Multidrug-Resistant Candida: Epidemiology, Molecular Mechanisms, and Treatment

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Invasive Candida infections remain an important cause of morbidity and mortality, especially in hospitalized and immunocompromised or critically ill patients. A limited number of antifungal agents from only a few drug classes are available to treat patients with these serious infections. Resistance can be either intrinsic or acquired. Resistance mechanisms are not exchanged between Candida; thus, acquired resistance either emerges in response to an antifungal selection pressure in the individual patient or, more rarely, occur due to horizontal transmission of resistant strains between patients. Although multidrug resistance is uncommon, increasing reports of multidrug resistance to the azoles, echinocandins, and polyenes have occurred in several Candida species, most notably Candida glabrata and more recently Candida auris. Drivers are overall antifungal use, subtherapeutic drug levels at sites of infection/colonization, drug sequestration in the biofilm matrix, and, in the setting of outbreaks, suboptimal infection control. Moreover, recent research suggests that DNA mismatch repair gene mutations may facilitate acquisition of resistance mutations in C. glabrata specifically. Diagnosis of antifungal-resistant Candida infections is critical to the successful management of patients with these infections. Reduction of unnecessary use of antifungals via antifungal stewardship is critical to limit multidrug resistance emergence.

Keywords. multidrug resistance; echinocandin; fluconazole; azole; amphotericin B; Candida; Candida glabrata; Candida C. auris.

Infections due to Candida species are major causes of morbidity and mortality and are associated with a wide variety of clinical manifestations ranging from superficial and mucosal infections to widely disseminated and bloodstream infections [1]. Global estimates suggest that invasive candidiasis occurs in more than a quarter of a million patients every year with incidence rates for candidemia of 2–14 per 100,000 inhabitants in population-based studies [1–4]. Candida albicans is still a leading cause of candidemia, but other species (non-albicans) of Candida now comprise >50% of bloodstream infections in many parts of the world [1]. Antifungal resistance is less common in C. albicans but has been reported with long-term antifungal use and with recurrent infections, such as those with chronic mucocutaneous candidiasis or recurrent oropharyngeal candidiasis in patients with uncontrolled human immunodeficiency virus infection. Several of the non-albicans Candida species, such as Candida krusei, are intrinsically resistant or less susceptible to several classes of antifungals, whereas others, including Candida glabrata, develop acquired resistance following exposure to antifungal agents. Resistance to >1 drug class (multidrug resistance) remains uncommon but has been increasingly reported, such as in Candida auris. Genetic and molecular mechanisms of resistance have been described for many strains, so that knowledge of these mechanisms may help guide selection of therapy. In these patients at risk for serious Candida infection, diagnosis remains difficult but is critical in allowing detection of resistance and determination of optimal treatment regimens.

In this review, we discuss the epidemiology of multidrug resistance, molecular mechanisms for resistance, and strategies for treatment and prevention.

DEFINITION AND LIMITATIONS

Standard definitions for multidrug-resistant (MDR), extensively drug-resistant (XDR), and pandrug-resistant (PDR) bacteria were recently established through a joint initiative by the European Centre for Disease Prevention and Control and the US Centers for Disease Control and Prevention (CDC) [5]. MDR was defined as acquired nonsusceptibility to at least 1 agent in 3 or more antimicrobial categories; XDR was defined as nonsusceptibility to at least 1 agent in all but 2 or fewer antimicrobial categories (ie, bacterial isolates remain susceptible to only 1 or 2 categories); and PDR was defined as nonsusceptibility to all agents in all antimicrobial categories. These definitions cannot be directly adopted for resistance in Candida. The main reason is that only 4 drug classes are available for systemic treatment of Candida infections including the azoles (fluconazole, itraconazole, isavuconazole, posaconazole, and voriconazole), polyenes (conventional amphotericin B and its lipid formulations), echinocandins (anidulafungin, caspofungin, and
micafungin), and, finally, the pyrimidine analogue flucytosine. Among these drug classes, only members of the first 3 are licensed for monotherapy against Candida infections and only fluconazole and echinocandins are recommended as frontline agents for invasive candidiasis. On this background and in absence of a standard definition for MDR Candida, we defined MDR as an isolate nonsusceptible to ≥1 agent in ≥2 drug classes and XDR as an isolate nonsusceptible to ≥1 agent in ≥3 drug classes.

**EPIDEMIOLOGY AND DRIVERS OF RESISTANCE**

Reports on resistance to antifungal agents are relatively rare (when compared to antibacterial agents) but became much more common with the introduction of additional classes of antifungal agents, particularly the azoles (especially fluconazole), which have been widely used against Candida infections. Thus, the development of resistance to the current clinically used azole antifungal agents has become an increasing problem. This is particularly true in patients requiring long-term treatment and in those receiving antifungal prophylaxis, highlighting the importance of antifungal stewardship [6,7]. Widespread acquired azole resistance was frequently described in patients with AIDS and oropharyngeal or mucosal candidiasis (particularly in the era prior to active antiretroviral therapy) and less frequently in invasive infections. In these patients, resistance can be stable or transient, in response to azole treatment [8]. Acquired echinocandin resistance has emerged over the past decade and particularly so in C. glabrata. Most cases occur after 3–4 weeks of therapy, but resistant mutants have been reported after short-term therapy and even in echinocandin-naive patients in high-incidence settings, suggesting potential transfer among hospitalized patients [9,10]. In addition, there is a growing awareness of the changing epidemiology of fungal infections, with a shift toward species that are intrinsically resistant to the most commonly used antifungal agents (namely, fluconazole) [11,12] (Table 1).

**Intrinsic Resistance**

Intrinsic or primary resistance is inherent (not acquired) resistance, which is a characteristic of all or almost all representatives of the species, and it is predictive of clinical failure. Examples of intrinsic resistance are the resistance of C. krusei to fluconazole and of many of the newly described C. auris strains associated with the global outbreaks of infection in healthcare settings with elevated minimum inhibitory concentrations (MICs) to several classes of antifungal drugs, including azoles, echinocandins, and polyenes (Table 1). The widespread use of azole antifungals has been associated with the emergence of resistant (C. krusei) or less susceptible species (particularly C. glabrata) in many regions of the world and in specific patient populations such as in transplantation, where azole use is widespread and continued for long-term for prophylaxis and therapy of infection [19,20].

Other Candida species with intrinsic resistance to fluconazole also have decreased susceptibility to the echinocandins so that they can be classified as MDR including Candida guilliermondii and the closely related species Candida fermentata, which are uncommon causes of infection but are occasionally associated with serious disease, including bloodstream infections [21].

More widespread has been the global emergence of C. auris, which has emerged as an important cause of healthcare-associated infections worldwide and can exhibit intrinsic MDR [22]. Initially C. auris was described from an external ear canal drainage in Japan in 2009 and later from bloodstream infection in Korea in 2011 [23]. Most subsequent cases occurred in India where a high degree of clonality among the isolates has been documented [24,25]. Recent reports have documented infection throughout the world, including the United States, most typically associated with healthcare-associated infections including transmission in healthcare facilities [16,24,26–29]. Patients with C. auris have similar risk factors to other Candida species infections, including abdominal surgery, broad-spectrum antibiotics, central venous catheters, and comorbid conditions [23]. The diagnosis is often difficult due to misidentification with commercial identification test methods, although matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF) can accurately identify the organism if C. auris is included in the library [30]. Overall mortality is high, ranging from 30% to 60%, and infections occur several weeks into the patient’s hospital admission. Infection control has been difficult as colonization and environmental contamination has been extensive [22,23]. Although breakpoints are not available for C. auris, most strains are resistant to fluconazole (MICs ≥64 mg/L) and about one-third of the isolates have elevated MICs (≥2) against voriconazole and amphotericin B. A few strains (7%) have elevated MICs to the echinocandins as well [23]. Overall, 41% were resistant to 2 drug classes (MDR) and 4% were resistant to 3 (azoles, echinocandins, and polyenes), which make them XDR [16]. Phylogenetically, C. auris is related to Candida haemulonii, for which it can be confused, which is known for its intrinsic resistance to fluconazole and amphotericin B.

**Acquired Resistance**

MDR Candida most commonly involves acquired resistance in species with intrinsic resistance, but occasionally MDR occurs in normally susceptible species. Most Candida species have a low rate (<3%) of echinocandin resistance [31]. An exception to that finding is for C. glabrata, which is noted to have increased rates of resistance, particularly in the setting of extensive echinocandin use [32,33]. These isolates are often associated with decreased susceptibility to other antifungals, particularly fluconazole and other azoles. A report from one US medical center demonstrated that over a 10 year-period, echinocandin resistance rose from 2%–3% to >13% in 2009–2010 [34]. Similar
findings were reported at other US hospitals, and a CDC survey showed rates of 3.1%–3.6% from 4 US cities in varying geographic regions [32]. Importantly, echinocandin resistance was associated with cross-resistance to azole antifungals in 36% of the echinocandin-resistant strains, so that concerns regarding MDR C. glabrata significantly increased. Also importantly, “hot spot” FKS mutations associated with resistance were common in those isolates with elevated MICs and more likely to be associated with clinical failure [33].

Other Candida species have also been reported to acquire MDR after antifungal exposure, including C. albicans and others, such as Candida kefyr and Candida lusitaniae [35–38]. Candida albicans resistance mutations have not been particularly common, although they can occur in the setting of long-term echinocandin use or in patients with lack of source control of the infection. These echinocandin and potentially MDR C. albicans isolates are associated with poorer responses in animal models of infection as well as in clinical infections. Less significant mutations may be associated with higher MICs, but can in some cases be overcome in animal models with higher doses of therapy [36, 39].

MOLECULAR MECHANISMS OF RESISTANCE

Amphotericin B exerts fungicidal activity via binding to ergosterol in the fungal cell membrane (Table 2). Upon binding, 6 ergosterol molecules form a pore through the membrane, leading to loss of intracellular compounds and cell death. Ergosterol is formed from a precursor, lanosterol, via several intermediate sterols. This biosynthesis involves a number of enzymatic steps encoded by ERG6, ERG11, ERG24, ERG25, ERG26, ERG27, 

Table 1. Intrinsic Susceptibility Patterns for Candida Species

<table>
<thead>
<tr>
<th>Species</th>
<th>AMB</th>
<th>Echinocandins</th>
<th>Fluconazole</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common Candida species</td>
<td></td>
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</tr>
<tr>
<td>C. albicans</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>Closely related to C. albicans; fluconazole resistance easily acquired [13]</td>
</tr>
<tr>
<td>C. dubliniensis</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td></td>
</tr>
<tr>
<td>C. glabrata</td>
<td>S</td>
<td>S</td>
<td>I</td>
<td>Efflux pumps often induced during azole therapy [14]</td>
</tr>
<tr>
<td>C. krusei</td>
<td>S</td>
<td>S</td>
<td>R</td>
<td></td>
</tr>
<tr>
<td>C. parapsilosis</td>
<td>S</td>
<td>S/I</td>
<td>S</td>
<td>Harbors an FKS1 hot spot alteration responsible for elevated echinocandin MICs. Wild-type population is categorized as susceptible by CLSI and as intermediate by EUCAST [15]</td>
</tr>
<tr>
<td>C. tropicalis</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td></td>
</tr>
<tr>
<td>Uncommon Candida species</td>
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<tr>
<td>C. auris</td>
<td>(X)</td>
<td>(X)</td>
<td>X</td>
<td>93% resistant to fluconazole, 35% to amphotericin B, and 7% to echinocandins; 41% resistant to 2 antifungal classes and 4% resistant to 3 classes [16]</td>
</tr>
<tr>
<td>C. bracharensis</td>
<td></td>
<td>X</td>
<td></td>
<td>Closely related to C. glabrata</td>
</tr>
<tr>
<td>C. lusitaniae</td>
<td></td>
<td>X</td>
<td></td>
<td>Closely related to C. glabrata</td>
</tr>
<tr>
<td>C. fermentati</td>
<td></td>
<td>X</td>
<td></td>
<td>Closely related to C. parapsilosis</td>
</tr>
<tr>
<td>C. guilliermondii</td>
<td></td>
<td>S/X</td>
<td>X</td>
<td>Closely related to C. glabrata</td>
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<tr>
<td>C. metapsilosis</td>
<td></td>
<td>X</td>
<td></td>
<td>Closely related to C. parapsilosis</td>
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<tr>
<td>C. nivariensis</td>
<td></td>
<td>X</td>
<td></td>
<td>Closely related to C. glabrata</td>
</tr>
<tr>
<td>C. orthopsilosis</td>
<td></td>
<td>X</td>
<td></td>
<td>Closely related to C. parapsilosis</td>
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<tr>
<td>C. ciferri</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
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<tr>
<td>C. inconspicua</td>
<td></td>
<td>X</td>
<td></td>
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<tr>
<td>C. humicula</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
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<tr>
<td>C. lambica</td>
<td>X</td>
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<td></td>
<td></td>
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<tr>
<td>C. lipolytica</td>
<td>X</td>
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<tr>
<td>C. norvegensis</td>
<td></td>
<td>X</td>
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<tr>
<td>C. palmioleophila</td>
<td>X</td>
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<tr>
<td>C. rugosa</td>
<td>X</td>
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<tr>
<td>C. valida</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>S. cerevisiae</td>
<td>X</td>
<td></td>
<td></td>
<td>Closely related to C. glabrata</td>
</tr>
</tbody>
</table>

CLSI and EUCAST breakpoints have been established for the common Candida species allowing classification of wild-type isolates into S (susceptible), I (intermediate), and R (resistant) categories. For the uncommon Candida species, breakpoints have not been established. For these species, an “X” denotes that the MICs for the antifungal compound are elevated compared to those for C. albicans.

Abbreviations: AMB, amphotericin B; CLSI, Clinical and Laboratory Standards Institute; EUCAST, European Committee on Antimicrobial Susceptibility Testing; I, intermediate; MIC, minimum inhibitory concentration; R, resistant; S, susceptible.

*Anamorphic state is C. robusta.*
ERG2, ERG3, ERG5, and ERG4 in sequential order. Combined mutations in ERG11 and in ERG3 or ERG5 and single mutations in ERG6 or in ERG2 have been associated with depletion of ergosterol and amphotericin B resistance in Candida; however, acquired amphotericin B resistance is a rare event [45–49]. Azoles are fungistatic against Candida and act by binding to and inhibiting the intracellular target enzyme ERG11p involved in the biosynthesis of ergosterol. More than 140 alterations have been described in the ERG11 target gene, some of which have been found exclusively inazole-resistant isolates, whereas others have also been found in susceptible isolates [50]. The impact of the alteration onazole resistance depends on location and specific substitution and has been challenging to dissect as several target gene mutations often occur simultaneously and often also play in concert with other resistance mechanisms [42, 50–52]. Gain of function (GOF) mutations in the transcription gene UPC2 that regulates ERG11 expression lead to supernumerary ERG11p concentration and consequently insufficient azole activity [52]. Finally, efflux pumps contribute to azole resistance in Candida [42]. The pleiotropic class of the ATP binding cassette (ABC) transporters (PDR) include the major azole drug transporters CDR1, CDR2, and specifically for C. glabrata also the CgSNQ2, and confer panazole resistance [40–42, 53]. The MDR1 transporter belonging to the major facilitator superfamily (MFS) is also involved in azole resistance in Candida but apparently does not confer resistance to posaconazole, itraconazole, or isavuconazole [53]. Expression levels of these drug transporters are determined by their specific regulators TAC1 for CDR1 and CDR2, and MRR1 for regulation of MDR1 expression. Hence, GOF mutations in these regulators have been related to overexpression of the efflux pumps and hence azole resistance [54, 55].

Echinocandin resistance has only been convincingly linked to one molecular mechanism, namely mutations in 2 hot spot regions of the target gene FKS1 (wild-type AA sequences for C. albicans hot spot 1: FLTLSLDP and hot spot 2: DWIRRYTL) or, in the case of C. glabrata, also in FKS2 (wild-type AA sequences hot spot 1: FLILSLRDP and hot spot 2: DWIRRYTL) [56]. In the vast majority of cases only a single mutation is responsible, although rare cases several alterations are found [57]. The level of resistance depends on the specific codon involved, the specific alteration, and in which species it is occurring. In example, a D to Y alteration at the eighth codon in hot spot 1 of FKS1 affects the MIC much more in C. krusei than in C. albicans, with a ≥2 to ≥4 two-fold dilution steps MIC elevation in C. krusei but only 1–2 steps in C. albicans [58]. The most significant MIC elevation is found for alterations involving the first and fifth amino acids (F [phenylalanine] and S [serine], respectively) in the hot spot 1 region of the FKS1 or FKS2 target genes [56]. Differential in vivo activity has been observed when comparing the 3 echinocandins against C. glabrata. In example, micafungin, but not anidulafungin and caspofungin, retained its activity against C. glabrata harboring the Fks2p-S663F alteration in an animal model, and anidulafungin remained clinically efficacious though caspofungin therapy failed in a clinical case involving a C. albicans isolate with heterologous Fks1p-R647R/G and P649P/L double mutations [56, 57]. However, these are the exceptions from the general rule that FKS1 and FKS2 hot spot alterations affect all 3 echinocandins. An overview of all the specific alterations and their impact can be found in [56].

Flucytosine is actively transported into the fungal cell by permease (encoded by FCY2). It is subsequently converted to 5-fluorouracil or to 5-fluorouridine monophosphate by the enzymes cytosine deaminase or uracil phosphoribosyltransferase
encoded by the FCY1 and FUR1 genes, respectively, and act by inhibiting transcription, DNA replication, and protein synthesis. Resistance emerge rapidly if used as monotherapy and has been ascribed to mutations in the FCY2, FCY1, and FUR1 genes [43, 44]. Moreover, 3 new biological processes that affect flucytosine resistance in C. glabrata was recently proposed including arginine homeostasis, cell wall remodeling, and the aquaglyceroporins of the Fps family [59].

**MDR Resistance Mechanisms**

Most MDR *Candida* infections involve isolates belonging to species with intrinsic resistance, for example, echinocandin resistance in *C. glabrata* and *C. krusei* [34, 58, 60, 61] or infections with *C. guilliermondii* or *C. auris*, which is intrinsically multidrug resistant and currently emerging in India and other continents as described above [16]. Multidrug resistance in species that possess no intrinsic resistance is rare, as in general it requires acquisition of several resistance mechanisms and these often come at a fitness cost [62, 63]. However, ERG3 and ERG2 alterations have individually been associated with azole and amphotericin B cross-resistance in *C. albicans* and *Candida dubliviensis* [45, 62, 64, 65]. Moreover, azole and polyene resistance have been found in *Candida* isolates harboring ERG11 mutations in combination with either ERG3 or ERG5 alterations [45, 46]. Finally, XDR has been described in a very few patients undergoing long-term and alternating antifungal therapy. A stepwise development of azole, echinocandin, and amphotericin B resistance was observed in *C. albicans* from a patient with mucosal infection over a 5-year period [49], and azole, flucytosine, and echinocandin resistance was acquired in *C. glabrata* due to acquisition of mutations in FUR1 (CgFUR1) and CgFKS2 and overexpression of CgCDR1 and CgCDR2 during 20 weeks of antifungal therapy in a hematopoietic stem cell transplant recipient [66].

**Multidrug-Resistant C. glabrata**

Over the past years, a rise in MDR *C. glabrata* has been reported. *Candida glabrata* has been significantly associated with prior fluconazole exposure and, when causing invasive infection, prompt echinocandin therapy without de-escalation [1, 12, 67–69]. In this context of prolonged and more broad-spectrum antifungal exposure, it was less surprising that this species was particularly prone to become MDR. However, it has recently become evident that other mechanisms may contribute to the overrepresentation of *C. glabrata* among MDR *Candida*. First, it was shown that MSH2 DNA mismatch repair gene mutations in *C. glabrata* facilitate rapid acquisition of fluconazole, echinocandin, and amphotericin B resistance [70]. The underlying resistance mechanisms were identical to those seen in clinical isolates with resistance; moreover, MSH2 mutations were found among clinical isolates [71]. These findings may also help explain why echinocandin resistance in *C. glabrata* in some studies has been associated to prior fluconazole exposure, although the drug targets and resistance mechanisms are completely different [10]. The implications of this finding are concerning, as it raises the question if fluconazole prescription even in the primary healthcare sector is also a potential driver of MDR *C. glabrata*. Second, Jensen et al reported a high rate of echinocandin-resistant *C. glabrata* in the oral microflora after candidemia treatment with ≥7 days of echinocandins, and Shields et al reported a high prevalence among *C. glabrata* isolates from abdominal candidiasis [72, 73]. These findings suggest that (1) subtherapeutic drug concentrations (potentially linked to the high protein binding of echinocandin drugs) at mucosal surfaces and in focal infections may facilitate resistance development and/or (2) that *Candida* biofilm of the oral cavity or on intraabdominal devices may be involved in resistance selection. Drug sequestration in the biofilm matrix reduces drug efficacy but also provides an environment of lower exposure that may facilitate selection of acquired resistance [74].

**Treatment and Prevention of MDR Candida Infection**

Treatment options for MDR *Candida* infections remain limited. Expert guidelines have few evidence-based data to guide their recommendations [12, 69]. Anecdotal experience has shown that in patients with *C. glabrata* infections that have elevated MICs to the echinocandins and fluconazole resistance as well (MDR strains), clinical failure rate is increased [9, 75]. In those patients, both expert panels and clinical experience suggest that liposomal amphotericin B combined with an extensive search for undrained or unremoved foci of infection (such as central catheters, abdominal abscesses, other hardware, or thrombophlebitis) are critical to a successful outcome [34]. In patients with MDR *C. albicans* infection, experimental animal data suggest that some less critical FKS mutations may be associated with higher response rates with higher doses of therapy, but clinical correlation of those data are lacking [36, 39].

In patients with MDR *C. auris*, limited experience is available to guide optimal approaches to therapy, but susceptibility data suggest that echinocandin resistance is less frequent than for the azoles such that, for clinically available antifungal agents, an echinocandin or amphotericin B remains the likely drug of choice in those infections [16, 22, 23]. In those settings, antifungal susceptibility testing is strongly recommended and complete mycological evaluation for underlying resistance mechanisms for those strains with elevated MICs may be reasonable. Data regarding combinations of antifungal agents from different classes are limited, so conclusive recommendations cannot be made. Newer therapies from additional drug classes are needed to improve outcomes in those patients.

Prevention strategies to limit development of MDR and XDR infections are critical. As previously discussed, effective source control for abdominal and device-related infections will reduce the burden of infection and eliminate persister cells, which may
become drug tolerant over time [36]. Additionally, devices and hardware should be removed to eliminate biofilms, which can be a drug-protected nidus of infection. Antifungal drugs should not be given in subtherapeutic doses, which can encourage acquisition of resistance, and therapy should not be continued for durations longer than indicated. Prophylaxis of infection is needed to prevent infection in established high-risk patients, but a careful attempt should be made to establish a mycological diagnosis of infection so that susceptibility testing can assist in antifungal management.

CONCLUSIONS

Antifungal drug resistance including MDR Candida species has become increasingly important in the management of invasive fungal infections. These infections are associated with high morbidity and mortality and can be associated with healthcare-associated transmission. The emergence of MDR C. glabrata has become common in many medical centers and presents significant management challenges. Similarly, C. auris has emerged as an important clonally spread species that is associated with MDR and XDR characteristics and is associated with long-term colonization and extensive environmental contamination. Outcomes are poor with these resistant infections; thus, an accurate mycological diagnosis and therapy guided by susceptibility testing should be used to optimize management. New therapies are needed to improve the outcome of patients with these infections.

Notes

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