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Candida auris: The Canary in the Mine of Antifungal Drug Resistance

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ABSTRACT: *Candia auris* has rapidly emerged as a fungal pathogen of worldwide importance. Its impact on global health is due in large part to the high frequency of multidrug resistance among *C. auris* clinical isolates. Although *C. auris* resistance to amphotericin B is an unusual feature of this organism, its notoriety should also serve as notice that other more commonly encountered fungal pathogens also show multidrug resistance. Here, we review the epidemiology and mechanisms of *C. auris* resistance and discuss why the emergence of *C. auris* provides justification for increased research into mechanisms of drug resistance and the development of novel antifungal drugs.

The ascomycete *Candida auris* is a haploid opportunistic pathogen of which several clades have simultaneously emerged around the globe in recent years.[1] *C. auris* is associated with high morbidity and mortality, multidrug resistance, problematic species identification, and transmission within healthcare settings. *C. auris* was originally identified in 2009 from the ear secretions of an elderly patient in Japan.[2] Subsequently, retrospective analyses of banked isolates of *Candida* spp. traced the earliest *C. auris* sample to a 1996 bloodstream isolate from a pediatric patient in South Korea.[3] Four clades have been characterized by whole genome sequencing, and they are grouped by geographic region: (I) South Asian (India, Pakistan, and the United Kingdom), (II) East Asian (Japan and South Korea), (III) South African (South Africa), and (IV) South American (Venezuela).[1] Strains within each clade are very similar, with less than 100 single-nucleotide polymorphisms, but there are significant genetic differences between clades.[1] Compared to other *Candida* species, *C. auris* is most closely related to *Candida hemeulonii*, *Candida pseudohemeulonii*, and *Candida lusitaniae*.[4−6]

In addition to colonizing the human body, *C. auris* is viable for extended periods of time on dry or wet animate or inanimate surfaces; this feature distinguishes it from other pathogenic *Candida* spp.[7,8] *C. auris* causes superficial wound infections and invasive infections.[9,10] Although the majority of *C. auris* samples have been isolated from patients with candidemia, it has also been recovered from other typical *Candida* spp. colonization and infection sites, including the respiratory and urogenital tracts, the ear−nose−throat, and skin.[9,10] Because most patients infected with *C. auris* have other comorbidities, estimates of attributable mortality are difficult.[10] The crude mortality for patients infected with *C. auris* worldwide is approximately 30%.[10] According to the Centers for Disease Control and Prevention (CDC), as of April 2019, there have been 654 clinical *C. auris* cases reported and 1207 colonized patients identified in the United States (Figure 1).[11]

Three classes of antifungal drugs are used to treat invasive fungal infections: polyenes, azoles, and echinocandins (Figure 2). Among all clades and isolates reported worldwide, resistance to fluconazole is common (∼44%), whereas resistance to other azoles can vary (voriconazole, ∼13%; itraconazole, ∼2%; posaconazole, ∼1%; and isavuconazole, ∼2%).[10] Resistance to the polyene amphotericin B is more common among *C. auris* strains (∼16%) than among other *Candida* species.[10] Although resistance to echinocandins such as caspofungin does occur (∼4%), it is less common, and thus echinocandins are the current recommended treatment option for invasive infections.[10,12]

C. auris displays virulence properties that are found in other *Candida* species, such as the ability to grow in a mammalian host; filamentous morphogenesis; biofilm formation; and secretion of phospholipase, aspartyl proteinase, and hemolysin.[5,13,14] As with other *Candida* spp., the virulences of strains from clades and clinical isolates appear to vary significantly.[14] Although *C. auris* morphology was initially thought to be restricted to yeast and pseudohyphae, it can form hyphae after passaging through a mammalian host or after exposure to low temperatures in vitro.[13] *C. auris* strains also show varying degrees of aggregation between clades.[15] In an in vivo *Galleria mellonella* infection model, aggregative strains tended to be less virulent than nonaggregating ones.[15] In addition, nonaggregating strains are more apt to form biofilms.[16] However, compared with *Candida albicans*, *C. auris* is less able to form biofilms.[16] Moreover, the biofilm structures formed by *C. auris* are generally less robust and are primarily composed of yeast cells with minimal extracellular matrix.[16] In vivo murine models of *C. auris* infection have been reported, but more research must be done before a clear picture of its virulence in

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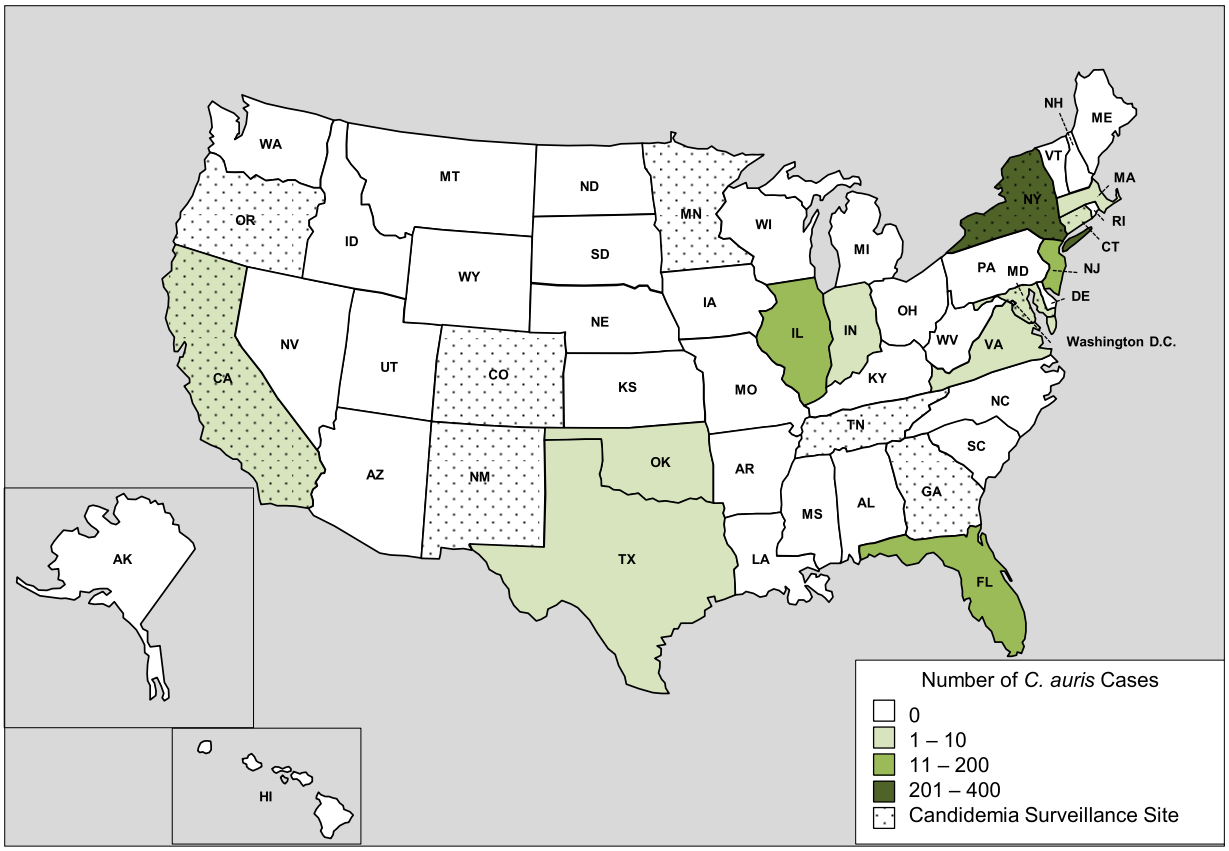

Figure 1. Reported clinical cases of *Candida auris* in the United States of America as of April 2019. Centers for Disease Control and Prevention (CDC) Emerging Infections Program (EIP) Candidemia Surveillance Sites are indicated by dots; however, dots do not indicate state-wide surveillance. See the CDC website for current information.[11]

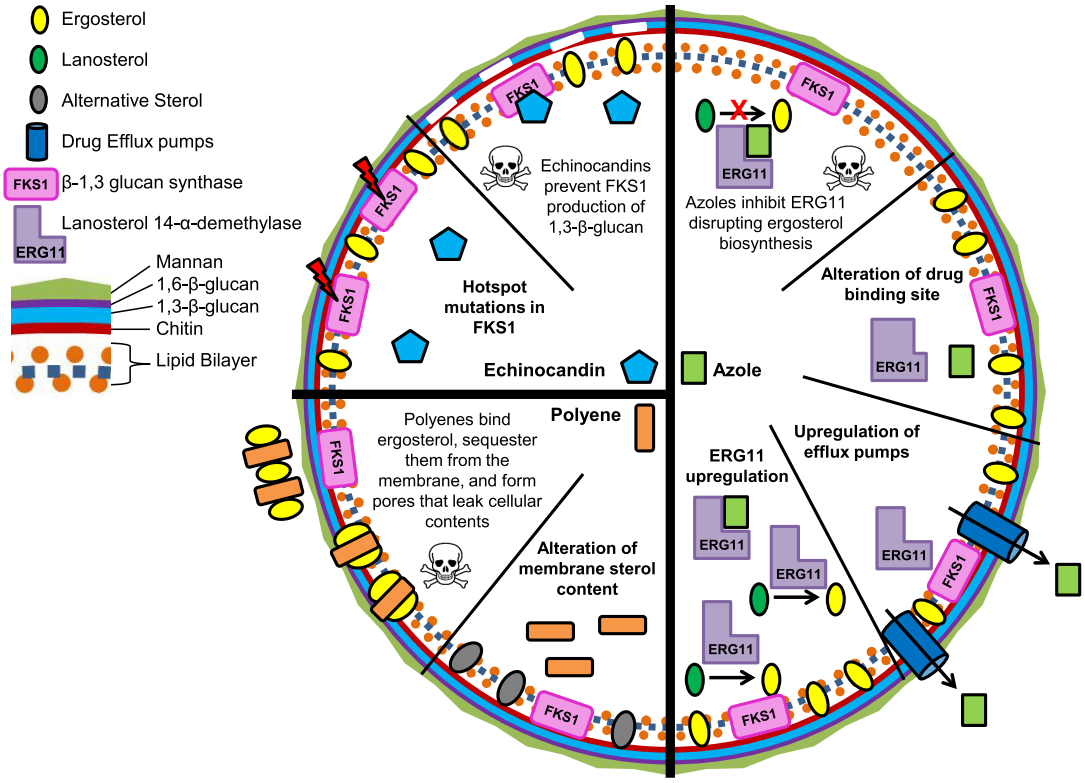

Figure 2. Common antifungal resistance mechanisms to clinical antifungals among *Candida* species. The skull and cross-bones symbol indicates normal antifungal activity without resistance. Mechanisms of antifungal resistance are in bold type.

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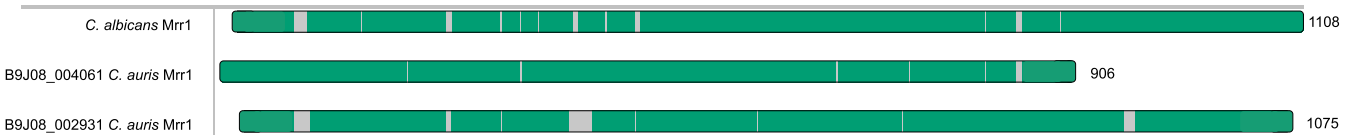

Figure 3. Alignment of Mrr1 homologues from *Candida albicans* and *Candida auris*. Graphical representations of the amino acid sequences of *C. albicans* Mrr1 and the two *C. auris* homologues are shown. Positions of significant alignment are indicated by the green color, whereas positions that lack similarity are shown by gray. The numbers at the end of each sequence represent the numbers of amino acid in each full-length factor, predicted from the primary sequence.

mammals can be formulated.[17] Ongoing basic and translational research will certainly improve our understanding of the biology and pathobiology of this important cause of candidal infections.

In the United States, the CDC is tracking clinical cases and colonization of *C. auris*. As of 2019, *C. auris* infections are nationally reportable, making it the second such reportable fungal disease after Coccidioidomycosis (Valley Fever).[18] Similar to candidemia caused by other *Candida* spp., the patient population ranges from neonates to the elderly and tends to be immunocompromised individuals that have had abdominal surgery or an organ transplant or that have immunosuppressive conditions such as cancer.[9,10] Patients generally present with comorbidities including diabetes, bloodstream infections, pulmonary diseases, chronic or acute kidney disease, cardiovascular disease, and liver disease.[9,10] In addition, patients frequently have received broad-spectrum antibiotics, have invasive medical devices, or have received parenteral nutrition.[10]

Overall, the species distribution and incidence of candidemia varies significantly by geographic area.[19] Looking at the number of *C. auris* related candidemia cases in the US, two of the three states (New Jersey and Illinois) with the greatest burdens are not states where candidemia surveillance is being conducted (Figure 1). A 2017 meta-analysis of articles published from 2009 to 2017 determined the global crude mortality (n = 316 patients, n = 94 demised) of disease caused by *C. auris* to be approximately 30%.[10] Importantly the *C. auris* crude mortality of 30% is similar to the crude mortality of candidemia caused by other *Candida* species.[20−23] However, *C. auris* has been made a nationally notifiable disease, whereas candidemia caused by other *Candida* species has not. This discordance represents a missed opportunity to understand the geographic distribution of infections with *Candida* species, antifungal resistance trends, and the true burden of candidemia in the United States.

A defining characteristic of *C. auris* is the high frequency with which drug resistant isolates are found. As mentioned above, the limited number of antifungal drugs means that treatment options are dramatically reduced by the loss of any drug to resistance. A survey of *C. auris* isolates from a CDC-based collection found that 1% of strains are resistant to *all three* classes of antifungal drugs: azoles, echinocandins, and polyene drugs.[24] Simply put, this type of multidrug resistant fungus is untreatable: there are no other drugs to use. Remarkably, fluconazole resistance approaches 100% in some isolate series, whereas amphotericin B resistance has reached 25% among the South Asian isolates. Echinocandin resistance is much lower at 5% across all isolates, suggesting that the appearance of truly multidrug resistant *C. auris* is likely to increase. This certitude makes understanding the molecular basis of antifungal drug resistance in this organism of paramount importance.

The best characterized species in terms of the molecular basis of antifungal drug resistance is the major human pathogen *Candida albicans* (Figure 2). Experiments from a variety of laboratories have shown that gain-of-function alleles in transcription factors such as *TAC1* and *MRR1*, along with the more recently appreciated *UPC2*, can confer robust resistance to azole drugs.[25−27] Tac1 and Mrr1 upregulate the expression of genes encoding ATP-binding cassette (ABC) transporter proteins like *CDR1* and major facilitator superfamily (MFS)-encoding genes like *MDR1*, respectively.[25,26] Activating mutant forms of Upc2 elevates the expression of genes in the ergosterol biosynthesis pathway. Central among these genes is *ERG11*, which encodes the enzymatic target of azole drugs.[28] *ERG11*-associated azole resistance is due to either increased gene transcription or amino acid substitutions in the coding sequence of the gene; the latter mutations can affect drug−protein binding. Finally, alterations in the *FKS1* gene, which encodes the β-glucan synthase target of echinocandins, are linked to resistance to this antifungal drug, and loss-of-function alleles of genes in the ergosterol pathway lead to increased amphotericin B resistance.[29,30]

C. lusitaniae, a species closely related to *C. auris*, contains nonsynonymous changes in its *MRR1* locus that lead to elevated azole resistance via induction of *MDR1* transcription, in a fashion analogous to what is seen in *C. albicans*.[31] Interestingly, a more distantly related *Candida* species, *Candida glabrata*, may develop multidrug resistance if a mutator allele of a DNA repair gene is present.[32] Studies with *C. auris* are at an early phase but no clear linkage tying multidrug resistance to alterations in DNA repair has been reported.

Although much remains to be learned of the molecular basis of development of drug resistance in *C. auris*, several basic mechanisms have been shown to contribute to this phenotype. For example, some azole resistant *C. auris* strains contain a variety of substitution mutant forms of *ERG11*.[33] Detailed analyses of these substitution derivatives of *C. auris* Erg11 demonstrated that although some mutants are likely to directly impact azole resistance, others appear to have little effect on susceptibility and more likely represent polymorphisms. The lack of linkage between some *ERG11* mutations and azole resistance was a strong indication that other mechanisms were also involved.

As observed in other *Candida* species, some fluconazole resistant isolates of *C. auris* exhibit strongly elevated expression of *CDR1* mRNA.[34−36] In contrast, other azole resistant *C. auris* isolates show increased *MDR1* transcription, although this effect was less pronounced than that for *CDR1*. Deletion of the *CDR1* gene restored fluconazole susceptibility, whereas removal of *MDR1* led to a relatively modest reduction in resistance, suggesting that *CDR1* may be more important and that other mechanisms may contribute to resistance in strains with elevated *MDR1* transcription. Finally, previous studies have also directly linked increased expression of ABC-

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transporter-encoding genes with azole resistance in *C. auris*. Specifically, multidrug resistant forms of *C. auris* have dramatically increased drug efflux activity compared with that of its close relative *C. hemeulonii*.[17]

Curiously, some *C. auris* isolates fail to upregulate either *CDR1* or other ABC-transporter-encoding genes when exposed to azoles. As noted above, this suggests that other non-transporter-based mechanisms may be involved. A recent genomic analysis of *C. auris* provided a potential explanation for the lack of efflux pump gene induction.[37] Specifically, Tac1, a key transcriptional regulator of *CDR1*, exists as two linked copies in the *C. auris* genome. These two direct repeats of *TAC1* are present on the same chromosome and are separated by approximately 400 base pairs. This supports the author's suggestion that ABC-transporter-encoding loci may be transcribed at a higher constitutive level in *C. auris*, possibly because of effects on the transcriptional control apparatus. We also found that *C. auris* contains two copies of the Mrr1 transcription factor (Figure 3). These two Mrr1 homologues are even more closely related to one another than the pair of Tac1 proteins. Interestingly, one of the Mrr1 proteins is truncated at its carboxy-terminus when compared with either the *C. albicans* Mrr1 or the other *C. auris* copy of Mrr1. Because the carboxy-terminal domains of these transcription factors frequently are involved in regulation, this alteration suggests that *C. auris* Mrr1 may have altered regulation relative to that in other species. Duplication of homologues of these transcription factors through aneuploidy and isochromosome formation play critical roles in *C. albicans* drug resistance, and by analogy, it is likely that these duplications play a similar central role in *C. auris* azole resistance.

The Mrr1 and Tac1 duplications are not the only genomic features that may contribute to *C. auris* drug resistance. For example, there are many copies of genes that encode for efflux pumps as well as apparently unique genes that respond to exposure of *C. auris* to either amphotericin B or voriconazole. In addition, it appears that some strains have large regions of chromosome duplications containing *ERG11*. Analyses of the molecular functions of these duplicated transcription factors will shed new light on their impact on gene regulation of drug resistance phenotypes.

One of the most unusual aspects of *C. auris* drug resistance is its decreased susceptibility to amphotericin B. Amphotericin B resistance is very uncommon in *Candida* species and in vitro selection experiments indicate that strains that develop resistance have decreased fitness in vitro and in vivo.[38] The vast majority of amphotericin B resistant *Candida* sp. isolates, both clinical and experimental, have mutations in ergosterol biosynthesis genes, such as *ERG2*, *-3*, *-6*, and *-11*. Most likely, these mutations lead to reduced levels of ergosterol in the plasma membrane. Because amphotericin B binds to ergosterol, this effectively depletes the target and, thereby, reduces susceptibility. In contrast, sequencing of amphotericin B resistant *C. auris* from a region with high prevalence in Colombia revealed no evidence of alterations in the coding sequences of ergosterol biosynthesis genes.[39] Instead, novel mutations were observed in a gene similar to *C. albicans* transcription factor *FLO8* and a putative membrane transporter along with two uncharacterized genes.[39] Thus, *C. auris* appears to have a unique mechanism of amphotericin B resistance. Clearly, more work is required to understand the mechanism of amphotericin B resistance in *C. auris*, particularly because this drug is frequently the agent of last resort in the treatment of recalcitrant fungal infections.

The emergence of *C. auris* has gained a great deal of attention in the medical and scientific communities as well as with the general public.[40] Although it is clearly an important medical problem in and of itself, the reasons for its importance are not unique to *C. auris*. Currently, isolates of *C. glabrata* that are resistant to both azoles and echinocandins are more commonly encountered in the clinic. However, the reason that these isolates are so troubling is the same for both of these multidrug resistant *Candida* species: we only have three classes of antifungals. Because of this, we have no drugs to treat triply resistant *C. auris* and are left with only amphotericin B, the oldest and most toxic antifungal currently in use, to treat azole−echinocandin resistant *C. glabrata*.

No area of anti-infective drug development has had so little real progress since the advent of the genomic age. As we continue to use the same three classes of drugs in the clinic, the problem of resistance will become increasingly commonplace: Darwin was right, and almost no other aspect of modern biomedicine so clearly demonstrates the power and impact of natural selection.

The mechanisms of resistance that contribute to the unique properties of *C. auris* highlight nicely what we do and do not know about the molecular and genetic basis of this important phenomenon. The roles of the usual suspects, including efflux pumps and their regulators and target protein mutations, are both consistent with pervious knowledge and troublingly incomplete. As such, we should use the unanswered questions raised by *C. auris* as an intellectual and scientific window into mechanisms that could explain uncharacterized resistance to azoles or echinocandins in other organisms. Furthermore, the unique propensity of this organism to express resistance to amphotericin B provides an opportunity to understand more about this drug's mechanism of action and cellular effects, two gaps in knowledge that remain despite the fact that amphotericin B has been used to treat fungal infections in humans for over 50 years.

Finally, the emergence of *C. auris* should lead us to reflect on the importance of collecting and analyzing clinical data and fungal isolates. Ongoing surveillance programs such as the SENTRY antifungal surveillance program as well as others have been important sources of global data and trends in susceptibility.[41] As discussed above, the CDC has been tracking *C. auris* as a reportable infection. However, it is crucial that data and trends for other fungal diseases be collected so that the next *C. auris* can be be identified and, just as importantly, so that changing trends in susceptibility are continuously assessed. The fragility of our antifungal pharmacopeia and the fragility of the patients who develop invasive fungal infections demand that we have the best available information to inform clinical decisions and antifungal stewardship. By listening to and understanding the full implications of the canary's song sung by *C. auris*, we can improve the treatment and prevention of invasive fungal infections in many settings.

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Notes

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