of fluconazole, there was no difference in *ERG11* expression between fluconazole-susceptible and fluconazole-resistant strains (Chowdhary et al., 2018). In presence of the antifungal, *ERG11* expression rises in resistant strains when compared to a control without fluconazole (Chowdhary et al., 2018). However, the effect of this drug on *ERG11* expression was not tested on susceptible strains. Therefore, conditionally increased expression of *ERG11* in presence of fluconazole has not been demonstrated to be specific to resistant strains, until now.

2.1.2. Mechanisms of Resistance to Echinocandins

Beta(1,3)D-glucan is a key component of the fungal cell wall and is encoded by the *FKS1* and *FKS2* genes, two subunits of the Beta(1,3)D-glucan synthase. Echinocandins

TABLE 1 | Pharmacodynamics of the four main antifungal classes and linked resistance mechanisms in *Candida* spp. in general and *C. auris* specifically.

Antifungal class	Target	Effect	Resistance mechanism(s) in non- <i>auris</i> <i>Candida</i> spp.	Resistance mechanism(s) in <i>Candida auris</i>
Azoles	Inhibits Lanosterol 14-alpha-demethylase (LD), the protein catalyzing the conversion of lanosterol to ergosterol	Weaker cell membrane, inhibiting growth and sensitizing to host immune system Accumulation of toxic intermediary compound	MSF efflux pumps overexpression due to mutation in Mrr1 transcription factor (TF). [a] <i>CDR</i> genes overexpression, encoding ABC efflux pumps, due to mutation in Tac1 TF. [a] Point mutation in gene encoding LD (<i>ERG11</i>) Upregulation of <i>ERG11</i> due to mutation in Upc2 TF. [a] <i>ERG3</i> mutation: Bypass ergosterol synthesis pathway to prevent toxic compound accumulation	Presence of MFS efflux pumps genes [b]. Higher ABC efflux pumps activity compared to <i>C. glabrata</i> . [c] Significant contribution of <i>CDR1</i> to resistance. [d] <i>ERG11</i> point mutation: Y132F; [f] K143R [f] Presence of <i>ERG3</i> [e] but no mutation associated with increased resistance reported
Echinocandin	Inhibits beta(1,3)D-glucan synthase	Defective cell wall formation	Mutation in <i>FKS1</i> and <i>FKS2</i> gene, encoding the target enzyme	Presence of <i>FKS1</i> and <i>FKS2</i> In <i>FKS1</i> three mutations linked to increased MIC: S639Y; [g] S639P; [g] S639F. [h]
Polyene	Binds ergosterol molecules in the cytoplasmic membrane	Affects membrane permeability by forming multimeric pores and causes oxidative damage	Membrane composition alteration to reduce target exposition Increase catalase activity to counter oxidative damage	5 SNPs in different genomic loci associated with reduced sensitivity. [i]
Nucleoside analogs	Transformed in the fungal cell in two products that respectively inhibit thymidine synthase and get incorporated in RNA	DNA and RNA synthesis inhibition	Modification of enzymes involved in 5-FC uptake or metabolism Competitive inhibition of 5-FC effect by increased pyrimidine synthesis	Amino-acid substitution (F211I) in <i>FUR1</i> , a gene involved in 5-FC metabolism found in a single flucytosine-resistant isolate [g]

Adapted from Krishnasamy et al. (2018). With additional information from: [a] Vandeputte et al. (2012), [b] Sharma et al. (2016), [c] Ben-Ami et al. (2017), [d] Chowdhary et al. (2018), [e] Rybak et al. (2019), [f] Healey et al. (2018), [g] Rhodes et al. (2018), [h] Kordalewska et al. (2018), [i] Escandón et al. (2019).

inhibit this enzyme, decreasing the amount of glucans in the cell wall (Martins et al., 2011).

In *C. albicans* and other non-*auris* *Candida* species, several mutations leading to echinocandin resistance were found in the same two regions of *FKS1* and *FKS2*. So, they were named “hot-spots” 1 and 2 (HS1 and HS2). In the *C. albicans* *FKS1* gene these “hot-spots” are located between amino acids 641–649 and 1,345–1,365 (Park et al., 2005). Sequencing of the corresponding hot-spot regions of 38 *C. auris* strains lead to the discovery of an S639F amino acid substitution that is correlated with pan-echinocandin resistance: it was present in all four resistant strains and absent in the 34 susceptible ones. This position in *C. auris* *FKS1* is aligned to the position 645 (also a Serine) in *C. albicans* (Chowdhary et al., 2018). Interestingly, this mutation is in the region aligning to the HS1 of *C. albicans* *FKS1*. Other studies observed different

mutations at the same location in echinocandin-resistant *C. auris* strains: S639Y and S639P (Rhodes et al., 2018). The latter was confirmed to cause echinocandin resistance *in vivo* in a mouse model (Kordalewska et al., 2018).

FKS2 was also found in a single copy in the *C. auris* genome (Sharma et al., 2016), but no mutation associated with echinocandin resistance were found in this gene to our knowledge.

2.1.3. Mechanisms of Resistance to Polyenes

As shown in the **Figure 1B**, several *C. auris* strains are resistant to Amphotericin B (AMB). In the *Candida* species, modifications of the sterol composition of the membrane have been highlighted as a resistance mechanism (Haynes et al., 1996; Nolte et al., 1997). In *C. albicans*, mutations in *ERG 2, 3, 5, 6* or *11* have been shown to have this effect

(Arendrup and Patterson, 2017). Rhodes et al. screened 27 *C. auris* isolates from the UK for SNPs in these genes in strains displaying reduced sensitivity to AMB. However, no variants explaining these differences in drug susceptibility were found (Rhodes et al., 2018).

2.1.4. Mechanisms of Resistance to Flucytosine (5-Fluorocytosine)

Flucytosine is a nucleoside analog that inhibits nucleic acid synthesis. After cell entry, flucytosine has to be activated to have an antifungal effect. This activation requires, among others, the protein encoded by the gene *FUR1* Waldorf and Polak (1983). In non-*auris* *Candida* species mutations in *FUR1* were demonstrated to be linked with flucytosine resistance (Vandeputte et al., 2012).

Rhodes et al. sequenced a flucytosine resistant *C. auris* strain and observed a F211I amino acid substitution in the *FUR1* gene (Rhodes et al., 2018). This specific missense mutation has no known equivalent in other *Candida* species, therefore additional studies are required to determine if this mutation is the cause of the resistance to flucytosine in the tested *C. auris* strain (Rhodes et al., 2018). However, this drug is less employed than other antifungals. Because of that, fewer studies have been performed to better understand the resistance of *C. auris* to this compound.

To summarize, some resistance mechanisms previously discovered in *Candida* species like *C. glabrata* and *C. albicans*, were also showcased by *C. auris*. They are listed in the last column of the **Table 1**. However, *C. auris* antifungal resistance is only partially explained by these previously described resistance mechanisms. In order to eventually design new therapeutic agents and more generally to improve patient care, further studies are needed to better understand the underlying mechanisms leading to the exceptionally high MIC ranges presented by some *C. auris* strains (see **Figure 1B**).

2.2. Biofilm: An Antifungal Resistant Way of Life

It was shown that MICs for several antifungals are higher in *C. auris* sessile cells (up to 4-, 20-, 60-fold for voriconazole, Amphotericin B, and Micafungin, respectively) compared to planktonic cells (Sherry et al., 2017). Similarly, minimal biofilm eradication concentrations were shown to be 512-fold higher than MICs for echinocandins and azoles (Romera et al., 2019). This phenomenon was previously shown for *C. albicans* (Hawser and Douglas, 1995). The molecular mechanisms responsible for these elevated MIC are still largely unknown in *C. auris* but some studies have already provided some insights.

MSF and ABC efflux pump-encoding genes were found to be upregulated (2- to 4-fold) in sessile cells compared to planktonic cells (Kean et al., 2018a). Concordantly, the activity of corresponding proteins was 2-fold increased. However, when treated with efflux pump inhibitors the antifungal sensitivity of sessile cells was increased 4- to 16-fold after 12 h. This suggests that efflux pumps play an important role in the resistance to antifungals displayed by this type of cells (Kean et al., 2018a).

In *C. albicans*, the exopolymer matrix is known to non-specifically bind to all classes of antifungals and sequester them outside the cells (Nett et al., 2010). As *Candida* spp. share a

core polysaccharide profile, it was suggested that this mechanism might be conserved in *C. auris* as well (Kean et al., 2018a). This was later confirmed in *in vivo* and *in vitro* assays (Dominguez et al., 2019).

3. NOSOCOMIAL PERSISTENCE

The capacity of *C. auris* to colonize and persist on surfaces is exceptional: it is able to persist longer on moist surfaces in comparison to *C. albicans* (Piedrahita et al., 2017). It also has a prolonged metabolic activity on surfaces, akin to *C. parapsilosis*, a known skin and plastic colonizer (Piedrahita et al., 2017; Welsh et al., 2017).

The increased survival of *C. auris* on surfaces was investigated by two studies. The first claimed it could be linked to an enhanced environmental stress resistance to temperature and other stressors (Kean et al., 2018b). The second hypothesizes that it could be due to the formation of biofilm. However, this remains to be proven as, so far, no biofilm forming isolate was recovered from environmental surfaces (Ku et al., 2018). It is to be noted that these two possibilities are not mutually exclusive, and that biofilm formation might even be the cause of the increased stress resistance (Ku et al., 2018).

The persistence of *C. auris* in nosocomial environments is heightened by the resistance of this pathogen to disinfection procedures. The efficacy of NaOCl and peracetic acid on stainless steel, polymer (polyester coverslips) and cellulose surfaces were tested. Both disinfectants showed a significant efficacy to kill *C. auris* cells on all surfaces. However, some viable cells remained after applying NaOCl on non-porous surfaces (stainless steel and polyester coverslips). In fact, higher concentrations of this disinfectant coupled to longer exposure times were required to lower regrowth, but even then, they were not able to completely eradicate the pathogen. For example, a 10,000 parts per million (ppm) NaOCl concentration coupled to a 5 min exposure on stainless steel, was enough to observe a significant reduction of colonies. However, substantial regrowth was observed after re-inoculation onto a rich medium (Kean et al., 2018b).

For peracetic acid, which is a high-level disinfectant, this regrowth was surface dependent, as no regrowth was observed for polymer as opposed to stainless steel. They performed the same experiments on *C. glabrata* and *C. albicans* and obtained similar results (Kean et al., 2018b).

This shows that high-level disinfection procedures may be insufficient for a complete surface cleansing and that the pre-established guidelines for surface disinfection have to be adapted to these *Candida* species (Kean et al., 2018b). Factors like the type of surfaces and exposure times should be considered when implementing these disinfection procedures (Kean et al., 2018b; Ku et al., 2018) not only cost and ease of use, as is it often the case (Ku et al., 2018).

Based on the results of two studies (Cadnum et al., 2017; Rutala et al., 2019), the CDC recommends using disinfectants effective against *Clostridioides difficile* spores. If not possible, they suggest alternatives such as hydrogen peroxide 0.5–1.4% or quaternary ammonium compounds supplemented with

isopropyl alcohol and/or ethyl alcohol². Finally, ultraviolet-C light could also be an interesting candidate for surfaces disinfection. It proved highly effective at killing *C. auris* colonies, given sufficient exposure time and distance. However, further studies would be necessary before implementing such methods in hospital settings (de Groot et al., 2019).

4. CONCLUSION

The pathogenic and virulent capacities of *C. auris* are profoundly worrying. Especially since outbreaks occurred independently in different regions of the world and that the associated isolates showed decreased susceptibility to the most commonly used antifungal drugs used for patient treatment (see **Figure 1**).

To explain the reduced antifungal susceptibility in *C. auris*, researchers made use of the extended knowledge already available on other *Candida* species, particularly *C. albicans*. As a result, some of the resistance mechanisms of *C. auris* were highlighted (see **Table 1**). More precisely, two point mutations in *ERG11* and the overexpression of the ABC transporter Cdr1 were proven to decrease fluconazole sensitivity. Furthermore, an amino acid substitution in *FKS1* was shown to reduce the sensitivity of *C. auris* to echinocandins, which is normally the drug of choice for treatment against this pathogen (Bidaud et al., 2018). Finally, a mutation in *FURI* was identified in a flucytosine resistant *C. auris* strain, but remains to be demonstrated as the cause of this

reduced sensitivity. Biofilm is thought to be a resistance mechanism *per se* as it was shown to decrease drug susceptibility. However, further research is still necessary to describe the whole variety of processes that take place in this growth form. It is important to note that biofilm is a complex structure that remains poorly understood and difficult to investigate, even in well-known species such as *C. albicans*.

The resistance properties of *C. auris* are coupled to a propensity to cause nosocomial infections. Its ability to adhere to a variety of nosocomial surfaces and survive disinfection are critical propagation factors. The presence of multiple types of surfaces poses a challenge for clinical institutions, as standard disinfection procedures are inefficient and unadapted for each type of them. This problem, also arises from the insufficient research on this subject. In addition, a better understanding of the mechanisms underlying *C. auris* disinfectant resistance would help to improve hygiene protocols and avoid future nosocomial outbreaks.

AUTHOR CONTRIBUTIONS

FC, AG, and LJ participated equally in the redaction of this review. AC supervised and participated in the redaction of this review.

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²CDC (2018). Infection Prevention and Control for *Candida auris*. Available online at: <https://www.cdc.gov/fungal/candida-auris/c-auris-infection-control.html> (accessed November 12, 2019).

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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