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ANTIMICROBIAL DEVELOPMENT AND DRUG RESISTANCE (KC CLAEYS AND J SMITH, SECTION EDITORS)

Antifungal Resistance and the Role of New Therapeutic Agents

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Abstract

Purpose of Review Advances in health care over time have led to an evolution in the epidemiology of invasive fungal infections. There is an increasing concern for antifungal resistance and emergence of less common fungal species for which optimal therapies are not well defined. The purpose of this review is to describe mechanisms of antifungal resistance and to evaluate the modern role of new and investigational antifungals.

Recent Findings Isavuconazole and ibrexafungerp represent the two newest antifungal agents. Evidence from in vivo and in vitro studies has been published recently to help define their place in therapy and potential roles in treating resistant fungi. Isavuconazole is a broad-spectrum triazole antifungal with evidence to support its use in invasive aspergillosis and mucormycosis. Its utility in treating voriconazole-resistant *Candida* should be confirmed with susceptibility testing if available. Ibrexafungerp is an oral glucan synthase inhibitor with little cross-resistance among currently available antifungals, including echinocandins. It is a promising new agent for invasive candidiasis, including azole-resistant *Candida* species, and in combination therapy with voriconazole for aspergillosis. Multiple antifungals, some with novel mechanisms, are in development, including rezafungin, oteseconazole, olorofim, fosmanogepix, and opelconazole.

Summary Both isavuconazole and ibrexafungerp are welcome additions to the arsenal of antifungals, and the prospect of more antifungal options in the future is encouraging. Such an array of antifungals will be important as antifungal resistance continues to expand alongside evolving medical practices. However, managing resistant fungal infections will grow in complexity as the unique role of each new agent is defined.

Keywords Antifungal resistance · Ibrexafungerp · Isavuconazole · *Candida* · *Aspergillus* · Azole resistance

Introduction

The landscape of invasive fungal infections is progressively changing, and there are many factors that are contributing [1]. Advances in healthcare practices are imposing risk for invasive fungal infection in a greater number of patients. Increasing rates of multidrug resistance among bacteria are pressuring clinicians to prescribe broad-spectrum antibacterial therapies, a well-known risk for invasive candidiasis. Evolution in the use of surgical procedures, implantable medical devices, and other invasive interventions stands to increase the risk of invasive fungal infections. More specifically, organ transplantation is one such surgery which also imposes risk from immune suppressant medications used to prevent rejection. The development of novel chemotherapeutic medications and immune modulators to treat patients with cancer and rheumatologic conditions is broadening the spectrum of immune-compromised patients. Not to mention, the routine use of anti-mold prophylaxis in certain immune-compromised patients is selecting for fungi historically considered less common or even rare, e.g., *Mucorales* species [2]. Lastly, emerging fungi like *Candida auris* not only have the potential to impact infection prevention

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strategies but this fungus is also a concerning threat to the continued viability of our current antifungal options due to its propensity for multidrug resistance [3]. As such, it is of utmost importance that the medical community have a solid understanding of modern antifungals, both Food and Drug Administration (FDA)–approved agents and those in development, and the implications of antifungal resistance. The information contained in the following review aims to serve as a resource in this regard.

Antifungal Resistance

Effective treatment of invasive fungal infections has generally relied on three classes of systemic antifungals: azoles, echinocandins, and polyenes. Members of the current generation of echinocandins, including caspofungin, micafungin, and anidulafungin, are all fairly interchangeable in terms of spectrum, safety, and clinical utility, but they are also equally affected by relevant resistance mechanisms. Amphotericin B represents the lone member of the polyene class, and its use is complicated by a relatively unforgiving profile of side effects. So, while three classes of systemic antifungals may seem sufficient, resistance to even one of these antifungals has the potential to limit therapeutic options, especially if other factors like toxicities or drug interactions are at play. The following sections aim to describe major mechanisms of resistance within the three antifungal classes as well as clinical implications related to treatment of fungal infections. Figure 1 is a pictorial representation of these mechanisms of antifungal resistance.

Azole Resistance

Some of the most commonly prescribed azole antifungals include fluconazole, voriconazole, and posaconazole. Agents in this class inhibit fungal growth by interfering with the enzyme lanosterol 14α-demethylase which is responsible for converting lanosterol to ergosterol, a key component in the fungal cell wall. Resistance to azole antifungals has been identified via both acquired resistance and

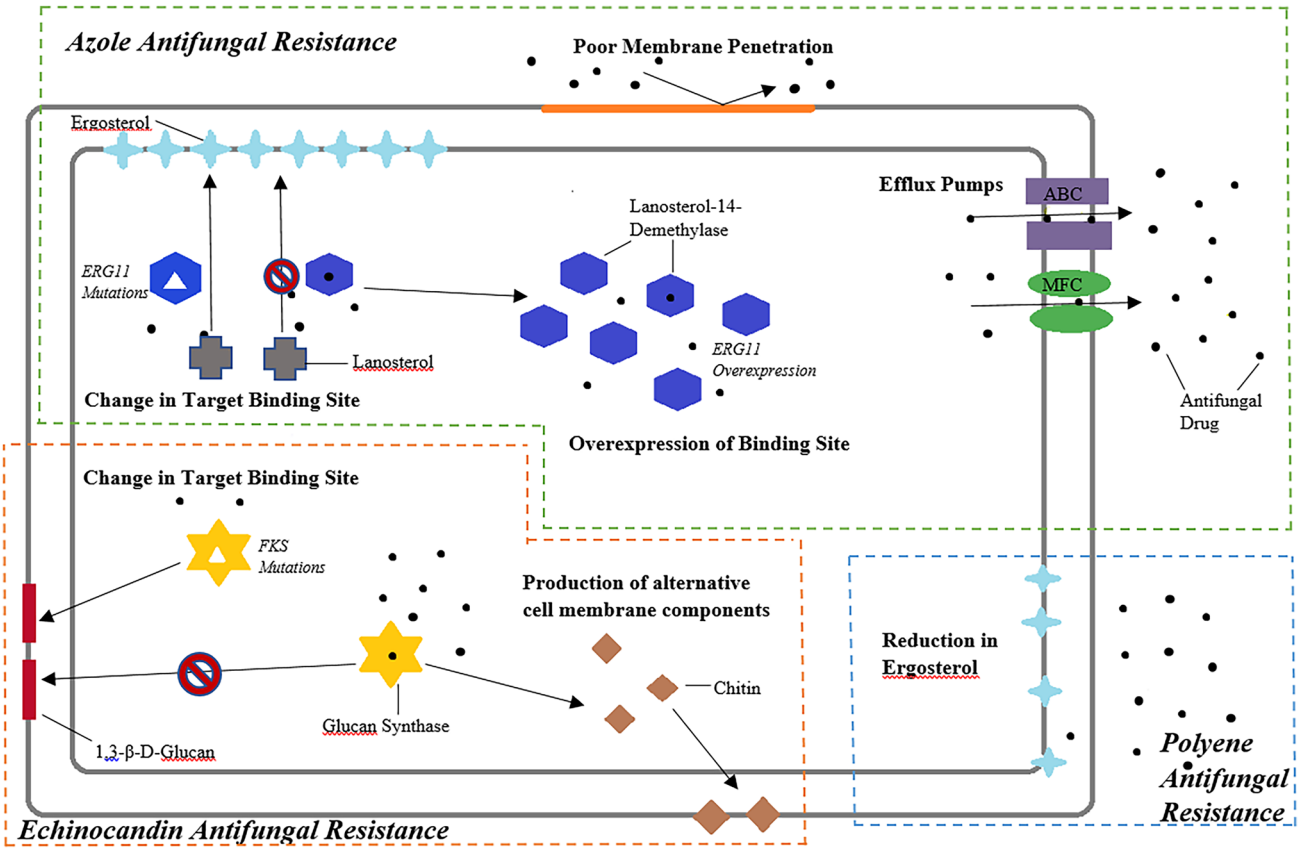

Fig. 1 Pictorial representation of mechanisms of antifungal resistance

intrinsic resistance. Azole resistance is increasing over time, especially among non-albicans *Candida* species. The SENTRY Antifungal Surveillance Program reported a steady emergence of fluconazole- and echinocandin-resistant *C. glabrata* and *C. tropicalis* isolates, with the highest rates of fluconazole-resistant *C. glabrata* isolates in North America (10.6%). Additionally, all *C. auris* isolates collected in this study were noted to be fluconazole resistant [4].

Resistance to azole antifungals in *Candida* species can occur by multiple mechanisms, but the most common are expression of drug efflux pumps and upregulation or mutations in the gene *ERG11*, which is responsible for production of lanosterol 14α-demethylase. There are two types of drug efflux pumps, (1) ATP-binding cassette (ABC) transporter pumps encoded by *CDR1* and *CDR2* genes, and (2) major facilitator superfamily (MFS) pumps encoded by *MDR1* and *FLU1* genes. Isolates expressing multidrug efflux pumps have reduced intracellular accumulation of fluconazole and elevated fluconazole minimum inhibitory concentration (MIC). Induction of the *ERG11* gene leads to excess ergosterol biosynthesis due to increased production of the azole target lanosterol 14α-demethylase. Mutations in *ERG11* itself, by way of amino acid substitutions, have the potential to produce a mutated lanosterol 14α-demethylase that has reduced azole binding affinity. The ability of *Candida* to produce biofilms is yet another contributor to azole resistance. Biofilms harbor organisms in high density, some of which have reduced growth rate or upregulated efflux pumps, as well as extracellular matrix material which can act as a physical barrier to azole drug penetration [5–7].

Voriconazole, posaconazole, isavuconazole, and itraconazole have demonstrated microbiologic activity against *Aspergillus* species. While *A. fumigatus* is the most common species involving invasive disease, other *Aspergillus* species have the potential to cause disease, including *A. flavus*, *A. niger*, and *A. terreus*. Non-fumigatus species of *Aspergillus* have been associated with breakthrough infections among patients receiving triazole prophylaxis, and many of these involve azole resistance [2, 8]. Resistance in *Aspergillus* is primarily mediated by mutations of the *cyp51A* gene that encodes for lanosterol 14α-demethylase, leading to reduced azole affinity for the enzyme. Overexpression of *cyp51A* is also possible in *Aspergillus*, leading to excess production of enzyme that overwhelms the azole antifungal at therapeutic concentrations. Upregulation of ABC transport proteins that reduce the intracellular concentrations of azoles through efflux is also possible [9]. Lastly, an emerging finding in *Aspergillus* species is the presence of cryptic or sibling species, which have been associated with reduced susceptibility to multiple antifungals [10•].

Echinocandin Resistance

Echinocandins (micafungin, caspofungin, and anidulafungin) represent a very important class of antifungals, particularly in the treatment of invasive candidiasis [11]. Echinocandin antifungals target the 1,3-β-D-glucan synthase causing a decrease in the synthesis of 1,3-β-D-glucan, an essential component in the fungal cell wall. This mechanism is distinct from that of azole antifungals, and for this reason, the echinocandins have generally retained activity against most azole-resistant *Candida* species. However, resistance to echinocandins is gaining momentum over time, especially among isolates of *C. glabrata* [12].

The most common form of resistance to echinocandins involves mutations in the *FKS1* gene of 1,3-β-D-glucan synthase. The amino acid substitutions associated with these mutations result in significantly reduced echinocandin susceptibility, and unfortunately, these mutations cause cross-resistance among all members of the echinocandin class [13]. Other *Candida* species have naturally occurring polymorphisms of *FKS* genes which cause relatively higher MICs to echinocandins. For example, *C. parapsilosis* has the substitution P660A and *C. guilliermondii* has L633M and T634A, producing inherently higher MICs to the echinocandins compared to wild-type isolates of other species, such as *C. albicans* and *C. tropicalis* [14, 15•]. However, echinocandins are still able to inhibit glucan synthase in *C. parapsilosis* at therapeutic concentrations. Although this is not a sufficient reason to avoid echinocandins in treating infections caused by *C. parapsilosis*, it may support sequencing treatment to an azole antifungal if susceptibilities support this decision [16]. Another mechanism of echinocandin resistance involves upregulated chitin production. Like glucan, chitin is a structural component of the fungal cell wall. In response to inhibition of 1,3-β-D-glucan synthase by an echinocandin and resulting decrease in synthesis of glucan, the organism upregulates production of chitin, which is associated with reduced susceptibility to echinocandins.

Polyene Resistance

The past two decades have seen continued evolution of the better-tolerated triazole and echinocandin antifungals, such that amphotericin B, the only commercially available systemic polyene, is no longer considered a primary choice for certain fungal infections, including invasive aspergillosis and invasive candidiasis. Polyene antifungals alter cell membrane permeability by binding to ergosterol and causing leakage of intracellular contents. Acquired resistance

to amphotericin B is rare and resistance usually develops by selecting inherently less susceptible strains of fungi. Organisms with intrinsically reduced susceptibility to amphotericin include less common (non-fumigatus) *Aspergillus* species, such as *A. terreus*, *A. flavus*, and *A. nidulans*, *Fusarium* species, and *Scedosporium* species [9]. Resistance to amphotericin B is characterized by a reduction in the ergosterol component of the fungal cell membrane. In a subset of *Candida* isolates, mutational defects in *ERG* genes have been shown to affect the synthesis of ergosterol [17]. Resistance mechanisms in *Aspergillus* remain less clear [9]. Amphotericin B continues to serve as a cornerstone therapy for cryptococcal meningitis, invasive *Mucorales* infections, and an alternative therapy for serious fungal infections involving azole-resistant molds, including breakthrough infections occurring in immune-compromised hosts receiving mold-active triazole prophylaxis [2, 8].

Candida auris

C. auris is an emerging pathogen that holds particular relevance as a resistant fungus. *C. auris* has been classified as a serious global threat according to the Centers for Disease Control and Prevention (CDC) [18]. What is most concerning is its ability to harbor multiple resistance determinants and to display transmission characteristics that are similar to bacteria. In this regard, it has the potential for nosocomial spread. Most isolates of *C. auris* in the USA have been resistant to azole antifungals [19], making the echinocandins critically important as a treatment modality for *C. auris* infections. A recent report describing two clusters of echinocandin-resistant *C. auris* strains, some of which were pan-resistant, raises concern about this species and its ability to spread within healthcare facilities [3]. Equally as concerning is the lack of treatment options that exist for infections due to pan-resistant *C. auris*.

Isavuconazole

At the time it was approved by the FDA, isavuconazole was the newest antifungal to hit the market in nearly a decade. Although mechanistically similar, isavuconazole provides clinical advantages to other triazoles such as lack of QTc prolongation and more consistent oral bioavailability [20], although drug interactions with isavuconazole are similar to those of other triazoles. Isavuconazole is FDA-approved to treat invasive forms of aspergillosis and mucormycosis [20]. In guidelines, isavuconazole is recommended as an alternative regimen for aspergillosis [21] and as a first-line agent in mucormycosis [22]. The following sections describe what is known about isavuconazole as a potential treatment of fungal infections involving resistant organisms.

Isavuconazole Against Resistant *Candida*

In the ACTIVE trial, a large, multicenter, phase 3, randomized, double-blind, double-dummy study of isavuconazole compared to caspofungin as initial therapy for invasive candidiasis, isavuconazole did not meet non-inferiority criteria [23••]. Echinocandins remain the preferred initial therapy for invasive candidiasis in guidelines [16]. However, in both arms of the ACTIVE trial, triazoles were utilized as oral step-down, isavuconazole and voriconazole respectively. So, while isavuconazole is not recommended as initial therapy of invasive candidiasis, it may still have purpose as oral step-down therapy, especially for infections involving resistant *Candida* species. Isavuconazole maintains in vitro activity against *Candida* species, including select fluconazole-resistant *Candida*. In a single-center study analyzing in vitro activity against bloodstream isolates, isavuconazole demonstrated activity against *C. glabrata* and *C. krusei* that are historically fluconazole-resistant [24]. Notably, the activity of isavuconazole against *C. auris* has been established. Arendrup and colleagues characterized the isavuconazole MIC distribution ranging from < 0.004 to 2 mg/L with an MIC_{50} of 0.125 mg/L against 122 *C. auris* isolates using EUCAST methodology [25]. Despite this in vitro data, one study noted its trailing effect with reduced but persistent fungal growth at isavuconazole concentrations above the MIC particularly with *C. glabrata*, *C. albicans*, and *C. tropicalis*, suggesting the possibility of variability in isavuconazole susceptibility depending on the method utilized, i.e., isolates with trailing effect may be reported as resistant though isavuconazole is still partially active against the isolate. Studies are still needed to determine whether such trailing has an impact on clinical outcomes when isavuconazole is utilized [26•].

Sanglard and Coste evaluated the activity of isavuconazole and other azoles against *Candida* isolates with known resistance mechanisms [27•]. Though to a lesser degree than fluconazole and voriconazole, isavuconazole MICs were increased in the presence of *CDR* gene efflux transporters. However, among isolates of *C. albicans* and *C. glabrata*, expression of the *MDR1* transporter had no effect on isavuconazole or posaconazole MICs, unlike fluconazole and voriconazole. Isolates with multiple *ERG11* mutations displayed 4- to 32-fold relative increases in isavuconazole MICs [27•]. Based on these findings, clinicians are advised to determine the isavuconazole MIC to guide decisions regarding use of isavuconazole as oral step-down in the treatment of invasive candidiasis caused by a fluconazole-resistant *Candida* species.

Others have performed in vitro studies of antifungal combinations with isavuconazole and an echinocandin against isolates of *C. auris*. These investigators discovered synergy in many of the isolates tested, suggesting that combination therapy with isavuconazole and an echinocandin is a

treatment option to consider for pan-resistant *C. auris* [28, 29]. The combination of isavuconazole and an echinocandin has been studied in vitro against other *Candida* species, and similar results were demonstrated [30]. However, the threat of pan-resistance in these species is less than that of *C. auris*. Despite in vitro data demonstrating antagonistic activity with amphotericin B and isavuconazole combination therapy in *C. glabrata* isolates, one case report described successful combination therapy with liposomal amphotericin B (LAmB) and isavuconazole in a liver transplant patient with invasive *C. glabrata* infection [31]. The patient maintained persistent candidemia with each individual therapy as well as caspofungin monotherapy, but the antifungal combination successfully cleared blood cultures and stabilized the infection.

Isavuconazole Against Resistant Molds

Isavuconazole demonstrated non-inferiority to voriconazole in the SECURE trial leading to FDA approval for treatment of invasive aspergillosis [32]. In general, isavuconazole and voriconazole MICs among isolates of *A. fumigatus* have strong correlation, suggesting that clinicians can feel confident in using voriconazole as a surrogate for susceptibility to isavuconazole [33•]. Outside of *Mucorales*, there are a couple of exceptions for which isavuconazole is more active than voriconazole. These include *A. lentulus* and *N. udagawae*, both of which have lower MICs to isavuconazole compared with voriconazole [34]. Posaconazole MICs are not as well correlated with isavuconazole as some isolates with an increased isavuconazole MIC retain a relatively lower posaconazole MIC [33•].

As with other triazoles, the activity of isavuconazole against *Aspergillus* species is affected by mutations in the *cyp*51A gene that encodes for lanosterol 14α-demethylase, particularly in those isolates with multiple gene alterations [35–37]. For this reason, isavuconazole is not a viable option to treat invasive infection caused by voriconazole-resistant *Aspergillus*, unless the isavuconazole MIC is known to be within the wild-type range, generally ≤ 1 mg/L [38]. Although the recommended isavuconazole regimen includes fixed-dose loading and maintenance doses, there are evolving data to suggest potential benefit in adjusting (increasing) the dose of isavuconazole to overcome relatively higher MICs of resistant strains [33•, 39, 40]. Recommended dosing of isavuconazole is expected to produce adequate drug exposure for wild-type strains of *Aspergillus* [40], and so therapeutic drug monitoring of isavuconazole is not currently recommended. As more studies are performed to define the lower and upper limits of isavuconazole concentrations that optimize efficacy and safety, an approach to increase isavuconazole doses to overcome higher MICs may be employed in the future. Although combination therapy with isavuconazole and an echinocandin has demonstrated the potential for synergy against azole-resistant *Candida*, results of combination studies targeting *Aspergillus* have been variable [41, 42].

Mucormycosis is a severe infection with limited treatment options and intrinsic resistance to multiple antifungals. Historically, lipid formulations of amphotericin B have been considered preferred treatment options. Among the triazole antifungals, both isavuconazole and posaconazole have microbiologic activity against *Mucorales*. The efficacy of isavuconazole in mucormycosis was demonstrated in the VITAL trial, a matched case–control analysis that compared patients on isavuconazole to those in the FungiScope registry on amphotericin B [43••]. Outcomes were similar between the isavuconazole and amphotericin B groups. Of the 37 patients who received isavuconazole, only 1 (3%) experienced disease progression. Results of this trial led to FDA approval of isavuconazole for the treatment of invasive mucormycosis.

In practice, isavuconazole represents a primary treatment option for invasive mucormycosis, especially for patients at high risk for amphotericin-related adverse effects, or as step-down oral therapy after initial treatment with amphotericin B. While evidence from the VITAL trial supports isavuconazole for mucormycosis, not all *Mucorales* species are inhibited by isavuconazole at therapeutic concentrations. Two studies have been performed to characterize the in vitro activity of isavuconazole against *Mucorales* [44, 45]. A consistent pattern emerged from results of these studies. Isavuconazole MICs against the *Lichtheimia*, *Rhizomucor*, and *Rhizopus* species tested were similar to wild-type *Aspergillus* species. However, MICs were higher against *Mucor circinelloides*, raising concern as to how effective isavuconazole would be in treating infections caused by this member of the *Mucorales* order. According to the supplementary data of the VITAL trial, there was only one isolate of *M. circinelloides* (isavuconazole MIC = 32 μ/mL) among the 22 isolates that underwent susceptibility testing. *Rhizopus* and *Rhizomucor* species accounted for 17 of the isolates. Notably, posaconazole MICs against many of the *Mucorales* isolates were generally lower by 2–3 dilutions, including *M. circinelloides*.

Ibrexafungerp

With increasing resistance of fungi to the currently available antifungals and the threat of emerging pathogens like *C. auris*, there is an urgent need for new agents that will remain active in the face of the resistance mechanisms noted previously. One promising new antifungal agent, ibrexafungerp, gained its FDA approval in January 2021 for the treatment of vulvovaginal candidiasis. Ibrexafungerp is a triterpenoid antifungal that produces fungicidal activity in *Candida* by

inhibiting 1,3-β-D-glucan synthase, similarly to the mechanism of action of echinocandins. Unlike the echinocandins, ibrexafungerp is orally bioavailable, approximately 50% in animal studies, making it the only oral glucan synthase inhibitor [46, 47].

Ibrexafungerp Against Resistant *Candida*

An initial study of ibrexafungerp demonstrated in vitro activity and efficacy against *Candida* species in murine models, including fluconazole-resistant strains [48]. Antifungal activity was also observed in 958 *Candida* isolates from blood cultures at a hospital in Spain. In this study, high rates of in vitro activity (99–100%) were demonstrated for the most common *Candida* species that cause disease in humans, including *C. albicans*, *C. parapsilosis*, *C. tropicalis*, *C. glabrata*, and *C. krusei*. Among isolates with a *FKS* mutation, all but one retained an ibrexafungerp MIC within the wild-type range, as did all fluconazole-resistant isolates [49]. These data suggest that ibrexafungerp is not affected by the resistance mechanisms that limit echinocandins, despite similar mechanisms of action [50, 51•]. However, other investigators have discovered certain *FKS* mutations that result in substantially increased ibrexafungerp MICs [52]. Lastly, ibrexafungerp has activity against *C. auris*, including isolates that are both azole and echinocandin resistant, making it an attractive choice for infections caused by pan-resistant *C. auris* [24, 53•].

Due to its aforementioned wide spectrum of in vitro activity, ibrexafungerp has become an attractive agent to investigate as treatment of various fungal infections, including those involving drug-resistant fungi. Currently, there are multiple studies focusing on evaluating ibrexafungerp. The FURI study is a multicenter, open-label clinical trial evaluating the efficacy and safety of ibrexafungerp in patients with a wide variety of fungal infections that are refractory or intolerant to standard of care antifungal treatment. Infections evaluated in FURI include invasive or cutaneous candidiasis, endemic mycoses, and different forms of aspergillosis. Outcome assessments include global response, recurrence of the baseline infection, and survival at days 42 and 84. An interim analysis was recently released summarizing the data of the initial 74 patients. Ibrexafungerp thus far has demonstrated a favorable clinical response in FURI with 62.1% of participants showing complete or partial response to therapy, 24.3% achieving stable disease, and 6.8% with progressive disease. Additionally, a subset analysis was performed for candidemia, intra-abdominal infections, *Candida* bone and joint infections, and oropharyngeal infections. For these diseases, a complete or partial response occurred in 72.7%, 58.3%, 62.5%, and 64.3% of cases, respectively [54]. Lastly, the CARES study is an ongoing multicenter, open-label, non-comparator, single-arm trial evaluating the use of ibrexafungerp in patients with infections caused by *Candida auris*. Participants will be assessed for efficacy by global success at the end of treatment with secondary outcomes aimed at evaluating adverse events.

Ibrexafungerp Against Resistant Molds

Ibrexafungerp has demonstrated fungistatic activity in vitro against a variety of *Aspergillus* species. An analysis of 71 isolates of four different *Aspergillus* species (*A. flavus*, *A. fumigatus*, *A. niger*, *A. terreus*) reported excellent in vitro activity against both wild-type and itraconazole-resistant isolates [55]. Additional studies have confirmed reliable activity against *Aspergillus*, including both cryptic species and *CYP*51A mutants, but its activity is variable against *A. ustus* complex and unreliable against *A. alliaceus* [56•]. With regard to non-*Aspergillus* molds, ibrexafungerp lacks microbiologic activity against *Mucorales*, *Fusarium* species, and *Purpureocillium lilacinum*, and it has marginal activity against *Scedosporium apiospermum*, *S. prolificans*, and *Scopulariopsis* species. Ibrexafungerp maintains potent activity against *Paecilomyces variotii* [57].

The SCYNERGIA study is a multicenter, randomized, double-blinded clinical trial evaluating the use of ibrexafungerp in combination with voriconazole in patients with invasive pulmonary aspergillosis. With an estimated enrollment of 60 participants, the primary outcome measures are based in safety, but secondary outcomes include a composite of the clinical, radiographical, and mycological response as well as mortality. The study's design to utilize combination antifungal therapy is noteworthy. The evidence to support combination antifungal therapy is not robust. Nonetheless, there is room to improve on the efficacy of triazole monotherapy for invasive aspergillosis, and combination therapy with a drug like ibrexafungerp may help in this regard. The nature of all these studies evaluating ibrexafungerp implies potential for broadening its indications in the future. Table 1 provides a summary of key information about ibrexafungerp and other antifungals in the pipeline, as discussed in the following section.

Antifungals in the Pipeline

Rezafungin, (CD101) a novel echinocandin, is a promising medication in the antifungal pipeline both for its unique dosing strategy and its potential utility against echinocandin-resistant isolates. The addition of a choline moiety to an otherwise similar echinocandin structure allows for both prolonged half-life (133 h) and improved in vitro activity due to its higher affinity for 1,3-beta-D-glucan synthase [58•]. Most *Candida* species, including *C. auris*, have rezafungin MICs that are readily achievable with proposed dosing; however, *C. parapsilosis* is

Table 1 Antifungals in the pipeline

Antifungal agent	Class	Mechanism of action (novel*)	Target fungi	Stage of development	Advantages	Anticipated place in therapy
Fosmanogepix (APX001)	Gwt1 inhibitor	Inhibits fungal enzyme Gwt1* (mannoproteins)	*Candida* spp. (not *C. krusei*) *C. auris* *Cryptococcus* *Aspergillus* spp. *Fusarium* spp. *Scedosporium* spp. *L. prolificans*	Phase 2	Active against resistant *Candida* spp.; broad mold activity (not *Mucorales*); encouraging CNS penetration	Candidiasis and IA, including treatment of azole- and echinocandin-resistant infections; cryptococcal meningitis; invasive mold infections other than *Mucorales*
Ibrexafungerp	Triterpenoid	Inhibits 1,3-beta-D-glucan synthase	*Candida* spp. *Aspergillus* spp.	FDA-approved (VVC)	Oral formulation; active against resistant *Candida* spp.	Treatment of candidiasis among patients with echinocandin-resistant *Candida* or when oral therapy is preferred for azole-resistant candidiasis; potential role in combination therapy of IA
Olorofim (F901318)	Orotomide	Inhibits dihydroorotate dehydrogenase*	*Aspergillus* spp. *Scedosporium* spp. *L. prolificans* Endemic fungi	Phase 2b	Limited toxicity; IV and oral formulation	IA and other mold infections with limited treatment options
Opelconazole (PC945)	Inhaled triazole	Inhibits 14-alpha demethylase	*Aspergillus* spp.	Phase 2b	Inhaled route avoids systemic toxicity	Antifungal prophylaxis in patients with lung transplant or cystic fibrosis; IA as combination therapy with systemic triazole
Oteseconazole (VT-1161)	Tetrazole	Inhibits 14-alpha demethylase	*Candida* spp.	FDA-approved (VVC)	Improved selectivity for fungal CYP450 (lower potential for toxicity and drug interactions); lower rates of recurrent VVC compared with fluconazole	Treatment of VVC among patients with history of multiple recurrences
Rezafungin (CD101)	Echinocandin	Inhibits 1,3-beta-D-glucan synthase	*Candida* spp. *C. auris* *P. jiroveci* *Aspergillus* spp.	Phase 3	Single or weekly IV dosing; optimized pharmacokinetic-pharmacodynamic profile	Treatment of candidiasis, particularly when single/weekly dosing improves convenience of care; prophylaxis in immunocompromised patients

CNS central nervous system, *IA* invasive aspergillosis, *IV* intravenous, *VVC* vulvovaginal candidiasis

the least susceptible species with wild-type MICs ranging up to 4 mg/L, owing to the previously described *FKS* polymorphisms common among *C. parapsilosis* [59]. Likewise, *FKS* mutations result in increased rezafungin MICs in a similar pattern as demonstrated with other echinocandins [60]. The probability of pharmacokinetic-pharmacodynamic target attainment was analyzed in a study of *C. albicans* and *C. glabrata* [61]. Single-dose (400 mg) and weekly dosing (400 mg followed by 200 mg weekly for 5 weeks) of rezafungin were studied. Both regimens performed well against isolates with wild-type MICs, achieving ≥ 90% probability of target attainment. However, against isolates with higher rezafungin MICs, such as those of isolates with *FKS* mutations, the weekly dosing regimen was best as it was still able to maintain probability of target attainment of ≥ 90% throughout the 6-week duration of dosing [61].

In human trials, a phase 2 study called STRIVE was performed to compare the two rezafungin dosing regimens listed above with caspofungin as treatment of invasive candidiasis. Overall cure (resolution of signs of infection plus mycological eradication) and all-cause mortality were similar across the three groups [62]. The ReSTORE trial is an ongoing phase 3 extension of the STRIVE study comparing weekly rezafungin to daily caspofungin as treatment of invasive candidiasis. Topline results of the ReSTORE trial were presented in April 2022. Non-inferiority was demonstrated with regard to mortality at day 30 and global cure at day 14. Lastly, rezafungin also demonstrates microbiologic activity against *Pneumocystis jiroveci* and is currently being studied as prophylaxis in recipients of a bone marrow transplant. In this ongoing phase 3 trial called ReSPECT, weekly rezafungin is compared to the combination of sulfamethoxazole/trimethoprim and a triazole antifungal, and participants are assessed for invasive fungal infections, including PJP, *Aspergillus* species, and *Candida* species.

Oteseconazole (VT-1161) is an oral tetrazole antifungal that targets lanosterol 14α-demethylase similarly to triazoles; however, its unique structure allows for increased affinity for CYP51 and improved selectivity for fungal CYP51 as opposed to human CYP450 enzymes, which may confer an improved safety and drug interaction profile compared with triazoles [63]. Oteseconazole demonstrates potent in vitro activity against the inherently azole-resistant *Candida* species *C. krusei* and *C. glabrata*, including isolates expressing *FKS* mutations [64, 65•]. Despite this, investigators have described reduced oteseconazole susceptibility in vitro among isolates expressing common forms of azole resistance, such as efflux pumps and *ERG11* mutations [66]. More research is needed to determine whether these resistance mechanisms confer MICs above the concentrations achieved in humans with proposed dosing of oteseconazole.

Safety and efficacy of oteseconazole were demonstrated in a phase 2 trial comparing oteseconazole to fluconazole for acute vulvovaginal candidiasis (VVC) [65•]. By 6 months of follow-up, none of the patients who received oteseconazole experienced mycological recurrence compared to 46.1% of patients who received fluconazole. More recently, initial results of the phase 3 ultraViolet trial were presented [67]. In this study, oteseconazole was compared to fluconazole in the treatment of acute VVC among subjects with recurrent VVC. Oteseconazole achieved similar rates of VVC resolution (93.2% vs 95.8%), but the rate of recurrence by week 50 was significantly lower with oteseconazole (5.1% vs 42.2%). Breaking at the time of this writing (May 2022) is news that oteseconazole was approved by the FDA for the treatment of recurrent yeast infections in females who are not of reproductive potential [68].

Olorofim (F901318), the first agent in a novel class called orotomides, interrupts pyrimidine synthesis by inhibiting the enzyme dihydroorotate dehydrogenase, making it distinct in mechanism from all other currently available antifungals. In vitro studies have been performed to establish the spectrum of activity of olorofim. It lacks activity against *Candida*, *Cryptococcus*, and *Mucorales*. The activity of olorofim against *Fusarium* is variable, with some species, particularly *F. solani*, demonstrating relatively higher MICs [69, 70]. Where olorofim holds the most promise is against *Aspergillus*. Olorofim demonstrates potency against most *Aspergillus* species, including cryptic species, and appears to be unaffected by azole resistance [70, 71]. In addition, molds for which therapeutic options have been limited, such as *Lomentospora prolificans* and *Scedosporium* species, are generally inhibited by olorofim at relatively low MICs [72]. The microbiologic activity against these molds was confirmed in a study demonstrating efficacy of olorofim in treating a mouse model of infection [73]. Lastly, olorofim is reported to have activity against endemic fungi, including *Histoplasma*, *Blastomyces*, and *Coccidioides*.

Although there is limited human data with olorofim, phase I studies demonstrated its tolerability among healthy participants with no serious adverse events reported [74, 75]. Two notable clinical trials are underway to evaluate the safety and efficacy of olorofim. The FORMULA-OLS trial is a phase 2b study to evaluate its use for invasive fungal infections for patients without suitable alternatives, and the OASIS trial is a phase 3 study comparing olorofim to liposomal amphotericin B for invasive aspergillosis. Olorofim gained "Breakthrough Therapy" designation from the FDA for two fungal infections where treatment options are limited, including central nervous system coccidioidomycosis and invasive aspergillosis, as well as "Qualified Infectious Disease Product" designation for multiple fungal infections.

Fosmanogepix (APX001) is a first-in-class prodrug for the active compound manogepix (APX001A). Manogepix targets the fungal enzyme Gwt1, which is responsible for anchoring mannoproteins to the fungal cell wall. These mannoproteins

facilitate adherence of the fungus to mucosal and epithelial cell surfaces in the host as part of the process for establishing infection. Manogepix has broad activity against both yeasts (*Candida* and *Cryptococcus*) and molds, including azole-resistant *A. fumigatus*, *Fusarium* species, *Scedosporium* species, and *L. prolificans*. Manogepix lacks activity against *C. krusei* and some *Mucorales*. Wild-type MICs for manogepix have been observed among *Candida* isolates demonstrating fluconazole resistance, but overall, fluconazole resistance is associated with relatively higher manogepix MICs, suggesting utility of manogepix susceptibility testing when considering fosmanogepix for treatment of fluconazole-resistant *Candida* infections [76]. Manogepix retains activity against *C. auris*, including multidrug-resistant isolates [77•]. Likewise, manogepix MICs of *C. glabrata* are generally unaffected by echinocandin resistance [78].

In a small open-label, non-comparative phase 2 study of 21 non-neutropenic patients with candidemia, fosmanogepix was successful in 80% of patients, and none of the patients experienced treatment-related serious adverse events or discontinuations [79]. The efficacy of fosmanogepix has been demonstrated in immunosuppressed murine models of pulmonary scedosporiosis and disseminated fusariosis [80]. Notably, a rabbit model study documented encouraging penetration of manogepix into cerebrospinal fluid and aqueous/vitreous humor, providing support for future studies of cryptococcal meningitis and *Candida* endophthalmitis [81]. Fosmanogepix is currently undergoing a phase 2 trial for patients with invasive aspergillosis. A trial evaluating its use for infections caused by *C. auris* was terminated early due to the COVID-19 pandemic.

Opelconazole (PC945) is a novel, long-acting, inhaled (nebulized) triazole antifungal designed to avoid systemic toxicity and to maximize drug concentration in the lungs. The spectrum of activity of opelconazole includes *Candida* species, including *C. auris* and *A. fumigatus* [82, 83]. Opelconazole is a promising agent as directed therapy or prophylaxis of fungal infections of the lungs, but it is not likely to have a role in the neutropenic host, either as treatment or prophylaxis, unless it is combined with a systemic antifungal. Tolerability of opelconazole has been demonstrated in a small study of healthy volunteers and subjects with mild asthma [84]. No episodes of bronchospasm or clinically significant changes in lung function occurred in association with opelconazole administration. Early clinical trials to evaluate opelconazole focused on unique patient populations, such as lung transplant recipients and patients with cystic fibrosis. However, some of these were terminated early due to the COVID-19 pandemic. A phase 3 trial of inhaled opelconazole when added to systemic antifungal therapy for treatment of refractory invasive pulmonary aspergillosis is planned. Proof of concept for this treatment modality was established in an in vitro model where synergy between inhaled opelconazole and systemic posaconazole or voriconazole was demonstrated [85].

Conclusions

With advances in medical practices and changing epidemiology of fungal infections, there is increasing need for expansion in antifungal therapy options. Making therapeutic decisions based on antifungal class assumptions or mechanism of action is no longer a reliable strategy, particularly when resistance to one or more agents is present or when the identified fungal species is less common. In this review, mechanisms of antifungal resistance are described alongside implications for antifungal activity. In vitro and clinical data for the two newest antifungal options, isavuconazole and ibrexafungerp, are examined, and their roles against resistant fungi are assessed. The most promising or unique antifungal agents under development are evaluated for their potential utility in the setting of antifungal resistance. As our understanding of antifungal resistance and the pace of adopting new antifungal therapies continue to grow, clinicians will be challenged by greater complexity in how fungal infections are managed. This review provides updated knowledge and awareness in this regard.

Compliance of Ethical Standards

Conflict of Interest All authors declare no competing or financial interests.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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