

Fluconazole resistance in *Candida* species: a current perspective

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Abstract: *Candida albicans* and the emerging non-*albicans* *Candida* spp. have significant clinical relevance among many patient populations. Current treatment guidelines include fluconazole as a primary therapeutic option for the treatment of these infections, but it is only fungistatic against *Candida* spp. and both inherent and acquired resistance to fluconazole have been reported. Such mechanisms of resistance include increased drug efflux, alteration or increase in the drug target, and development of compensatory pathways for producing the target sterol, ergosterol. While many mechanisms of resistance observed in *C. albicans* are also found in the non-*albicans* species, there are also important and unexpected differences between species. Furthermore, mechanisms of fluconazole resistance in emerging *Candida* spp., including the global health threat *Candida auris*, are largely unknown. In order to preserve the utility of one of our fundamental antifungal drugs, fluconazole, it is essential that we fully appreciate the manner by which *Candida* spp. manifest resistance to it.

Keywords: *Candida*, fluconazole resistance, *ERG11*, drug efflux, ergosterol

Introduction to *Candida* infections

Candida spp. exist as commensals of the skin, mouth, and gastrointestinal tract. Their growth and spread is kept in check by coexisting microbial flora, intact epithelial barriers, and defenses of the innate immune system. While *Candida* spp. are normal flora of the human body, they also possess the ability to transition to pathogens that cause a wide spectrum of conditions, ranging from superficial infections of the hair and nails to life-threatening systemic infections.¹ In fact, *Candida* account for approximately 75–88% of all fungal infections in the US.^{2–4} Additionally, in both adult and pediatric populations, the presence of candidemia results in an increase in mortality and hospital length of stay, culminating in an annual attributable cost of \$1.7 billion in the US alone, making *Candida* not only a clinical concern but an economic concern as well.^{5,6}

The epidemiology of *Candida* infections has been in flux in recent decades, most likely due to our own medical practices. Risk factors for infection with *Candida* are similar to those of fungal infections in general and vary in cause, but are generally due to medical intervention or health status of the patient. Risk factors fall into three distinct categories: factors that promote colonization of *Candida*, factors that suppress the immune response to *Candida*, and factors that provide a direct route for *Candida* infection.⁷ Historically, 92–95% of all cases of *Candida* infection are a result of the five most common species: *Candida albicans*, *Candida glabrata*, *Candida parapsilosis*, *Candida tropicalis*, and *Candida krusei*. And while this still holds true, there has been

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a shift in the species distribution among *Candida* infections. In past decades, *C. albicans* comprised >50% of all candidemia. However, the non-*albicans Candida* (NCAC) species are being encountered more frequently as human pathogens and, in some cases, NCAC species are more frequently isolated than *C. albicans*. In the US, *C. glabrata* is the second most common *Candida* spp., followed by *C. tropicalis* and *C. parapsilosis*.⁸ This rise in the NCAC species is possibly due to their inherently high levels of antifungal drug resistance (discussed later), but it is important to consider that improvements to laboratory detection and identification may simply provide more specific identification than in the past and account for emergence of less common species.

The global picture of candidemia has been recently expanded further with the emergence of the multidrug-resistant species *Candida auris*. Originally recognized in 2009 from an ear canal specimen in Japan, *C. auris* has since been reported from many countries including South Korea, South Africa, Kenya, India, Pakistan, Colombia, Venezuela, the UK, and the US.^{9–14} Further complicating our understanding of this newly emerging species are difficulties in identification – several identification platforms misidentify *C. auris* as other species of *Candida* – and difficulties in eradicating this organism from health care facilities.^{15,16}

Fluconazole

One of the most commonly prescribed antifungal drugs for *Candida* infections is fluconazole, a triazole antifungal.¹⁷ The azoles function by inhibiting the cytochrome P450 enzyme lanosterol demethylase (14 α -demethylase), encoded by *ERG11*, in the ergosterol biosynthesis pathway. More specifically, the free nitrogen atom of the azole ring binds an iron atom within the heme group of the enzyme.¹⁸ This prevents the activation of oxygen and in turn the demethylation of lanosterol, which inhibits the process of ergosterol

biosynthesis.¹⁹ As ergosterol is an essential component of fungal cell membranes, this inhibition is toxic; methylated sterols accumulate in the fungal cellular membrane, and cell growth is arrested.²⁰

Fluconazole is fungistatic rather than fungicidal, so treatment provides the opportunity for acquired resistance to develop in the presence of this antifungal. In the US, *C. albicans* has a low incidence of fluconazole resistance, approximately 0.5–2%. *C. tropicalis*, *C. parapsilosis*, and *C. glabrata*, on the other hand, have higher rates at 4–9%, 2–6%, and 11–13%, respectively.^{21,22} The emerging yeast *C. auris* can exhibit a rate of resistance to fluconazole as high as 93%.²³ Alternatively, without prior introduction of the antifungal, fluconazole resistance may also be innate, as is seen with *C. krusei*.^{24,25} Understanding the mechanisms underlying fluconazole resistance is a crucial part of managing our limited antifungal repertoire and keeping fluconazole a possible option to treat many *Candida* infections.

Molecular mechanisms of fluconazole resistance

The development of fluconazole resistance in *Candida* spp. has been well characterized in *C. albicans*. As the epidemiology of candidemia shifts to include more instances of NCAC species, it has become crucial to characterize fluconazole resistance in these species as well. Several mechanisms have been noted to involve genes of the ergosterol biosynthesis pathway; others involve drug transporters, changes in ploidy, and loss of heterozygosity (LOH; Table 1).

Increased drug target

Many *C. albicans* clinical isolates overexpress *ERG11*, the gene encoding the target of the azoles. In many cases, the level of overexpression is minimal or else observed in combination with other resistance mutations, making it difficult to

Table 1 Summary of molecular mechanisms of fluconazole resistance in *Candida* spp.

Mechanism	Gene(s) involved ^a	Regulator(s) involved ^a	Species
Drug target overexpression	<i>ERG11</i>	<i>UPC2</i>	<i>Candida albicans</i> , <i>Candida parapsilosis</i> , <i>Candida tropicalis</i>
Drug target alteration	<i>ERG11</i>		<i>C. albicans</i> , <i>C. parapsilosis</i> , <i>C. tropicalis</i> , <i>Candida auris</i>
Bypass pathways	<i>ERG3</i>		<i>C. albicans</i> , <i>C. tropicalis</i>
Efflux pump overexpression			
ABC transporters	<i>CDR1</i> , <i>CDR2</i> , <i>SNQ2</i> , <i>ABC1</i>	<i>TAC1</i> , <i>PDR1</i>	<i>C. albicans</i> , <i>Candida glabrata</i> , <i>C. parapsilosis</i> , <i>Candida krusei</i>
MFS transporters	<i>MDR1</i> , <i>TPO3</i>	<i>MRR1</i>	<i>C. albicans</i> , <i>C. parapsilosis</i> , <i>C. tropicalis</i> , <i>C. glabrata</i>
Aneuploidy/loss of heterozygosity	<i>ERG11</i>	<i>UPC2</i> , <i>TAC1</i>	<i>C. albicans</i>

Note: ^aGenes and regulators that have been directly linked to the resistant phenotype in clinical isolates.

Abbreviations: ABC, ATP-binding cassette; MFS, major facilitator superfamily.

assess the direct impact of such overexpression on the resistant phenotype. Studies have shown that this overexpression often involves Upc2p, a zinc cluster transcription factor that is induced upon ergosterol depletion.²⁶ Mutations in Upc2p provide gain of function (GOF) for this regulator, resulting in constitutive transcriptional activity and increased production of Erg11p.^{27–29} One large study of *C. albicans* evaluated the impact of various Upc2p mutations on *ERG11* expression as well as on the fluconazole-resistant phenotype. It identified several mutations that were associated with increased *ERG11* expression as well as increased ergosterol production.³⁰ This increased production of the azole target dilutes the activity of the fluconazole and results in resistance.

The significance of increased *ERG11* expression in fluconazole-resistant NCAC is varied. While overexpression of *ERG11* has been observed in several resistant *C. parapsilosis* isolates, these isolates also harbored additional resistance mechanisms which likely participated in their resistant phenotype.^{31,32} Moreover, when *UPC2* was sequenced in such isolates, a single heterozygous mutation was identified in a single isolate – the remaining isolates contained no *UPC2* mutation – indicating that the overexpression of *ERG11* was *UPC2*-independent, a finding that has been observed in some *C. albicans* isolates as well.^{28,32} Likewise, several studies have identified higher expression of *ERG11* in fluconazole-resistant clinical isolates of *C. tropicalis* as compared to fluconazole-susceptible isolates.³³ However, sequencing of *UPC2* revealed mutations that were present in both resistant and susceptible isolates. Further characterization of the cause(s) of increased *ERG11* expression is needed in these NCAC species.

Unlike in other species of *Candida*, *ERG11* does not appear to play a major role in fluconazole resistance in *C. glabrata*, and there are only two clinical isolates reported to display overexpression of *ERG11*.^{34,35} The contribution of this overexpression to fluconazole resistance in these isolates is unclear. The same is true for *C. krusei*; a single report of increased *ERG11* expression observed in four clinical isolates can be found in the literature.³⁶ The role of *ERG11* overexpression in fluconazole resistance in *C. auris* is currently unknown.

Alteration in drug target

Point mutations in the coding region of the *ERG11* gene impact susceptibility to fluconazole. These mutations lead to amino acid substitutions which alter the structure of the protein and render binding of the azoles less efficient.^{37,38} This reduced binding affinity decreases azole susceptibility. Over 140 substitutions have been described in *C. albicans* *ERG11*,

indicating that this enzyme is highly permissive for structural changes.³⁹ Rather than being found dispersed throughout the coding region, the majority of *ERG11* amino acid substitutions fall into distinct “hot spot” regions within the protein: amino acids 105–165, 266–287, and 405–488.⁴⁰ A handful of these substitutions have been conclusively linked to resistance (Table 2).^{39,41–46} One large study performed allelic transfer to determine the impact of 10 specific substitutions found in clinical isolates of *C. albicans* on fluconazole resistance. Protein modeling studies suggested that substitutions impact fluconazole-susceptibility cluster in the predicted enzyme catalytic site, a fungus-specific external loop, or a heme-interaction surface site.⁴⁷ More commonly, substitutions are not conclusively linked to a resistant phenotype but, instead, are observed in isolates which are azole resistant but not in isolates that are azole susceptible.^{39,48} This is suggestive but not confirmatory of causing resistance.

Studies in NCAC indicate far lower variability in *ERG11* sequence. A single amino acid substitution, Y132F, either alone or in combination with an R398I substitution, has been observed exclusively in fluconazole-resistant clinical isolates of *C. parapsilosis* and not in susceptible isolates.^{31,32,49} The point mutation Y132F has also been noted in a single resistant isolate of *C. tropicalis*.⁵⁰ Additionally, a single *C. tropicalis* isolate which contained a truncated Erg11p resulting from a deletion mutation and led to high-level fluconazole resistance was identified.⁵¹ A single instance of an *ERG11* mutation has been reported in *C. glabrata*; a clinical isolate containing a missense mutation produced no membrane ergosterol and had high resistance to fluconazole.⁵²

Table 2 *ERG11* amino acid substitutions linked to fluconazole resistance in clinical isolates of *Candida albicans*

Amino acid substitution	Hot spot	Reference
A61V		38
A114S	I	39
F126L	I	40
Y132F, Y132H	I	38–41,43
K143E, K143R, K143Q	I	38,39,42,43
F145L	I	43
Y257H		39
N435V	III	39
S405F	III	34,38,40,43
D446E	III	43
G448E	III	39,43
F449S, F449V	III	38,40,43
G450E	III	43
G464S	III	36,38,40,43
R467K	III	37
I471T	III	41
D502E		39

A chief mechanism underlying innate fluconazole resistance in *C. krusei* is a reduced susceptibility of Erg11p.^{53–55} This has not been concluded from changes in gene sequence but from the observation that a relatively high concentration of drug is required to inhibit the synthesis of ergosterol with *C. krusei* Erg11p compared to other fungal species. Other studies have detected point mutations in *ERG11* and linked them to reduced susceptibility, but these studies are in relation to azoles other than fluconazole.^{56,57}

As with many topics in *C. auris*, much is unknown concerning the contribution of *ERG11* point mutations to fluconazole resistance. However, one recent study determined that a collection of *C. auris* isolates with elevated minimum inhibitory concentration (MIC) values to fluconazole carried point mutations which had been previously shown to impact drug resistance in other *Candida* spp.: Y132F, K143R, and F126T. These mutations were present in geographically distinct clades, with the isolates within a particular region having the same mutation. Isolates which did not carry one of these *ERG11* mutations had lower MIC values to the azole drug class. All of this information culminates in the conclusion that the point mutations in the target protein play a role in the fluconazole-resistant phenotype of these isolates.²³

Alterations in sterol biosynthesis

The development of bypass pathways within sterol biosynthesis may also occur and result in resistance to fluconazole. Considered an infrequent mechanism of resistance, this primarily results from loss-of-function mutations in *ERG3*. This inactivation of the enzyme $\Delta^5,6$ -sterol desaturase permits the cell to bypass production of toxic methylated sterols in the presence of the azoles and minimizes the effect of fluconazole on the cell.^{58,59} This has been experimentally induced in the laboratory as well as observed in clinical isolates of *C. albicans* and, to a lesser extent, *C. tropicalis*.^{51,60–63}

Increased drug efflux

In addition to mechanisms involving the ergosterol biosynthesis pathway, efflux of antifungal drug via transport proteins is found in a wide array of fungi. This results in a failure of the drug to accumulate intracellularly, resulting in resistance. In *Candida* spp., there are two main classes of efflux proteins – the major facilitator superfamily (MFS) class and the ATP-binding cassette (ABC) family. Each function to translocate compounds across the fungal cell membrane, and constitutive upregulation of members of each of these families can mediate resistance to fluconazole.

ABC transport proteins have a broad substrate specificity and rely on the hydrolysis of ATP for energy.⁶⁴ Of the

28 individual ABC proteins predicted in *C. albicans*, two are well characterized and definitively linked to fluconazole resistance – the highly homologous *Candida* drug resistance 1 (Cdr1p) and *Candida* drug resistance 2 (Cdr2p).^{65,66} Only *CDR1* is expressed at detectable levels under standard conditions in susceptible isolates, and its deletion can lead to hypersusceptibility. *CDR2* is not usually expressed, and its deletion will not impact susceptibility in a drug-susceptible isolate.^{67–69} Many fluconazole-resistant isolates overexpress *CDR1* and *CDR2*, and deletion of one or both genes results in reduction of this resistance.⁶⁶ Constitutive upregulation of both *CDR1* and *CDR2* results from GOF mutations in the transcriptional regulator, *TAC1*. Currently, 19 different point mutations have been confirmed as GOF in *TAC1*; there are many candidate mutations still awaiting investigation.^{70,71}

Homologous ABC transporters have also been identified in and linked to fluconazole resistance in NCAC species, including CgCdr1p, CgCdr2p, and CgSnq2p in *C. glabrata* (with corresponding transcriptional regulator, CgPdr1p), CpCdr1p in *C. parapsilosis*, and CkAbc1p in *C. krusei*.^{32,72–76} Increased expression of Ct*CDR1* has been detected in fluconazole-resistant isolates, although it is noteworthy that these isolates were passage-derived in the laboratory as opposed to clinically derived.⁷⁷ Evaluation of clinical isolates of *C. tropicalis* has not reliably demonstrated this resistance mechanism.^{33,78} To date, there has been no investigation of the role of efflux pumps in fluconazole resistance in *C. auris*.

Compared to the ABC family of transporters, members of the MFS class have a more narrow range of substrate specificity and are powered by electrochemical proton-motive force.⁷⁹ There are approximately 95 MFS transport proteins predicted in the *C. albicans* genome.⁸⁰ Only one, Mdr1p, has been linked to fluconazole resistance; overexpression of *MDR1* has been observed in resistant *C. albicans* clinical isolates, and deletion of *MDR1* from overexpressing isolates reduces resistance.^{66,81} Regulation of Mdr1p expression is controlled by the transcription factor Mrr1p, and point mutations within this factor induce overexpression of its target gene.⁸² There are currently 15 different Mrr1p GOF mutations reported in *C. albicans*.⁸³

MFS transporters play only a minor role in fluconazole resistance in the NCAC species. Loss of *MDR1* in fluconazole-resistant *C. parapsilosis* isolates results in only a modest decrease in resistance.³² Likewise, no significant difference in expression of *MDR1* has been observed in *C. tropicalis* fluconazole-resistant isolates as compared to fluconazole-susceptible.³³ Recently, an MFS transporter in *C. glabrata*, Tpo3p, was shown to impact fluconazole

susceptibility (upon deletion of this transporter, resistance to fluconazole decreased).⁸⁴ Meaningful homologs of Mdr1p have not been identified in *C. krusei* or *C. auris*.

Aneuploidy and other chromosomal abnormalities

Additional mechanisms of fluconazole resistance that involve gene amplification have also been identified. Aneuploidy may develop in laboratory strains or clinical isolates of *C. albicans* following routine culture and genetic manipulation. Such alterations in gene copy number provide a means for genetic variation without impairment of cell growth.^{85,86} One study analyzed gene copy number in clinical isolates of *C. albicans* and determined that aneuploid chromosomes were seven times more common in fluconazole-resistant isolates as compared to fluconazole susceptible. They also reported specifically isochromosome formation of chromosome 5 (chr5) to be associated with fluconazole resistance in *C. albicans*. Increases or reductions in resistance could be tied, respectively, with gain or loss of this chr5 isochromosome, as duplication of this segment accords additional copies of *ERG11*, its transcriptional regulator *UPC2*, as well as efflux pump regulator, *TAC1*.⁸⁷

LOH of specific genomic regions is also implicated in fluconazole resistance. It is most commonly associated with genes involved in resistance mechanisms, including *ERG11*, *TAC1*, and *MRR1*, with point mutations arising in the heterozygous state, and evolving to homozygosity. Instances of this mechanism occurring in sequentially collected clinical isolates of *C. albicans* have been reported.^{87,88}

There is little information regarding chromosomal abnormalities in the NCAC species. Ploidy changes do occur in *C. tropicalis*.⁸⁹ One report showed that in response to fluconazole exposure, an intermediate trimera morphology associated with gene duplication forms in several NCAC including *C. parapsilosis*, *C. tropicalis*, and *C. glabrata*.⁹⁰ Other reports observe fluconazole resistance in the presence of chromosomal abnormalities in both *C. glabrata* and *C. krusei* in the form of increased copy number of *ERG11* and the formation of segmental aneuploidies.^{76,91,92} The causal link between these findings and fluconazole resistance however has not been demonstrated in the NCAC.

Additional considerations in fluconazole resistance

Beyond the traditionally recognized mechanisms of resistance against fluconazole, much is still unknown. Well-understood molecular mechanisms do not always completely account for

the high-level resistance observed in many clinical isolates, and this highlights the importance of continued investigation. There are instances of *ERG11* overexpression in several *Candida* spp. that cannot be linked to activating mutations within their transcriptional regulator, *UPC2* – pointing to additional, unknown regulators of this key gene.^{30,32,33} It is also likely that alternate regulators of drug efflux pumps, such as *CaCAP1* and *CaFCR1*, can regulate the transport of drug from the cell but may be underappreciated or overlooked in studies which focus on the most commonly described regulators.^{93–95} Additionally, signal transduction pathways that promote response in *Candida* spp. to the stress imposed by fluconazole also likely play a role in fluconazole resistance, but the contributions of these pathways are not yet completely defined.^{96,97}

Deficient drug import should be an additional consideration. Fluconazole uptake into the fungal cell is required for the drug to reach its target protein, Erg11p. The most comprehensive investigation into this process used biochemical analyses to determine that fluconazole is imported by facilitated diffusion mediated by an unknown transporter, at least in *C. albicans* and *C. krusei*.⁹⁸ While this import is inadequately understood, it is certainly relevant to a discussion on resistance. It is possible that a mutation in a putative import transporter could impair the cell's ability to uptake this antifungal and generate resistance.

Several studies have reported fluconazole-resistant isolates which simultaneously overexpress *CDR1* and *MDR1* and/or have multiple changes to genes involved in ergosterol biosynthesis.^{44,99–101} In fact, it is quite uncommon to find an isolate with high-level resistance attributable to a single mechanism (the exception being *PDR1* mutation in *C. glabrata*).¹⁰² Most often, it is the combination of multiple mechanisms, acquired stepwise over time, that give rise to high-level resistance. This is observed clinically in patients undergoing long-term fluconazole treatment. In vitro, this additive effect of multiple mechanisms has been illustrated by the progressive introduction of point mutations in *ERG11*, *MRR1*, *TAC1*, and *UPC2* in an otherwise drug-susceptible *C. albicans* and by the dissection of individual mutations appearing in a resistant clinical isolate of *C. albicans*.^{103,104} Moreover, the functional importance of individual mutations varies in terms of impact on resistance. For example, the change in fluconazole MIC imparted by CaErg11p point mutation K143R is higher than that of F449V.⁴⁷

The expense paid by the cell for acquiring resistance mutations under antifungal stress is a fitness cost. This cost, resulting from altered membrane sterol content, structural changes in 14 α -demethylase, or disregulated gene expression, may

result in a competitive disadvantage against other, more “fit” organisms within the host in the absence of the drug. Multiple analyses demonstrate this to be accurate in both in vitro and in vivo models of *Candida* infection, although in vitro growth conditions do impact fitness assays.^{62,63,103,105,106} As a result, compensatory mechanisms arise which work to alleviate the fitness cost of such developed resistance.^{107,108} The methods by which *Candida* spp. develop compensatory mechanisms to alleviate the fitness cost of resistance is another area for consideration, but it is beyond the scope of this manuscript.

Finally, as the landscape of candidemia expands to include newly emerging species (*C. auris* for example), detecting resistance in these species will be of paramount importance. It could be hypothesized that mechanisms present in the extensively studied *C. albicans* would be operative in these species as well, but recent investigation into many NCAC species, *C. glabrata* for example, has shown that this may not tell the whole story. Moving forward, it will be essential to use a methodical approach of next-generation sequencing and global transcriptional analysis to identify the determinants of fluconazole resistance in newly emerging species.

Conclusion

The emergence of drug resistance can be considered an inevitable consequence of the selective pressures imposed by antifungal drugs. In the past two decades, several genes and mutations which increase resistance to fluconazole in clinical isolates, primarily in *C. albicans*, have been elucidated. In order to preserve the utility of fluconazole, a central antifungal option, it is important that we fully appreciate the manner by which all *Candida* spp. exhibit resistance to it.

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Disclosure

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