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New Options in Antifungal Therapy: New Drugs, Inhaled Antifungals, and Management of Resistant Pathogens

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Abstract

Purpose of review This review aims to update the reader on recent information related to available antifungal pharmacotherapy and inform on agents that may be available for clinical use in the near future. Additionally, alternate drug delivery of existing agents, therapeutic drug monitoring, and management of resistant fungal pathogens will be discussed.

Recent findings Rezafungin (a once-weekly echinocandin) and ibrexafungerp (an oral glucan synthase inhibitor) appear to be the investigational agents that are nearest to widespread use in clinical practice. Emerging information on isavuconazole (mean inhibitory concentrations, drug interactions, side effect profile) suggests increasing utilization is likely to continue. Newer formulations of posaconazole and itraconazole offer more favorable pharmacokinetic profiles, potentially making them more reliable treatment options for clinicians versus the original formulations.

Summary While the number of available antifungal agents remains comparatively limited, recent data and new formulations of existing agents are available to aid clinicians until the next wave of new antifungal drug approvals.

Introduction

The management of fungal infections is an ongoing challenge for clinicians. Of particular concern is the risk of opportunistic, invasive fungal infections (IFIs) in the growing immunocompromised population [1]. Systemic antifungal therapy research and drug approvals are lacking compared to other anti-infective drug classes. There are currently only four classes of antifungals from which to choose: polyene, azole, echinocandin, and flucytosine. The addition of the echinocandins in 2001 (caspofungin), followed closely by the availability of expanded spectrum azoles (voriconazole and posaconazole) represented a positive shift in practice, giving the bedside clinician more options to treat fungal disease. Unfortunately, this is still a relatively limited arsenal of antifungals, and IFIs are still a significant burden to society in terms of morbidity, mortality, and financial outcomes [2].

Clinicians often must be creative in their clinical approach, balancing the risk of toxicity and drug interactions with the uncertainty of efficacy and delivery of drug to the site of infection. There have been no new systemic agents approved since isavuconazole in 2015; however, reformulations of oral posaconazole and itraconazole show more favorable pharmacokinetic profiles and will likely be more reliable treatment options than their original formulations. Antifungals in the investigational pipeline will help fill existing gaps in the armamentarium, but the timing of their availability remains unknown. Additionally, emerging data on the dosing and therapeutic drug monitoring (TDM) of existing antifungals will assist in optimizing patient care. Management of IFIs, particularly those with resistant pathogens, often requires an understanding of the drug properties and use of TDM in order to employ an aggressive regimen that improves patient outcomes.

Recently approved agents and formulations

Isavuconazole

The most recently approved antifungal agent by the US Food and Drug Administration (FDA) was isavuconazole in 2015. Isavuconazole sulfate is a triazole antifungal approved for the treatment of invasive aspergillosis and mucormycosis [3]. It is formulated as a pro-drug; isavuconazonium sulfate is hydrolyzed in the blood to the active metabolite isavuconazole. Isavuconazole inhibits ergosterol biosynthesis in a similar manner to other azoles via inhibition of cytochrome P450-lanosterol 14α-demethylase (CYP51), thus rendering the fungal cell membrane dysfunctional. Enhanced binding to the CYP51 fungal protein through a unique side chain results in a broader antifungal spectrum [4].

Isavuconazole has demonstrated broad-spectrum in vitro activity against many fungi of clinical importance, including *Aspergillus* species, *Candida* species, *Cryptococcus* species, and Zygomycetes [5]. For *Candida* species, in vitro activity of isavuconazole is similar to that of voriconazole, and the mechanisms contributing to isavuconazole resistance are similar to other azoles [6–8]. Although potent activity has been demonstrated against *Aspergillus* species, azole cross-resistance has been noted [9]. While activity against many genera of Zygomycetes has been illustrated, isavuconazole minimum inhibitory concentrations (MICs) vary and are typically higher than those of posaconazole [5]. Isavuconazole activity is preserved in *Cryptococcus* isolates with elevated fluconazole MIC values. Isavuconazole's antifungal spectrum also includes dimorphic fungi, such as *Blastomyces dermatitidis*, *Histoplasma capsulatum*, and *Coccidioides posadasii*. Reduced isavuconazole activity has been demonstrated for *Fusarium* and *Scedosporium* species.

Data for the FDA approval of isavuconazole for the treatment of invasive aspergillosis is based on a multicenter phase 3 randomized, double-blind, non-

inferiority study that compared efficacy and safety of isavuconazole versus voriconazole for the treatment of suspected invasive mold disease [10]. Isavuconazole was found to be non-inferior to voriconazole for the primary efficacy endpoint of 42-day all-cause mortality (19% versus 20%, adjusted treatment difference – 1% (95% CI – 7.8 to 5.7)). The approval of isavuconazole for mucormycosis is based on a single-arm, open-label trial with a primary endpoint of overall response at day 42 as determined by the data review committee [11]. By day 42, 11% of patients had a partial response and 81% had stable or progressive invasive fungal disease or died; other patients were missing assessments. The overall end-of-treatment clinical response rate was 45%, similar to response rates published in data with liposomal amphotericin B [12]. The investigators also performed a matched case-control analysis with patients from a global fungal database that demonstrated comparable mortality rates seen previously in patients with mucormycosis (isavuconazole 33% versus amphotericin B 39%, $p = 0.775$) [13]. In a study of patients with candidemia or invasive candidiasis, the pre-specified non-inferiority margin of 15% was not met. Isavuconazole showed a lower overall response at end of intravenous therapy (IV) compared to caspofungin (60.3% versus 71.1%, adjusted treatment difference – 10.8% (95% CI – 19.9 to – 1.8)) [14]. These findings are consistent with historical data of overall response rates showing more favorable results with an echinocandin than with an azole antifungal [15]. Clinical outcome data for isavuconazole in the treatment of other fungal infections, including cryptococcosis and endemic mycoses, is limited [16]. Additionally, robust experience with isavuconazole for prophylaxis of invasive fungal disease is lacking, but recent publications note breakthrough fungal infection rates similar to those with posaconazole in hematologic malignancy patients [17, 18].

Isavuconazonium sulfate is supplied in both intravenous and oral formulations. The FDA-approved dosing regimen for treatment of invasive fungal infection is the same regardless of the formulation used, as the oral capsule is ≥ 98% bioavailable. Patients should receive a loading dose of isavuconazonium sulfate 372 mg (equivalent 200 mg active isavuconazole) every 8 h for a total of 6 doses prior to a maintenance regimen of 372 mg once daily. While the package insert recommends against opening the capsule for patients who are unable to tolerate oral medications, emerging data suggests administration via enteral feeding tube results in adequate absorption and serum drug levels [19]. Once absorbed, isavuconazonium sulfate is hydrolyzed to active isavuconazole in the blood via esterases. The drug is highly protein-bound and widely distributed throughout the body with the exception of urine. Isavuconazole is then hepatically metabolized through CYP3A4, CYP3A5, and glucuronidation before ultimately being excreted in feces. For IV administration, the single-dose vial requires reconstitution and dilution, but the product does not require a cyclodextrin additive for solubility, which avoids potential toxicity. Monitoring for drug-drug interactions is of the utmost importance as isavuconazole is a CYP enzyme substrate as well as a moderate CYP3A4 inhibitor. When used with common CYP3A4 substrates such as tacrolimus, sirolimus, everolimus, and cyclosporine, dose adjustments of these medications may be required due to decreased metabolism and closer monitoring is recommended [20]. Clinicians should use extreme caution when using isavuconazole in combination with strong CYP3A4 inducers such as rifampin due to increased isavuconazole clearance [3]. Commonly reported side effects include

gastrointestinal disturbances and headache. Isavuconazole may shorten the QTc interval, and to a lesser degree than other azoles, hepatotoxicity may occur. When directly compared to voriconazole, fewer treatment-emergent adverse reactions were observed [21].

SUBA-itraconazole

Itraconazole is a broad-spectrum antifungal that exists in capsule, solution, and intravenous (IV) formulations. The IV formulation is no longer available in the USA. The oral bioavailability of itraconazole depends on gastric acidity due to the compound's weakly basic characteristics and varies based on the formulation used. The solution is often preferred for treatment due to increased bioavailability, but some patients have difficulty tolerating the liquid formulation [22]. In an effort to optimize the bioavailability and tolerance of itraconazole products, the FDA in 2018 approved a reformulation of the capsule that is manufactured using spray drying technology [23]. Spray drying is a pharmaceutical technique that enhances water solubility of drugs to optimize their bioavailability via evaporation of the manufacturing solvent. Utilizing this procedure with a new pH-dependent polymeric matrix creates a solid-state itraconazole nanoparticle product with enhanced dissolution and absorption properties [24–26]. The capsule is marketed under the brand name Tolsura® in the USA and is referred to as SUBA-itraconazole by the manufacturer due to its superior bioavailability.

Using phase 1 crossover trial data comparing the new formulation of itraconazole with the innovator capsule product (Sporanox®), a population pharmacokinetic model was developed for itraconazole and the active metabolite hydroxyitraconazole [27]. Non-linear kinetics were observed outside the single-dose setting. The reformulated capsule showed less variation in bioavailability between subjects and had a relative bio availability of 173% compared to sporanox®. Regardless of the formulation, subjects in the fed state showed a 27% reduction in bioavailability and a 58% decrease in transit absorption rate constant compared to those in the fasted state. SUBA-itraconazole was compared to conventional itraconazole liquid as antifungal prophylaxis in 57 patients who were undergoing allogeneic HSCT or were at intermediate or high risk of invasive fungal infection [28••]. The time to achieve therapeutic drug levels was significantly shorter with SUBA-itraconazole compared to itraconazole liquid (6 days, 95% CI 5–11 versus 14 days, 95% CI 12–21, $p < 0.0001$). SUBA-itraconazole use was also associated with higher mean trough concentrations at steady-state and less interpatient variability in trough concentrations. Treatment failures (defined as failure to obtain therapeutic levels after 14 days of therapy, therapy intolerance, or development of probable or possible IFI) were lower in the SUBA-itraconazole arm (7.4% versus 23.3%, $p = 0.096$). Both treatment failures in the SUBA-itraconazole group were due to cessation of therapy for mucositis requiring intravenous antifungals. Of the seven treatment failures in the liquid itraconazole arm, five were due to failure to obtain therapeutic levels, in addition to one due to mucositis and one due to gastrointestinal intolerance. SUBA-itraconazole (fed state/fasted state ratios of 78.09%, 90% CI 74.49 to 81.86%) and hydroxyitraconazole concentrations (fed state/fasted state ratios of 84.98%, 90% CI 82.02 to 88.06%) have been shown to be similar in fed and fasted states for the area under the concentration-time curve over the dosing interval [29]. Additionally, when coadministered

with omeprazole, there was a 22% increase in total plasma exposure compared to giving the drug without acid suppression. The increased bioavailability and decreased variability of SUBA-itraconazole make this reformulation an attractive option for clinical use, especially in patients who cannot tolerate a high-fat meal or require proton pump inhibition. Dosing is not interchangeable across different itraconazole formulations. SUBA-itraconazole is available as 65 mg capsules and is administered as 130 mg once or twice daily with the frequency depending on indication [23]. A loading dose of 130 mg three times daily may be considered for the first 3 days of therapy in life-threatening situations.

Posaconazole delayed-release tablets

Posaconazole is another broad-spectrum antifungal that has inconsistent pharmacokinetics when administered orally. The bioavailability of the oral solution requires gastric acidity and a high-fat meal. Additionally, impaired gastric motility raises concern for suboptimal absorption. Posaconazole was previously only available in an intravenous and oral solution formulation. The delayed-release tablets were produced in an effort to provide an oral dosage form with enhanced bioavailability [30••]. Posaconazole and a pH-sensitive polymer are combined via hot melt extrusion technology to form a product that does not crystallize and is, in turn, more soluble. The polymer also allows the drug to withstand the acidic gastric environment of the stomach and subsequently release in the comparatively basic environment of the small intestine, leading to enhanced bioavailability.

In practice, leukemia patients transitioned from posaconazole suspension to delayed-release tablets had significantly higher median posaconazole concentrations (748 ng/ml versus 1910 ng/ml, $p < 0.01$) [31]. Target serum posaconazole levels of greater than 700 ng/ml for prophylaxis were achieved 97% of the time with the tablet compared to 57% with the suspension; similarly, target levels of greater than 1000 ng/ml for treatment were obtained in 83% of patients receiving the tablet versus only 24% of those receiving the suspension. In patients with myeloid malignancies requiring antifungal prophylaxis, 97% of patients receiving the delayed-release tablet attained the steady-state concentration target of > 700 ng/ml compared to 17% of those administered the suspension. Greater steady-state concentrations and rates of target attainment were seen without the worsening of any of the adverse events evaluated (hepatotoxicity, QTc prolongation, and breakthrough fungal infections) [32]. The posaconazole delayed-release tablet dose-concentration relationship has also been evaluated in lung transplant recipients; daily doses less than the FDA recommended 300 mg were often sufficient to achieve target concentrations of > 700 ng/ml [33]. Due to patient variability and potential drug interactions, some patients may need doses greater than 300 mg/day, and therapeutic drug monitoring is recommended when treating serious infections. While the manufacturer does not recommend that the delayed-release tablets be crushed, there is some limited experience with this approach (due to the product's novel hot melt extrusion technology) when used in combination with therapeutic drug monitoring [34].

Notable antifungal agents currently in development

The echinocandins are the newest class of antifungals to come to market, boasting fungicidal activity with minimal adverse effects and few drug-drug

interactions. Agents from this class are often the drug of choice for invasive candidiasis, demonstrating more favorable response rates compared to azoles [14, 15]. Currently available echinocandins are administered intravenously once a day; however, two investigational antifungals, rezafungin and ibrexafungerp, offer increased flexibility in administration, frequency and route [35••, 36••]. While there is a convenience associated with the standard dosing of the echinocandins, concerns exist as to whether this approach always provides optimal pharmacokinetics/pharmacodynamics because of the concentration-dependent killing of the agents in the class [37].

Rezafungin

Rezafungin is an echinocandin modified from the chemical structure of anidulafungin. The structure modification results in rezafungin's evasion of the main route of elimination of echinocandins, which is chemical degradation via cleavage of the echinocandin ring [38]. In humans, this translates to a longer half-life (~ 80 h following the first weekly dose and ~ 150 h following subsequently weekly doses) that allows for once-weekly intravenous dosing [39]. A dosing strategy targeting a higher Cmax and AUC while maintaining a satisfactory safety profile aligns well with concentration-dependent killing antifungals, and optimizing the drug effect in this way may lead to improved outcomes and decreased resistance in vivo. Rezafungin's spectrum of activity is comparable to existing echinocandins, with potent in vitro activity against *Candida* and *Aspergillus* species [40, 41]. STRIVE was a phase 2 study assessing two dosing regimens of rezafungin completed by Thompson and colleagues [42]. Due to similar findings of efficacy and safety of once-weekly rezafungin to once-daily caspofungin in STRIVE, a phase 3 multicenter, randomized trial is underway with a primary outcome of 30-day all-cause mortality [43]. In ReSTORE, rezafungin dosed with a 400 mg IV load in week 1 followed by 200 mg IV once weekly is being compared to caspofungin dosed as a 70 mg IV load on day 1 followed by 50 mg IV once daily with an option to step down to oral fluconazole for treatment of candidemia and/or invasive candidiasis.

Ibrexafungerp

Bioavailability of echinocandins is limited by their large molecular size, thus necessitating parenteral administration [44]. Ibrexafungerp is a novel oral glucan synthase inhibitor that addresses this issue, as well as concerns with echinocandin resistance. While ibrexafungerp inhibits β-1,3-glucan synthase similarly to the echinocandins, its semisynthetic chemical structure is much different, making ibrexafungerp the first in the "-fungerp" or triterpene class of antifungals [45]. Ibrexafungerp is derived from the naturally occurring enfumafungin, and the binding site on glucan synthase is independent, but partially overlaps with that of the echinocandin class. The spectrum of antifungal in vitro activity includes *Candida* and *Aspergillus* species. The drug is fungicidal and demonstrated comparable activity to caspofungin in time-kill studies [36, 46]. The activity of ibrexafungerp was evaluated in wild-type and echinocandin-resistant *Candida* species using Clinical and Laboratory Standards Institute (CLSI) broth microdilution (BMD) methods [47]. FKS mutations yielded 84.0% of non-wild-type *Candida glabrata* isolates resistant to at least one echinocandin, and only 24.0% resistant to ibrexafungerp. These data along with that of Jimenez-Ortigosa and colleagues illustrates distinct differences in

resistance profiles of echinocandins and ibrexafungerp [45]. Dissolution of oral ibrexafungerp is enhanced in the fed state, and it is highly protein bound with a large volume of distribution [36]. Ibrexafungerp is hepatically metabolized and ultimately excreted in the feces and bile. In vivo data to date suggest low to moderate impact on coadministered CYP2C8 and CYP3A4 substrates [48, 49]. A phase 2 study has been completed in patients with documented invasive candidiasis comparing oral step down therapy of ibrexafungerp or standard of care following IV echinocandin [50]. Oral ibrexafungerp was well-tolerated when dosed at 750 mg and achieved target exposures and response rates similar to the standard of care. The most common adverse events included gastrointestinal distress. The FURI study is an ongoing multicenter single-arm study evaluating the efficacy and safety of ibrexafungerp in adults with documented invasive fungal disease intolerant or refractory to standard of care [51]. An interim analysis showed a positive therapeutic response or stable disease in 17 of 20 patients who completed ibrexafungerp with no adverse event concerns [52].

Alternate delivery methods of available agents

Due the limited number of approved indications for the available antifungals, and the generally limited number of approved antifungal agents altogether, clinicians have often resorted to alternate delivery methods in an attempt to treat difficult infections. The rationale for use of these alternate delivery methods was usually to achieve drug penetration in sufficient concentrations at the site of infection in situations where penetration was questionable, or in an attempt to mitigate potential toxicities of systemically administered agents through localized administration. Use of nystatin, amphotericin B, flucytosine, and azole antifungals has been reported via various routes (e.g., intrathecal, percutaneous, topical, intranasal, inhalation, peritoneal, and bladder irrigation) for decades. While an in-depth review of this usage is beyond the scope of this article, the reader is referred to a review article by Arthur and colleagues on alternate administration of antifungals prior to the early 2000s and an article by Walraven et al. for a more recent review of antifungal lock therapy [53, 54]. Beginning in the early 2000s, the available options to treat fungal infections dramatically increased with the approvals of voriconazole, posaconazole, and the echinocandins, potentially lessening the need for use of the older agents in alternative ways.

Antifungal delivery via the inhalation route with amphotericin B has previously been described for the prophylaxis of *Aspergillus* in some immunosuppressed populations such as lung transplant and bone marrow transplant, though the degree to which the available evidence supports this use is controversial [55]. Again, the rationale is often to increase the concentration of the drug at the target site and to minimize systemic adverse effects. In these transplant populations, use of inhaled antifungals for prophylaxis may also help clinicians avoid some of the strong drug-drug interactions with azole antifungals that potentially complicate the overall therapy plan. Articles by Le and colleagues on aerosolized antimicrobials in general and specifically antifungal agents offer clinicians a review on pertinent issues of particle size (mean mass aerodynamic diameter, 1–5 μm being optimal) and nebulization delivery device (ultrasonic, jet, vibrating mesh) in addition to findings from earlier

studies using inhaled antifungal agents [55, 56]. None of the available amphotericin B formulations (deoxycholate, lipid complex, liposomal) were specifically developed for inhalation, but all have been used in clinical practice.

An early study using the deoxycholate formulation in lung transplant patients showed a 20–25% incidence of *Aspergillus* infection [57]. Drew and colleagues compared inhaled amphotericin B deoxycholate with the lipid complex formulation in a lung transplant population noting no difference in the incidence of invasive fungal infections between agents; however, they suggested a tolerability benefit of the lipid complex formulation. Only 2% of the patients developed invasive fungal infections, but 10–15% were deemed to have failed prophylaxis [53]. This rate of IFIs is similar to two other studies in lung transplantation using inhaled lipid complex and liposomal formulations [58, 59]. A 10-year, single-center review of over 400 lung transplant patients found an overall *Aspergillus* incidence of 13%, with 5% being invasive [60]. A slight tolerability benefit of both the lipid complex and the liposomal formulation versus the deoxycholate was also suggested by SanMartin et al. in their lung transplant population [61]. The preparation, technique, and frequency varied between studies but generally ranged from three times daily to bi-weekly dosing [57, 53, 58–61].

In a prospective study of patients with hematologic disease and neutropenia, Rijnders et al. observed a 2% incidence of invasive pulmonary aspergillosis in their inhaled liposomal amphotericin B arm versus. 13% in the placebo arm [62]. This was similar to the rate of invasive fungal infections shown in an observational study using the inhaled lipid complex formulation in a stem cell transplant population [63]. However, an earlier study by Schwartz and colleagues in post-chemotherapy patients with neutropenia or bone marrow transplant patients failed to show a benefit with the deoxycholate formulation versus the control group [64]. While many factors contribute to the risk of IFIs in lung and bone marrow transplantation (e.g., degree of immunosuppression, environmental factors), inhaled amphotericin B has been shown to be an option for prophylaxis at multiple centers, but the strength of the evidence is limited and recent literature is lacking. Inhaled voriconazole has been attempted, but its evidence is limited to a few cases and pre-clinical studies [65–68].

Management of resistant pathogens

Use of antifungals to treat disease, in both humans and the environment, leads to antifungal resistance. Echinocandin resistance in *Candida glabrata* isolates is on the rise, which is concerning due to the azole resistance already seen in these organisms [69]. Fluconazole-resistant *Candida* species were classified as an urgent threat by the Centers for Disease Control (CDC) in 2013. Azole resistance is also an issue in *Aspergillus* species [70]. In the current era of antifungal resistance, clinicians have a limited antifungal armamentarium. Guidelines for the management of invasive candidiasis and aspergillosis syndromes provide little direction to clinicians in the setting of resistant disease due to lack of outcomes data [71, 72]. Amphotericin B is recommended as a primary consideration for resistant invasive disease but is associated with serious adverse effects. Management of resistant pathogens requires a working knowledge of

antifungal susceptibility, pharmacokinetic/pharmacodynamics concepts (including therapeutic drug monitoring), and existing combination antifungal data.

Awareness and understanding of susceptibility are important in determining presence of a resistant fungal pathogen. Breakpoints are set based on MIC distributions, pharmacokinetic/pharmacokinetic parameters, and clinical outcome data. When a microorganism has a set breakpoint, the MIC value can be interpreted and used to predict in vivo success with a certain antimicrobial [73]. Many fungal pathogens do not have defined antifungal breakpoints due to insufficient evidence. The epidemiological cutoff value (ECV) can be utilized to identify isolates that may harbor mutations but this is not necessarily predictive of clinical success. ECVs are based off the distribution of MICs within a species, and the value divides the population into wild-type versus non-wild-type strains (strains likely to contain a resistant mutant and thus may not respond to antifungal therapy). Interestingly, recent data with a small number of patients receiving isavuconazole and voriconazole found no difference in clinical outcomes with *Aspergillus* species with MICs up to 16 μg/mL [74]. The Clinical and Laboratory Standards Institute (CLSI) and the European Union Committee on Antimicrobial Susceptibility Testing (EUCAST) publish antifungal MIC breakpoints and ECVs [75, 76].

While antifungal TDM is not warranted in every clinical scenario, attainment of evidence-based therapeutic targets is imperative in the management of resistant pathogens. A thorough review detailing antifungal TDM and drug level targets based on the clinical scenario has been published by Ashbee and colleagues and is recommended for those unfamiliar [77]. While data is lacking for isavuconazole, TDM should be considered for itraconazole, voriconazole, posaconazole, and flucytosine. Unfortunately, little is known about commonly recognized target trough concentrations of itraconazole for treatment in relation to the MIC of the specific fungal pathogens. Voriconazole has a narrow therapeutic index, along with unpredictable inter- and intra-patient pharmacokinetics, and TDM has been shown to be important to ensure efficacy and avoid toxicity [78]. The typical goal trough concentration for voriconazole is > 1 mg/L, and some studies have suggested targeting trough concentration:MIC ratios to have a higher probability of clinical response. Concentration:MIC ratios are often easier to obtain than AUC:MIC ratios, though AUC:MIC ratios have been the traditional pharmacodynamic parameter studied with the azoles [79, 80]. Similarly, target trough concentrations that correlate to an AUC:MIC ratio have been described for posaconazole. These targets are more likely to be achieved with the delayed-release tablet formulation [81]. Monitoring of serum concentrations of flucytosine is primarily based on the concentration-safety relationship and prevention of resistance versus a concentration-efficacy association [82, 83]. Monitoring of other antifungals is not routinely recommended at this time. The clinical utility of TDM with the newest azole, isavuconazole, has yet to be elucidated, as no thresholds for efficacy have been set. In patients receiving prolonged therapy, a serum level of ~ 5 mg/L was found to be associated with adverse effects, primarily gastrointestinal toxicity [84, 85]. There may be a future role for TDM with echinocandins due to concerns

regarding current dosing strategies and optimal concentration-dependent killing and the prevention of resistance [37, 86].

Combination antifungal therapy should be considered in invasive fungal diseases associated with significant mortality, questionable drug distribution to the site of infection, high pathogen MICs, or unreliable attainment of described pharmacokinetic/pharmacodynamic efficacy parameters for the antifungal agent and pathogen in question. Clinical synergism and antagonism of a proposed combination must be considered prior to employing the regimen. Combining agents with different targets (e.g., echinocandins and amphotericin B) is ideal, and data supporting this combination in mucormycosis salvage therapy is encouraging [87]. However, in vitro concerns exist with some combinations. For example, because azoles inhibit the synthesis of ergosterol, they remove the drug target of amphotericin B [88, 89]. Based on available data, this antagonism may be dependent on which azole is used and at what dose. Amphotericin plus flucytosine has been clinically shown to decrease mortality in cryptococcal meningitis, while in vitro studies have suggested both synergism and partial antagonism with the combination. [90–92]. Administration of flucytosine in combination with another antifungal agent is important due to the high emergence of resistance when it is used as monotherapy [93, 94]. Current guidelines also endorse combination antifungal use in salvage treatment situations for aspergillosis and mucormycosis, as well as certain invasive *Candida* infections, but do not provide specific dosing guidance or dosing recommendations [71, 95, 72]. The authors have experience with the initial use of intravenous amphotericin B in combination with an azole until satisfactory azole levels are achieved.

Conclusion

The management of fungal infections will continue to be challenging for clinicians in the current era of increasing IFIs and antifungal resistance. The options available today are more varied than what was available prior to the early 2000s; however, new antifungal approvals have been comparatively slow versus other anti-infective classes. Promising early data with investigational agents previews an even larger antifungal toolbox in the coming years. The increased use of therapeutic drug monitoring and patient-specific dosing strategies will likely become more prominent in the management of severe and resistant fungal infections in the meantime.

Compliance with ethical standards

Conflict of interest
Sarah Cotner and Kyle Dawson declare that they have no conflict of interest.

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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Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

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