Infection and Drug Resistance

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REVIEW

Candidemia: Evolution of Drug Resistance and Novel Therapeutic Approaches

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Abstract: Candidemia and invasive candidiasis are the most common healthcare-associated invasive fungal infections, with a crude mortality rate of 25–50%. *Candida albicans* remains the most frequent etiology, followed by *C. glabrata, C. parapsilosis* and *C. tropicalis*. With the exception of a limited number of species (ie: *C. krusei, C. glabrata* and rare *Candida* species), resistance to fluconazole and other triazoles are quite uncommon. However, recently fluconazole-resistant *C. parapsilosis*, echinocandin-resistant *C. glabrata* and the multidrug resistant *C. auris* have emerged. Resistance to amphotericin B is even more rare due to the reduced fitness of resistant isolates. The mechanisms of antifungal resistance in *Candida* (altered drug-target interactions, reduced cellular drug concentrations, and physical barriers associated with biofilms) are analyzed. The choice of the antifungal therapy for candidemia must take into account several factors such as type of patient, presence of devices, severity of illness, recent exposure to antifungals, local epidemiology, organs involvement, and *Candida* species. The first-line therapy in non-neutropenic critical patient is an echinocandin switching to fluconazole in clinically stable patients with negative blood cultures and azole susceptible isolate. Similarly, an echinocandin is the drug of choice also in neutropenic patients. The treatment duration is 14 days after the first negative blood culture or longer in cases of organ involvement. An early removal of vascular catheter improves the outcome. The promising results of new antifungal molecules, such as the terpenoid derivative ibrexafungerp, the novel echinocandin with an enhanced half-life rezafungin, oteseconazole and fosmanogepix, representative of new classes of antifungals, are discussed.

Keywords: candidemia, *Candida*, antifungal resistance, management of candidemia, novel antifungals

Introduction

Candidemia and invasive candidiasis are the most common healthcare-associated invasive fungal infections. The incidence varies with geographical region and local epidemiology. Analysis of large multicentric surveys reports an overall pooled incidence rate of 3.88 per 100,000 inhabitants per year (range 1.0 to 10.4) with an increasing trend from the 1990s (median 2.18) to the following periods (median 4.67 in the year 2000–2010 and 3.22 in the last decade).[1] This trend may be justified by a progressive increase in high-risk population related to the prolonged survival of critically ill patients and aging population.

Most of the episodes are hospital-acquired with a reported incidence of 0.17–2.7 episodes per 1000 discharges, 0.30–4.9 per 10,000 patient days.[2] However, community-acquired candidemia is emerging as a consequence of an increasing use of long-term intravenous devices such as tunneled intravascular and peripherally inserted central catheter (PICC).[3]

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Received: 19 October 2021
Accepted: 30 November 2021
Published: 19 December 2021

Despite treatment, mortality remains high: crude mortality rate varied from 25% to 50%, while the attributable mortality rate is estimated around 10–20%.[1,3]

Candidemia has a significant economic burden due to the prolonged stay in hospital, mainly in intensive care unit, and the use of expensive antifungal therapy. A mean total cost per patient with candidemia and invasive candidiasis ranging from $48,487 to $157,574 was reported in a systematic review including five studies.[4]

Organisms

Candida albicans is the most frequent cause of candidemia and invasive infections and, although it remains the most common pathogen overall causing these infections, the prevalence of other species has been increasing over time.

The SENTRY program analyzing 20,788 invasive isolates collected from 135 medical centers in 39 countries noted a progressive decrease of the frequency of *C. albicans* from 57.4% in 1997–2001 to 46.4% in 2015–2016 and a parallel increase in *C. glabrata, C. parapsilosis, C.tropicalis, C. krusei* and other more rare species.[5]

The increase of *C. glabrata* infections may be associated with an increased fluconazole use for treatment and prophylaxis (this species is frequently isolated from hematological patients receiving fluconazole prophylaxis) or/and with the trend toward increasingly older hospitalized patients whose alimentary tract is frequently colonized by this species.

The species distribution varies by geographic areas with *C. glabrata* most common in North America (24.3%) and least common in Latin American region (7.1%), and *C. parapsilosis* more common (24.3%) in Latin America.[5] Mediterranean countries have higher relative incidences of *C. parapsilosis* and less *C. glabrata* and *C. albicans* than North or Central European countries. The species distribution in Asia shows a high incidence of *C. tropicalis* that in China ranks three accounting for 18.7% of the *Candida* bloodstream isolates after *C. albicans* (32.9%) and *C. parapsilosis* (27.1%) and in some reports from India it is the most prevalent isolated species.[5]

The relative frequency of the *Candida* species also depends on the different patient populations considered (ICU, medical, surgical wards, hematology, neonatology).

With the exception of a limited number of species (such as *C. krusei, C. glabrata* and rare species) azole and echinocandin resistance is quite uncommon and, when it occurs, often develops after long-term use of antifungals for treatment or prophylaxis. Acquisition of amphotericin B resistance is even more rare due to the reduced fitness of resistant isolates.[6] Although flucytosine presents excellent activity against most *Candida* species, high rates of acquired resistance to this drug are frequently observed during monotherapy.

In large-scale surveillance studies of bloodstream isolates, the overall prevalence of azole and echinocandin resistance in *C. albicans* is less than 1%.

Fluconazole resistance in *C. glabrata* is not uncommon, ranging from 5.6% to 15.7%.[7] High rates of fluconazole-resistant *C. glabrata* have been reported both from sentinel and population-based surveillance studies conducted in the USA, Australia, Denmark and Belgium.[8] Cross-resistance between fluconazole and voriconazole was complete for *C. glabrata* isolates (0% susceptible to voriconazole among fluconazole-resistant strains).[5]

The haploid genome of this species favors the development of tolerance and resistance to azoles.

Also, echinocandin resistance occurs more frequently in *C. glabrata* (1.7–3.5%) than in other *Candida* species (0–0.7%) and this can be due to both the haploid genome and preferential use of echinocandins for treatment of these infections.[5,7] The increasing azole resistance in *C. glabrata* encouraged the use of echinocandins for the treatment of infections caused by this species and this provoked a selective pressure for echinocandin resistance.[9] No echinocandin resistance was present in a collection of isolates from 2001 to 2004, while, starting from 2006 with the growing use of these antifungals, echinocandin resistance was present in 8–11% of fluconazole resistant *C. glabrata* bloodstream isolates.[5,9]

The presence, albeit limited, of multidrug-resistant *C. glabrata* isolates is worrying.

The introduction use of matrix-assisted laser desorption ionization-time-of-flight mass spectrometry (MALDI-TOF) and molecular methods allowed to identify two cryptic species of *C. glabrata* (*C. nivariensis* and *C. bracarensis*) that are azole-resistant, but very susceptible to echinocandins.[5]

C. parapsilosis is a species complex of three cryptic species identified by MALDI-TOF or molecular methods: *C. parapsilosis sensu stricto* that is the most prevalent cause of fungemia, and two less common species *C. orthopsilosis* and *C. metapsilosis*.

The lower mortality rate seen with *C. parapsilosis* is consistent with its reduced virulence relative to *C. albicans*.[10] *C. parapsilosis* is a skin colonizer and it is able to colonize intravascular catheters and rapidly grows

in high-glucose containing parenteral nutrition administered to patients.

The ability of adherence to intravenous catheters and medical devices and of colonizing the hands of healthcare workers may contribute to invasive infections and clonal outbreaks. *C. parapsilosis* poses a serious threat to newborns, especially those born prematurely and with low birth weight. The prolonged use of total parenteral nutrition and the transition from the hands of healthcare workers are considered the origin of neonatal infections.

Fluconazole resistance was generally considered to be uncommon among *C. parapsilosis* isolates, however recent reports from different parts of the world suggest that fluconazole resistance in *C. parapsilosis* may emerge following drug pressure of fluconazole treatment and prophylaxis, with subsequent patient-to-patient transmission within the hospital environment.[8] Cross-resistance to azoles was also described: in the SENTRY surveillance study, 67.3% of the fluconazole-resistant isolates were also voriconazole.[5]

C. parapsilosis is intrinsically less susceptible to echinocandins because of naturally occurring FKS1 mutations. However, even if *C. parapsilosis* consistently displays higher MIC values compared with other *Candida* species, an equal outcome was observed in clinical trials.[11,12]

Clonal spreading of echinocandin-resistant *C. parapsilosis* by the hands of healthcare workers has been reported.[13] The ability to form tenacious biofilms on vascular catheters and other medically implanted devices is responsible to the resistance to azoles.

C. tropicalis occurs particularly in patients with cancer, chronic liver disease, and hematological malignancies. Resistance to fluconazole occurs in 1.1% of the isolates of this species up to 37.8% in Asia Pacific area, while echinocandin resistance (0.5–0.7%) is reported only in North and Latin America isolates.[5,14]

Infections by *C. krusei* are rare but characterized by poor response to standard antifungal therapy and a high mortality rate (40–58%). This species is inherently resistant to fluconazole, therefore this azole should never be used. On the contrary 95% of the isolates were susceptible to voriconazole.[5]

In the last years, the selective pressure of prophylaxis contributed to the emergence of less common multiresistant yeast pathogens, most of them identified using MALDI-TOF or sequence-based methods.

Due to the rare number of studied isolates species, specific breakpoints do not exist; however, elevated fluconazole and echinocandin MIC values (MIC50/90, >4 mg/L) were observed for isolates of *C. fermentati, C. guilliermondii, C. lipolytica*, whereas azole-resistant species *C. norvegensis* and *C. inconspicua* as well as *C. dubliniensis, C. kefyr*, and *C. pelliculosa* were very susceptible to echinocandins.[5]

C. palmioleophila, often misidentified as *C. guilliermondii* or *C. famata*, is an emerging pathogen in Denmark. Isolates of this species, differently from *C. guilliermondii*, are highly susceptible to echinocandins and less susceptible to posaconazole and voriconazole and resistant to fluconazole.[15]

C. lusitaniae shows low azole MIC values and elevated echinocandin MICs. In addition, this species, despite the low amphotericin B MIC value in the initial isolates, should be regarded as a poor target for amphotericin B as resistance mutation arises spontaneously.[15]

Among these rare species, *C. auris* has raised considerable concern because of the fast global spread and some peculiar characteristics. This yeast is able to colonize inert materials and can persist for weeks on surfaces in healthcare environments, leading to high transmissibility and protracted outbreaks. Therefore, isolation of patients, wearing of protective clothing by healthcare workers, screening of patients of the affected wards, skin decontamination with chlorhexidine, and daily and terminal cleaning and disinfection of the patient care environment with effective products (hydrogen peroxide, alcohol-quaternary ammonium compounds, and chlorine-based products) is essential.[16,17]

C. auris can be resistant to any or all the systemic antifungal drugs available.

A systematic review reported a fluconazole resistance rate of 44.3%; a wide range was observed depending on the geographic area, from 15.4% in Japan to 90% in India.[18–20]

Also, variable voriconazole susceptibility patterns are reported according to the different clades that are correlated to geographic origin. Variable levels of resistance to the other triazole antifungals, to candins (0–7%) and amphotericin B (8–35%) do not seem to have significant clade-specific differences.[20,21] Resistance to all three classes of commonly prescribed antifungal drugs (pan-resistance) has been reported from multiple countries.

Mechanisms of Antifungal Resistance

Candida antifungal resistance may be primary or secondary depending on the species. Intrinsic, or primary,

resistance is a characteristic of all isolates of the species, without a previous exposure to drugs; a typical example is the resistance of *C. krusei* to fluconazole. Secondary, or acquired, resistance develops in susceptible isolates as a consequence of the exposure to drugs, usually prolonged treatment or prophylaxis.

Up to now, there are only four classes of antifungals available for the treatment of systemic fungal infections: azoles and polyenes, acting at level of the fungal membrane, echinocandins, acting on the fungal wall, and flucytosine interacting with nuclear acid synthesis. Figure 1 displays the mechanisms of action (Figure 1A) and the mechanisms of resistance (Figure 1B) of the different classes of antifungals.

Azoles act on the biosynthesis of ergosterol by inhibiting the enzyme lanosterol 14-α-sterol demethylase, leading to the accumulation of toxic sterols in the membrane and consequently to the alteration of the function of the membrane.[22,23] Azoles have a fungistatic activity against *Candida*, as well as other yeasts, and this characteristic together with the wide use of these antifungals as prophylaxis has led to the widespread resistance to azoles.[24] One mechanism associated with azole resistance is the reduction of the drug concentration in the fungal cell caused by the activation of efflux pumps, encoded by the *CDR* genes of the ATP-binding cassette superfamily and by the *MDR* genes. The induction of efflux pumps encoded by *CDR* genes confers resistance to all azoles, on the contrary the induction encoded by of the *MDR* genes seems to lead only to fluconazole resistance.[22] Another way in which *Candida* develops resistance to azoles is the alteration or up-regulation of the gene encoding the azole target enzyme, the *ERG11* gene for *Candida*. Mutations in *ERG11* prevent the binding of azoles to the enzymatic site. The intrinsic resistance of *C. krusei* to fluconazole is attributed to the reduced affinity of *ERG11*p for this azole.[22] Furthermore, as an adaptive response to azole exposure, *Candida* can activate a bypass pathway such as the one based on the mutation in the *ERG3* gene that prevents the formation of the toxic sterol 14-a-methyl-3,6-diol, allowing normal functionality of the cell membrane.[22]

Echinocandins act on the biosynthesis of (1,3)-β-D-glucan synthase, encoded by *FKS1* and *FKS2* genes, preventing the correct synthesis of glucan and leading to the loss of cell wall integrity. Echinocandins have fungicidal activity against the majority of *Candida* species. Echinocandins resistance or reduced susceptibility are mainly due to mutations in the highly conserved regions of *FKS* genes; levels of resistance depend on the hot spot mutations and expression level of these genes.[22,23,25] An adaptive response to echinocandin treatment is the increased production of other wall components, such as the chitin.[22,25]

The polyenes act by binding directly ergosterol in the membrane, causing the formation of channels through which ions and other cellular components escape, leading to the death of the fungal cell. Amphotericin B has usually a fungicidal activity. Acquired resistance is a consequence of a reduction in ergosterol content in the cell membrane due to alterations in some *ERG* genes (*ERG1*, *ERG2*, *ERG3*, *ERG4*, *ERG6*, *ERG11*).[23] For this reason, treatment with an antifungal, such as an azole, that decreases cellular sterol concentrations can lead to polyene resistance.[23] Acquisition of resistance is extremely rare as mutations that conferred resistance to amphotericin B drastically diminish tolerance to external stresses from the host: amphotericin B-resistant mutants were hypersensitive to oxidative stress, febrile temperatures, and killing by neutrophils and also had defects in filamentation and tissue invasion.[6]

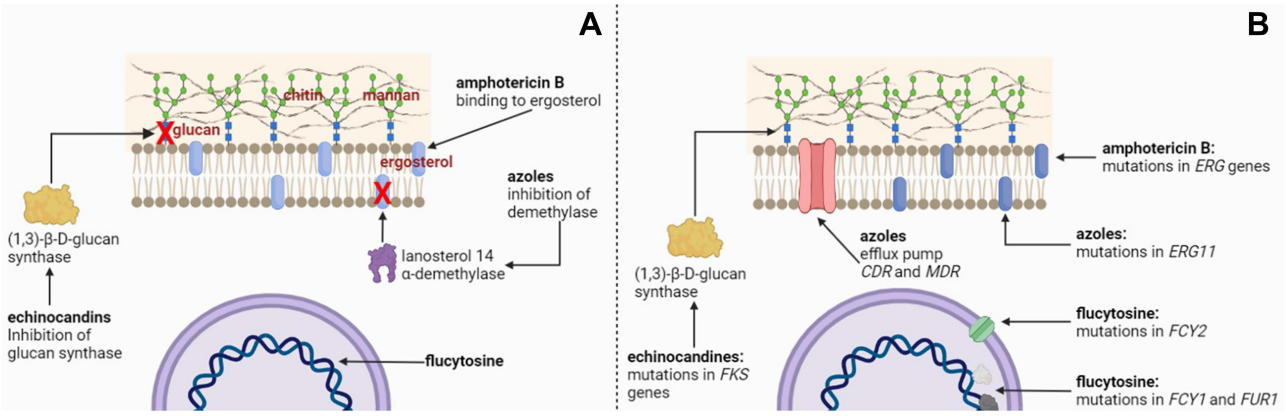

Figure 1 Antifungals: mechanisms of action (**A**), mechanisms of resistance (**B**). Created with BioRender.com.

Flucytosine (5-fluorocytosine, 5FC) is an antifungal that targets nucleic acid biosynthesis. It is transported into the fungal cell by a permease, encoded by the *FCY2* gene, and here is converted into two metabolites, 5-fluorouracil and 5-fluorouridine monophosphate, by the enzymes encoded by the genes *FCY1* and *FUR1*, respectively. The active metabolites inhibit transcription, DNA replication and protein synthesis. Resistance to flucytosine, that emerge when used in monotherapy, have been attributed to mutations in the *FCY2*, *FCY1* and *FUR1* genes.[26] In *C. glabrata*, arginine homeostasis, cell wall remodeling and aquaglyceroporins of the Fps family have emerged as mechanisms of resistance to flucytosine.[27]

Biofilm is another important drug resistance mechanism. The extracellular matrix (ECM) acts as a physical barrier between microorganisms and drug or host immune response and promoting the development of cells able to tolerate high concentrations of antifungals. Other factors can play an important role in conferring resistance to microorganisms organized in the sessile form: alterations in efflux pump expression, changes in cell membrane and wall composition, changes in cellular stress response.[24] Morphology, characteristics of the ECM, and ability to confer antifungal resistance may differ depending on the *Candida* species: *C. albicans* biofilm exhibits a heterogenous structure of blastospores and hyphae in an ECM of polysaccharide material; *C. glabrata* biofilm is composed by cells in a multilayer structure tightly packed or in clusters of cells; *C. tropicalis* biofilm is formed by a network of yeasts, pseudohyphae and hyphae, with high germination of hyphae; and *C. parapsilosis* biofilm has clusters of yeast cells adherent to the surface and thin ECM.[28]

Fluconazole, voriconazole and itraconazole fail to eliminate *Candida* biofilms, whereas echinocandins and amphotericin B lipid formulations are known for their antibiofilm activity, with differences between young and mature biofilms. Studies showed that MICs of liposomal amphotericin B and amphotericin B lipid complex (L-AMB) used against *C. albicans* biofilms are similar to those obtained against planktonic cells. Also echinocandins are active in vitro against *Candida* biofilms,[28–30] but differences depending on the species are observed: low MICs for all echinocandins against biofilm of *C. albicans* and *C. krusei*, and high MICs for *C. lusitaniae* and *C. guilliermondii*, are reported. Micafungin seems more active than the other echinocandins against *C. parapsilosis* biofilm.[31]

Tests in vitro performed on catheters infected separately with *C. albicans* and *C. glabrata* isolates, and treated with micafungin, caspofungin and posaconazole, showed that all three antifungals, especially micafungin, lead to a reduction in *Candida* biofilms.[28]

The activity of 12h L-AMB locks was equivalent to those of micafungin and caspofungin against biofilm of *C. albicans* and *C. glabrata*, but less efficient against *C. parapsilosis* mature biofilms. However, overall eradication of the biofilm from the catheter was never obtained with any antifungal.[32]

Multidrug resistance (MDR) was defined by the US Centers for Disease Control and Prevention as acquired nonsusceptibility to ≥1 agent in at least 3 antimicrobial categories, but since only fluconazole and echinocandins are recommended as first-line agents for invasive candidiasis, MDR *Candida* can be defined as an isolate nonsusceptible to ≥1 agent in ≥2 drug classes.[26] The development of MDR *Candida*, although rare compared to antibacterials, is a matter of concern especially in light of the changing epidemiology of *Candida* infections, showing a shift towards species intrinsically resistant to the most commonly used antifungal drugs. In fact, MDR *Candida* mainly involves acquired resistance in species with intrinsic resistance[26] such as echinocandin resistance in *C. krusei, C. glabrata, C. guillermondii* or *C. auris*. MDR occurs more rarely in species without inherent resistance as this requires the acquisition of different resistance mechanisms which have a fitness cost; for instance, *C. albicans* has been reported to acquire MDR after antifungal exposure in the setting of longterm echinocandin use.[26]

Of particular concern are the increasingly reported cases of MDR of *C. glabrata* and *C. parapsilosis*.

Management of Candidemia

The choice of antifungal therapy for the treatment of candidemia must take into account several variables such as type of patient (neutropenic or non-neutropenic patient), presence of acute and chronic comorbidities, presence of devices (urinary or central vascular catheter), severity of illness, recent exposure to antifungal agents (azole or echinocandin), local epidemiology, organs involvement, *Candida* species (Table 1).[33] In the previous literature, the rate of mortality appears to be related to the presence of certain risk factors such as age, higher APACHE score, immunosuppression, renal failure, triazole exposure in both neutropenic and non-neutropenic patients.[34–36] On

Table 1 Clinical Conditions/Risk Factors Associated with Candidemia, Resistance Rates, Antifungal Treatment According to Different *Candida* Species

***Candida* spp.**	**Patients at Risk/Risk Factors**	**Rate of Resistance**	**Therapy**
C. albicans	All patients	Fluconazole: 0.1–0.4% Echinocandins: 0–0.1% Amphotericin B: rare	• Echinocandins (1) • Fluconazole, 800 mg then 400 mg (2) • Liposomal amphotericin B, 3–5 mg/kg/day (3)
C. parapsilosis	ICU patients Neonates Vascular catheter	Fluconazole: 0.6 up to 53% Echinocandins: 0–0.1% Amphotericin B: rare	• Echinocandins (1) • Fluconazole, 800 mg then 400 mg (2)
C. glabrata	Older age Diabetes Cancer Hematological malignancies Stem cell transplantation Azole prophylaxis	Fluconazole: 2.6–10.6% Echinocandins: 0%-2.8% Amphotericin B: rare	Fluconazole and voriconazole are not recommended for frequent azoles resistance • Echinocandins (1) • Liposomal amphotericin B, 3–5 mg/kg/day (3)
C. tropicalis	Corticosteroid therapy Hematological malignancies Stem cell transplantation	Fluconazole: 1.1–37.8% Echinocandins: 0–1.3% Amphotericin B: rare	• Echinocandins (1) • Fluconazole, 800 mg then 400 mg (2) • Liposomal amphotericin B, 3–5 mg/kg/day (3)
C. krusei	Corticosteroid therapy Hematological malignancies Stem cell transplantation Azole prophylaxis	Fluconazole: innately Echinocandins: 0–0.7% Amphotericin B: rare	Fluconazole is not recommended for frequent azoles resistance • Echinocandins (1) • Liposomal amphotericin B, 3–5 mg/kg/day (3) • Voriconazole (4)
C. auris	Diabetes Cancer Hematological malignancies ICU patients Invasive procedures	Fluconazole: 15.4–90% Voriconazole: 50% Echinocandins: 2–8% Amphotericin B: 15–30%	• Echinocandins (1)

Notes: (1) Caspofungin: loading dose 70 mg, then 50 mg daily; micafungin: 100 mg daily; anidulafungin: loading dose 200 mg, then 100 mg daily. (2) In stable patients without previous exposure to azoles. (3) If isolates are not susceptible to azoles and echinocandins or in the presence of organ involvement. (4) 6 mg/kg q12h × 2 doses (load) then 3–4 mg/kg q12h.

the contrary, early initiation of antifungal therapy and adequate control of the source of infection are factors that reduce mortality in patient with candidemia.[37,38]

The Infectious Diseases Society of America (IDSA) and European Society of Clinical Microbiology and Infectious Diseases (ESCMID) guidelines for the management of candidemia recommend performing transesophageal echocardiography and fundoscopy. Data from the literature showed a percentage of endocarditis equal to 8.3%[39] and a percentage of ocular involvement equal to 16% in patients with candidemia.[40]

The presence of organ involvement affects the choice of the type of antifungal to be administered, in relation to their penetration in the different districts, and the duration of the antifungal therapy.[33,41]

The antimycogram of *Candida* isolates should be always performed for a correct selection of the antifungal agent.[33] However, even in the presence of an in vitro susceptible strain, there could be clinical resistance linked to the pharmacokinetics and pharmacodynamics of the antifungal drug.

Non-Neutropenic Patients

The first-line therapy in the non-neutropenic critical patient is an echinocandin (caspofungin: loading dose 70 mg, then 50 mg daily; micafungin: 100 mg daily; anidulafungin: loading dose 200 mg, then 100 mg daily), according to the IDSA and European Association for the Study of the Liver (EASL) guidelines.[33,41] Fluconazole, intravenous or oral, 800 mg (12 mg/kg) loading dose, then

400 mg (6 mg/kg) daily, can be administered in clinically stable patients, who have not been exposed to azoles and are not at risk for *C. glabrata* infection.[33] Furthermore, these guidelines recommend step down strategy in patients in therapy with echinocandin who are clinically stable with negative blood cultures and *Candida* isolate susceptible to azoles, switching to fluconazole (for *C. albicans, C. parapsilosis* and *C. tropicalis)* or voriconazole (for *C. krusei)* within 10 days.[33,41,42] All three echinocandins demonstrated a broad spectrum, fungicidal activity, antibiofilm activity, favorable safety profile and limited drug interactions.[33,41,43] However, these drugs do not reach therapeutic concentrations in the eye, urine and central nervous system.[42] No differences in efficacy and tolerability between echinocandins were reported in the literature, however only anidulafungin has been compared with fluconazole.[44] This clinical trial showed that patients with candidemia treated with anidulafungin had a better outcome than those treated with fluconazole. This finding was also confirmed in a subsequent sub-analysis carried out by the same authors, in which anidulafungin showed greater efficacy with respect to fluconazole, especially in *C. albican*s infections,[45] and in another retrospective analysis performed in ICU patients.[46] In particular, this secondary analysis showed, a global response rate equal to 70.8% for anidulafungin and 54.1% for fluconazole, all-cause mortality equal to 10.1% versus 20.3% at 14 days and 20.2% versus 24.3% at 28 days for anidulafungin and fluconazole, respectively.

Furthermore, acquired resistance for echinocandins in *Candida* is rare. However, over the years, there has been an increase in resistance to echinocandins, especially in *C. glabrata*.[47,48] Probably, the greater use of these drugs favored the acquisition of resistance mechanisms. For this reason, de-escalation to fluconazole or voriconazole is recommended in stable patients with *Candida* susceptible species. In previous literature, is also reported less in vitro activity of echinocandins in *C. parapsilosis*,[47,48] but no clinical studies have demonstrated the superiority of fluconazole or other antifungal therapy in the treatment of *C. parapsilosis* infections.[49–51]

Voriconazole represents a therapeutic alternative in fluconazole-resistant isolates of *C. krusei, C. guilliermondii, C. glabrata* for transition from an echinocandin or amphotericin B to oral therapy.[33] Respect to other antifungal drugs, voriconazole presented multiple drug-drug interactions, variable pharmacokinetics, and renal toxicity in case of parenteral formulation.[33,41]

Amphotericin B has a broad-spectrum activity, except for *C. lusitaniae*. Lipid formulation of amphotericin B (3 mg/kg daily) is considered in patients with intolerance or absence of clinical and microbiological response to echinocandins and/or azoles and in patients with suspicion of other fungal infections.[33]

The duration of treatment recommended by the guidelines in uncomplicated candidemia is 14 days after the first negative blood culture, but it is longer in cases with organ involvement.

The antifungal regimen of choice in *Candida* endocarditis is liposomal amphotericin B and the surgery is recommended.[41] In ocular candidiasis, fluconazole or voriconazole must be used, if the isolates are susceptible, and liposomal amphotericin B alone or combined with flucytosine, when the susceptibility is unknown due to the better penetration in this district.[41]

In non-neutropenic patients, candidemia is very frequently associated with the presence of central vascular catheter (CVC) (70% of cases) and several retrospective studies have demonstrated a better outcome and a shorter duration of candidemia in patients with early CVC removal.[33] The IDSA guidelines recommended that earlier CVC removal is possible when the source of infection is the CVC, individualizing this decision for each patient. If the catheter removal is not possible, echinocandin or amphotericin B is preferable to fluconazole, for their greater penetration into the biofilm.[41]

Neutropenic Patients

In neutropenic patients, treatment of fungal infection plays a crucial role in improving survival. For invasive candidiasis and candidemia, therapy should be administered for 14 days after the last positive blood.[36] In these cases, echinocandins are the antifungal therapy of choice, with no difference between anidulafungin, caspofungin or micafungin. The overall recommendation assigned a lower score to anidulafungin due to the low number of neutropenic patients in the clinical trial.[44] Also, liposomal formulation of amphotericin B could be used but is less recommended due to the potential toxicity.[51] The other formulations of amphotericin B, as the conventional amphotericin B, are excluded due to their nephrotoxicity.[52] Regarding azoles, only fluconazole received a weak recommendation in infections sustained by susceptible isolates. Although some trials support the use of this antifungal, they did not take into account the growing rate of resistance.[53,54] Voriconazole could be

limitedly used in infection where a mold cover is desirable. For the other azoles, the data are limited and cannot suggest their use.[55] Furthermore, data on antifungal combination are not conclusive; however, the combination therapy could be helpful in severe and complicated infections.[36]

In some neutropenic patients, chronic disseminated candidiasis (or hepato-splenic candidiasis) is a disease that usually occurred after chemotherapy. Data on these infections are limited, but there are some recommendations similar to those of the invasive candidiasis. Lipid formulations of amphotericin B alongside the use of an echinocandin are encouraged, followed by fluconazole in infections with susceptible isolates.[33] Unlike candidemia, the therapy should be prolonged for at least 8 weeks or until the splenic lesion is resolved.[33,36]

In infections related to CVCs, the removal of the catheter seems to have a crucial role (specially in infections sustained by *C. parapsilosis*) unless an echinocandin was used for the treatment. In the latter case, the studies reported a favorable outcome even though the numbers are low.[50,51,56]

New Antifungal Agents

Antifungal resistance in *Candida* is growing in the last years and underlines the necessity of new antifungal to treat multi-drug resistant isolates. Although the last class of antifungal agent was licensed more than 20 years ago, to date there are some new antifungal agents currently in clinical trials and some of them already in Phase III.

Ibrexafungerp is a novel terpenoid derived from enfumafungin with mechanism of action similar to echinocandins. It binds the 1,3-glucan synthase, but via alternative binding sites rendering it unaffected by FKS mutations.[57] Differently from echinocandins, ibrexafungerp can be administered both intravenously and orally and could be used in different fungal infections, from superficial to life-threatening.[58] Several clinical trials studied the effectiveness of ibrexafungerp in invasive candidiasis, invasive pulmonary aspergillosis and vulvovaginal candidiasis (VVC). The recent Phase III trial VANISH 303 detected higher rate of clinical cure, mycological eradication and overall success of oral ibrexafungerp compared with placebo in VVC.[59] Moreover, ibrexafungerp is active against clinical isolates of *Candida*, including strains resistant to echinocandins and other antifungal agents.[60,61]

Rezafungin is a novel echinocandin with an enhanced half-life and a long stability. These features enabled the administration once-weekly instead of the daily dose of the other echinocandins.[62] Rezafungin showed similar or little less activity compared to other echinocandins, but overall better results than azoles or amphotericin B.[63,64] In Phase II trial, rezafungin with a weekly dose regimen of 400 mg in the first week followed by a 200 mg administration demonstrated similar effectiveness compared to caspofungin in patients with candidemia or invasive candidiasis.[65]

Representative of a new class of antifungal agents, oteseconazole is a tetrazole that inhibits lanosterol demethylase. In phase II studies, oral formulation of oteseconazole was administered in patients with VVC and demonstrated tolerability and similar effectiveness compared to fluconazole.[66,67] In vitro, this new antifungal agent showed potent in vitro activity against fluconazole-resistant *Candida* isolates, though in some strains MICs were high suggesting novel resistance mechanisms.[68,69]

As otesaconazole, also fosmanogepix is a novel drug belonging to a new class of antifungal that completed a Phase 2 clinical trial for candidiasis in non-neutropenic patients (NCT03604705). Fosmanogepix is a prodrug that is converted into the active formulation manogepix by the systemic phosphatase. This drug inhibits Gtw1, an enzyme involved in mannoproteins trafficking and anchoring.[70] In vitro, it demonstrated a potent effect against *Candida* spp. (including echinocandin- and azole-resistant strains) resulting the most active drug compared to anidulafungin, micafungin and fluconazole.[71] Notably, strains with acquired resistance to fluconazole also showed increased MIC to manogepix though the mechanism of this correlation remains unexplained.[72]

Conclusions

As the use of antifungals is widespread in modern medicine, resistant fungal infections, including those caused by *Candida* spp., have been on the rise. While *C. albicans* isolates display low resistance rates to the most common drugs utilized in clinical practice, other *Candida* species could represent a problem in terms of clinical management due to the increasingly reported low susceptibility profiles to antifungals. In particular, resistance to azoles and echinocandins among *C. glabrata* as well as resistance to fluconazole among *C. parapsilosis* are not rare phenomena nowadays. Additionally, we are facing with an increasing isolation of "new", "MDR" opportunistic pathogens, such as *C. auris*, for which few available antifungal molecules are active. Hence, at least three priorities should be pursued for a better management of fungal infections. First, appropriate species

identification methods and antifungal susceptibility testing via standardized procedures are of utmost importance and should be implemented. Second, drugs with unique mechanisms of action able to overcome the resistance mechanisms should be introduced to our current armamentarium. Finally, in order to minimize the selection of resistant strains, an effort must be made to avoid empirical therapy as much as possible.

Disclosure

AP and AMT received speaker honorarium from Gilead. The other authors report no conflicts of interest in this work.

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