THERAPEUTIC ADVANCES in
Infectious Disease

Review

Update on therapeutic approaches for invasive fungal infections in adults

Catherine-Audrey Boutin and Me-Linh Luong

Ther Adv Infect Dis

2024, Vol. 11: 1–21

DOI: 10.1177/20499361231224980

***Abstract*:** Invasive fungal infections are increasingly encountered with the expansion of iatrogenic immunosuppression, including not only solid organ and hematopoietic stem cell transplant recipients but also patients with malignancies or autoimmune diseases receiving immunomodulatory therapies, such as Bruton Tyrosine Kinase (BTK) inhibitor. Their attributable mortality remains elevated, part of which is a contribution from globally emerging resistance in both molds and yeasts. Because antifungal susceptibility test results are often unavailable or delayed, empiric and tailored antifungal approaches including choice of agent(s) and use of combination therapy are heterogeneous and often based on clinician experience with knowledge of host's net state of immunosuppression, prior antifungal exposure, antifungal side effects and interaction profile, clinical severity of disease including site(s) of infection and local resistance data. In this review, we aim to summarize previous recommendations and most recent literature on treatment of invasive mold and yeast infections in adults to guide optimal evidence-based therapeutic approaches. We review the recent data that support use of available antifungal agents, including the different triazoles that have now been studied in comparison to previously preferred agents. We discuss management of complex infections with specific emerging fungi such as *Scedosporium* spp., *Fusarium* spp., *Trichosporon asahii*, and *Candida auris*. We briefly explore newer antifungal agents or formulations that are now being investigated to overcome therapeutic pitfalls, including but not limited to olorofim, rezafungin, fosmanogepix, and encochleated Amphotericin B. We discuss the role of surgical resection or debridement, duration of treatment, follow-up modalities, and need for secondary prophylaxis, all of which remain challenging, especially in patients chronically immunocompromised or awaiting more immunosuppressive therapies.

Keywords: Aspergillus, fungal infections, mucormycosis

Received: 23 July 2023; revised manuscript accepted: 19 December 2023.

Correspondence to:
Me-Linh Luong
Department of Medicine, Division of Infectious Diseases, Université de Montréal, Centre Hospitalier de l'Université de Montréal (CHUM), F Building, 6th Floor, Room F06.1102F, 1051 Sanguinet, Montreal, QC, H2X 0C1, Canada
me.linh.luong.med@ssss.gouv.qc.ca

Catherine-Audrey Boutin
Division of Infectious Diseases, Department of Medicine, Centre Hospitalier de l'Université de Montréal (CHUM), Montreal, QC, Canada

Introduction

Invasive fungal infections (IFIs) are increasingly encountered with the expansion of iatrogenic immunosuppression, including not only solid organ transplant (SOT) and hematopoietic stem cell transplant (HSCT) recipients, but also patients with malignancies or autoimmune diseases receiving immunomodulatory therapies. Despite advancement in diagnostic and therapeutic against IFI, their attributable mortality remains high. This high morbidity and mortality can be attributed in part to (1) increasing complex immunosuppressive therapy, (2) global emergence of resistance, (3) limited of access to antifungal susceptibility testing, and (4) antifungal treatment with limited efficacy and significant toxicity profile. This review summarizes previous recommendations and most recent literature on management of invasive mold and yeast infections in adults to guide optimal evidence-based therapeutic approaches.

Part 1: Treatment of invasive yeast infection

Candida *spp*

Antifungals arsenal. Over the last decade, the epidemiology of invasive candidiasis (ICs) has slowly evolved. Although *Candida albicans* still

predominates, recent epidemiological data of IC have shown a global increase of non-albicans *Candida* spp.[1–3] *C. glabrata* (*Nakaseomyces glabrata*) now accounts for a significant proportion (12–30%), part of which is the result of improved identification technologies and selective pressure from fluconazole use.[3–6] The international SENTRY Antifungal Surveillance Program reported 8.1% fluconazole resistance among *C. glabrata* (2006–2016).[3] The rate of echinocandins resistance among *C. glabrata* was reported at 3.5%, but recent data suggest a higher rate among strains implicated in candidemia.[3,7] Resistance strongly impacts mortality as shown in reports of invasive diseases with echinocandins resistant *C. tropicalis* among patients with hematological malignancies.[8] Thus, given the increasing rate of antifungal resistance, azoles susceptibility testing should be performed for all strains causing invasive disease and echinocandin susceptibility testing should be performed for *C. glabrata* and *C. parapsilosis* and for patients previously treated with an echinocandin.[9] Nevertheless, resistance defined by breakpoints may not be the only factor contributing to breakthrough infection as breakthrough fungemia with susceptible strains have been reported in immunocompromised patients with profound and prolonged neutropenia and/or compromised in the skin or mucosal barrier.[10]

Management of IC among adults has not significantly changed over the last decade. Echinocandins are the first-line therapy for IC, regardless of species.[11–13] Acceptable alternatives include fluconazole or liposomal amphotericin B (LAmB). Isavuconazole (ISA) did not achieve non-inferiority in overall response when compared to caspofungin (CAS) in the ACTIVE trial [60.3% for ISA *versus* 71.1% for CAS; adjusted difference −10.8 (95% CI −19.9, −1.8)].[14] Newer triazoles should therefore not be used as first-line therapy. Changing antifungal class may be considered in the setting of breakthrough candidemia. A summary of recommendations is presented in Table 1.

Stepdown therapy with fluconazole or voriconazole, based on antifungal susceptibility testing (AFST) results should be considered for patients who have cleared their candidemia. Higher fluconazole dosing should be used for *C. glabrata* (12 mg/kg daily) based on higher minimum inhibitory concentration (MIC) values (MIC 16–32 µg/mL).[11,20,21] Antifungals should be given for a total of 14 days after blood clearance and central lines removed when feasible.[11] Neutropenic patients should have neutrophils recovery prior to discontinuation of antifungal therapy or transitioned to antifungal prophylaxis if indicated.

Adjunctive measures. In case of candidemia, removal of indwelling catheter is important and should be done as soon as possible.[11,13] While there are no randomized controlled trial showing the superiority of early catheter removal among candidemic patients, several large observational studies have shown favorable outcome with early catheter removal.[22] When central venous catheter (CVC) removal is not feasible, LAmB and echinocandins should be considered for their effectiveness within the biofilm.[13,23]

Evaluation for metastatic foci should be performed especially if candidemia is prolonged or refractory to therapy. Although endocarditis is uncommon, its reported incidence among patients with candidemia varies between 2.5% and 11.9% and is sometimes suspected solely based on echocardiography imaging in patient without clinical sign.[24] Routine echocardiography to rule-out endocarditis remains controversial.[24,25] The ESCMID guidelines recommend routine transesophageal echocardiography for all patient with candidemia; in contrast, t he Infectious Diseases Society of America (IDSA) guidelines recommends performing an echocardiogram only if endocarditis is suspected in the setting of persistent candidemia, a new heart murmur, heart failure, or embolic phenomena, occurring more frequently among patients with prior endocarditis, valvulopathy, or intravenous drug use.[11,13,24,26,27] If endocarditis is confirmed, antifungal treatment should initially consist of LAmB (+/− flucytosine) or high-dose echinocandin, with subsequent stepdown to an azole, if susceptible.[11,13] Therapy should be prolonged for at least 6 weeks and surgical valve replacement should be considered.[11,13] Lifelong secondary treatment should be considered when surgery is not performed.[11]

Ophthalmologic examination is necessary to assess the presence ocular candidiasis. Routine ophthalmologic examination among patients without ocular symptoms is a matter of debate among experts. The American Academy of Ophthalmology recommends against ocular exam

Table 1. Summary of available and investigational antifungal agents recommended for the treatment of invasive fungal infections.

	Antifungal therapy				
	Empiric or first-line	**Stepdown (with AFST if available)**	**Alternative (with AFST if available)**	**For refractory disease**	**Drugs in the pipeline with undergoing or published human studies**
***Candida* spp.**	Echinocandin	FLC VRC (*C. krusei*)	LAmB	LAmB +/– echinocandin	**Rezafungin** STRIVE (phase II)[15]: first line *versus* CAS ReSTORE (III)[16] : first line *versus* CAS **Ibrexafungerp** MSG-10 (II)[17]: stepdown *versus* FLC MARIO (III)[a]: stepdown *versus* FLC **Fosmanogepix** APX001-201 (II)[18] : first line C4791012 (III)[b]: first line *versus* CAS
C. auris	Echinocandin*	Echinocandin	LAmB	Echinocandin + LAmB	**Ibrexafungerp** CARES (III)[c]: first line or stepdown or salvage **Fosmanogepix** Vazquez *et al.* (II)[19]: first line
***C. neoformans* or *gattii* (CM induction)**	LAmB +/– FLC + 5FC	LAmB + 5FC FLC + 5FC	LAmB + 5FC AmBd + 5FC FLC + 5FC	LAmB + 5FC	–
Trichosporon asahii	VRC	VRC	LAmB	VRC + LAmB	**Ibrexafungerp** FURI (III)[d]**: salvage
***Aspergillus* spp.**	VRC ISA, POS	VRC ISA, POS	LAmB	VRC + anidulafungin	**Olorofim** FORMULA-OLS (II)[e]: salvage or resistance OASIS (III): salvage *versus* LAmB **Ibrexafungerp** FURI (III)[d]: salvage **Fosmanogepix** AEGIS (III)[f]: salvage or resistance **Opelconazole** PC945 (II)[g]: prophylaxis or PET
Mucorales	LAmB	ISA POS	ISA POS	LAmB + CAS LAmB + POS	–
***Scedosporium* spp.**	VRC	VRC	POS	VRC + either terbinafine, echinocandin, miltefosine, or LAmB	**Olorofim** FORMULA-OLS (II)[e]: salvage or resistance **Fosmanogepix** AEGIS (III)[f]: salvage or resistance
L. prolificans	VRC + terbinafine	VRC +/– terbinafine	POS + terbinafine Echinocandin + LAmB or VRC	VRC + terbinafine +/– LAmB or echinocandin	**Olorofim** FORMULA-OLS (II)[e] : salvage or resistance **Fosmanogepix** AEGIS (III)[f]: salvage or resistance
***Fusarium* spp.**	LAmB + VRC	VRC	POS	VRC + either terbinafine or LAmB	**Olorofim** FORMULA-OLS (II)[e]**: salvage or resistance **Fosmanogepix** AEGIS (III)[f]: salvage or resistance

[a]ClinicalTrials.gov identifier: NCT05178862.
[b]ClinicalTrials.gov identifier: NCT05421858.
[c]ClinicalTrials.gov identifier: NCT03363841.
[d]ClinicalTrials.gov identifier: NCT03059992.
[e]ClinicalTrials.gov identifier: NCT03583164.
[f]ClinicalTrials.gov identifier: NCT04240886.
[g]ClinicalTrials.gov identifier: NCT05037851.
*Combination therapy of echinocandin + LAmB if high rates of pan-resistance (e.g. South Asia).
**Might be included in study as resistant or refractory IFI cases.
AFST, Antifungal Susceptibility Testing; AmBd, Amphotericin B deoxycholate; CAS, Caspofungin; CM, Cryptococcal meningitis; 5FC, Flucytosine; FLC, Fluconazole; IFI, Invasive fungal infection; ISA, Isavuconazole; LAmB, Liposomal Amphotericin B; PET, Pre-emptive Therapy; POS, Posaconazole; VRC, Voriconazole.

for all patients with candidemia given the low reported incidence of true candidal eye diseases (<2%) and suggests referring only those with symptoms or those unable to report symptoms.[28–30] On the other hand, both the IDSA and ESCMID guidelines advise for a dilated ocular examination performed by an ophthalmologist within 7 days of candidemia (or after counts recover if neutropenic), based on a higher incidence of ocular diseases (16%), mainly chorioretinitis.[11,13] Ocular candidiasis is a challenging complication that warrants prolonged antifungal therapy with an agent with optimal ocular penetration (i.e. fluconazole, voriconazole, or a combination of LAmB and 5FC for 4–6 weeks) and may require intraocular intervention such as vitrectomy and intravitreal antifungal.[11,28]

Among neutropenic patients with candidemia, abdominal imaging [ultrasound, CT scan, or magnetic resonance imaging (MRI)] should be performed routinely to exclude hepatosplenic candidiasis. Repeat imaging should be done at the time of neutropenia recovery. Follow-up CT imaging should be obtained every 3 months for hepatosplenic candidiasis, and antifungal therapy should be continued until recovery or calcification of the lesions on imaging, which usually takes approximately 6 months.[11]

Candida auris

C. auris has emerged as a serious global threat in over 30 countries and its multidrug resistance is associated with mortality as high a 60%.[31–33] Several factors contribute to its recent rise, including increase in international travel, drug pressure, and challenges associated with its laboratory identification.[32] *C. auris* is typically resistant to azoles (90%) and can be variably resistant to echinocandins (2–10%) and amphotericin B (AmB) (8–35%).[32,34,35] Extended AFST including azoles, echinocandins, and polyenes should be performed. Although there are no interpretative criteria, results are often inferred from closely related *Candida* spp. MICs or using the Centers for Disease Control and Prevention (CDC) tentative breakpoints.[4,31] In North America where rate of echinocandin resistance to echinocandins is below 5%, echinocandins are the preferred class for initial therapy. Patients with breakthrough infection or with prolonged exposure to echinocandins should be treated with a combination therapy including LAmB with an echinocandin.[31,32] In South Asia where the rate of multidrug resistance is higher (up to 30% resistant to three antifungal classes), initial combination therapy (echinocandin + LAmB) is recommended.[33,36–38] Removal of CVC is especially important as *C. auris* is known to colonize skin and the environment which contributes to its nosocomial spread.[31]

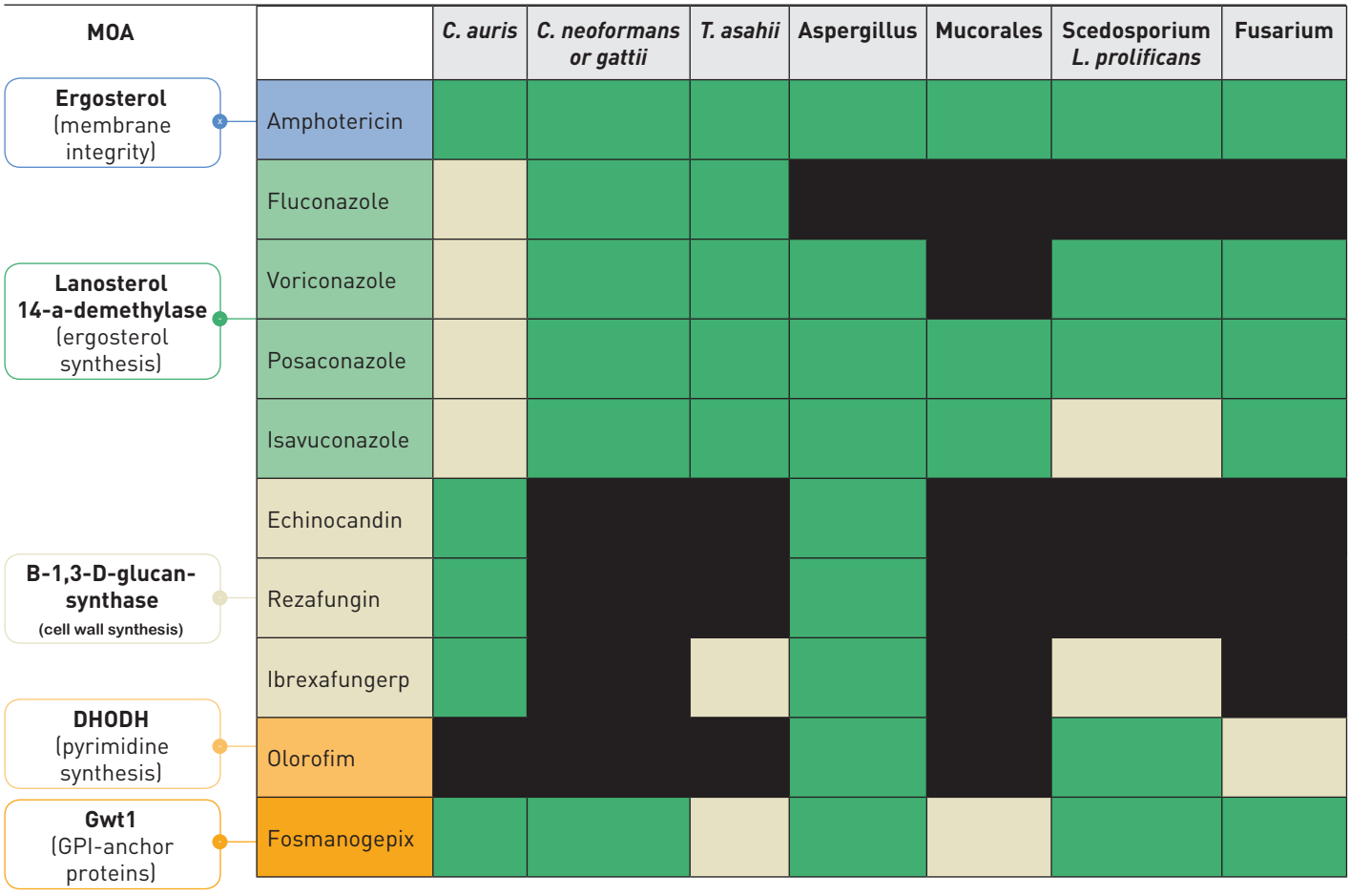
Future drug options for Candida *spp. including* C. auris. Newer antifungal agents or formulations are being developed and investigated in hope of facilitating management of ICs, including cases of *C. auris*. The most promising drugs will be briefly discussed here and are included in Table 1 (ongoing studies) and Table 2 (mechanism of action and spectrum of activity).

Rezafungin (RZF) is a new echinocandin with prolonged half-life formulated for once weekly intravenous administration. Its pharmacokinetics could eventually permit subcutaneous administration, making it an asset for outpatient management without the need for a CVC.[43] The STRIVE study, a phase II double-blind randomized trial evaluating RZF in comparison to CAS for the treatment of IC documented an overall cure rate (clinical and mycological cure) at 5 days of 62.3% for RZF *versus* 55.7% for CAS.[15] In the randomized phase III ReSTORE trial that followed, RZF was non-inferior to CAS (+/− stepdown to fluconazole) in global cure at 14 days in the modified intention-to-treat (ITT) analysis [59% *versus* 61%; −1.1% (95% CI −14.9, 12.7)].[16]

Ibrexafungerp (SCY-078) is a new oral antifungal of the glucan synthase inhibitor class. A phase II study (MSG-10) reported favorable and similar outcomes to fluconazole among six patients who received ibrexafungerp as stepdown therapy for IC.[17] A randomized, double-blind phase III study for treatment of IC is ongoing (MARIO study; ClinicalTrials.gov identifier: NCT05178862). It is also being studied for the treatment of *C. auris* infection in a single-arm, non-comparative phase III international study; interim results showed partial or complete response in 8/10 patients (CARES trial; ClinicalTrials.gov identifier: NCT03363841).

Fosmanogepix (APX001, E1211) is a novel antifungal with a new mechanism of action; it inhibits the Gwt1 enzyme involved in maturation of glycosylphosphatidylinositol or GPI-anchored

Table 2. Simplification of antifungal mechanisms of action and spectrum of activity.[39–42]



• *In vitro* or *in vivo* activity against most isolates • Marginal or variable activity • No significant activity.
Inspired by Lamoth *et al*.[39]
MOA, mechanism of action; x, Disruption of; –, Inhibition of.

proteins. It is available in both intravenous and by mouth formulations. Its spectrum of activity is broad and include many resistant yeasts and molds including *Candida* spp. and *Aspergillus* spp., with variable activity against Mucorales.[44] Fosmanogepix has however shown higher MIC for *C. krusei*, potentially secondary to efflux or cell permeability differences.[44] A phase II study (APX001-201) of fosmanogepix as first-line treatment was previously completed with a microbiological cure of 80% in non-neutropenic patients with candidemia.[19,44] A phase III clinical trial is currently ongoing for first-line treatment of IC in comparison to standard of care (C4791012; ClinicalTrials.gov identifier: NCT05421858). Fosmanogepix could hopefully be used in the setting of non-krusei IC diseases that have failed or are resistant to fluconazole and echinocandins. It has also shown potent *in vitro* activity against *C. auris*, and it was effective in treating invasive *C. auris* infection in 89% (8/9) of invasive cases in South Africa (Clade III) in a phase II single-arm study.[19]

Cryptococcus spp

Cryptococcus spp. (*neoformans* or *gattii*) is an opportunistic yeast that can cause severe pneumonia and disseminated disease, including debilitating central nervous system (CNS) infection among immunocompromised hosts. Management of cryptococcal meningitis (CM) has been an evolving topic. Most of the literature on treatment is based on randomized controlled trial (RCT) involving patients living with HIV who still represent most cases worldwide. However,

cases are increasingly encountered among non-HIV immunocompromised hosts including patients with hematological malignancies and SOT recipients.[45,46]

Historically, the treatment of CM in patients with HIV included 2 weeks of AmB and flucytosine, based on data showing improved survival and better fungal clearance with combination therapy compared to AmB monotherapy.[47–49] In 2013, a large RCT compared three treatment regimens against CM and observed a survival advantage among patients treated with AmB and flucytosine combination compared to AmB combined with fluconazole or AmB monotherapy, thus confirming that combination therapy is preferred over monotherapy. Subsequently, the ACTA trial confirmed that flucytosine as partner drug with AmB was associated with lower mortality than fluconazole. In addition, the ACTA trial demonstrated that 1 week induction therapy (with combination therapy) was non-inferior to the previously 2-weeks standard.[50] This was particularly helpful for low-income countries and was reflected in previous World Health Organization (WHO) guidelines, which recommended transition to high-dose fluconazole (1200 mg) after completion of 1 week of AmB and flucytosine. Most recently, the AMBITION trial changed the treatment paradigm in low-income settings. This trial showed that a single, high dose (10 mg/kg) of LAmB, given with an oral backbone of fluconazole and flucytosine, was noninferior to the WHO – recommended regimen of 7 days of amphotericin B deoxycholate (AmBd) plus flucytosine in patients living with HIV.[51] Fewer grade 3 or 4 adverse events were seen in the single high-dose LAmB group than in the control group (50.0% *versus* 62.3%).[51] The WHO has since updated its guidelines to reflect the results of the AMBITION protocol and now recommends a single high dose (10 mg/kg) of LAmB with 14 days of flucytosine (100 mg/kg per day divided into four doses per day) and fluconazole (12 mg/kg), as first line among patients living with HIV.[52] In case of refractory HIV-related CM, salvage therapy with the combination of LAmB, voriconazole, and recombinant interferon-γ (rINF-γ) may be considered.[53] Adjuvant rINF-γ 1b in treatment of CM in AIDS patients may be beneficial in some cases.[54]

During induction therapy, repeated lumbar punctures should be done to ensure decrease in the opening pressure and again at day 14 to document clearance of yeast growth to transition to consolidation therapy.[48,52] Routine use of adjunctive corticosteroid therapy during the induction phase is not recommended, except for major complication of intracranial hypertension.[48,52] Recommended first-line consolidation treatment remains fluconazole (400–800 mg) for 8 weeks, followed by a lower dose (200–400 mg) in maintenance therapy for more than 6–12 months and until immune reconstitution in HIV.[48,52]

Future drug options for Cryptococcus. New drugs olorofim and rezafungin lack activity against *Cryptococcus* spp., but manogepix has shown activity *in vitro*.[39,55] *In vivo* mouse study of encochleated AmB for CM showed promising results.[56]

Trichosporon asahii

Trichosporon spp. are opportunistic yeasts that are being increasingly encountered among immunocompromised hosts, especially neutropenic patients.[57] They account for 4.5–20% of non-candida yeasts causing fungemia.[58] *T. asahii* (formerly *T. beigelii*) is the predominant species isolated in culture (73–74%).[59,60] *Trichosporon* spp. are usually resistant to echinocandins.[59] High MICs to fluconazole and AmB are also frequently documented; voriconazole appears to have the lowest MICs.[57,59,61] Antifungals activity against *T. asahii* are presented in Table 2.

Despite *in vitro* data, clinical response to triazoles, mainly voriconazole, seem to be favorable. In a large systematic review of published cases of *T. asahii* infections ($n = 140$), clinical improvement with triazoles was superior to AmB (74.1% *versus* 70.6%; $p = 0.015$).[57] Combination of a triazole and AmB was not beneficial compared to monotherapy (clinical efficacy 57.9% *versus* 74.1%; $p = 0.25$).[57] A large cohort of patients with trichosporonosis ($n = 115$; 73% *T. asahii*) reported better survival rate among patients treated with voriconazole compared with other antifungals ($p = 0.042$).[60] In that study, high MICs to fluconazole correlated with mortality in those receiving fluconazole.[60] Thus, based on *in vitro* and clinical data, the ESCMID/ECMM guidelines recommend voriconazole as first-line therapy for *Trichosporon* infection.[58] AmB is an alternative or adjunct in therapy.[58,62] Data on the use of posaconazole or ISA are lacking. Duration of fungemia after blood clearance remains uncertain however

treatment options, ranging from 6 weeks to 3 months, have been reported.[63–65] Antifungal therapy should be continued until resolution of organ disease, if present.

Future drug options for T. asahii. Most antifungals in development are unlikely to provide good coverage for *T. asahii*. Fosmanogepix has shown poor activity in preliminary *in vitro* studies, although ibrexafungerp showed variable results.[66,67] Some cases might be included in the ongoing FURI trial (ibrexafungerp for treatment of refractory IFI; ClinicalTrials.gov identifier: NCT03059992).

Part 2: Treatment of invasive mold infections

Aspergillus *spp*

Antifungals arsenal. The incidence rate of invasive aspergillosis (IA) has significantly increased in the last two decades with the expansion of transplantation and immunomodulatory therapies.[68] It is the most prevalent invasive mold infection (IMI) (19–43% of all IFI), and *Aspergillus fumigatus* remains the most frequent isolated species (58%).[46,69,70] International surveillance data estimate that the resistance of *A. fumigatus* to azoles is approximately 1.4–5.8%, with higher rates reported in some European countries.[71] Cryptic *Aspergillus* spp. within the section *Fumigati* such as *A. lentulus* and *A. udagawae* are more frequently associated with higher azoles MIC values, and efforts should be made to differentiate those from *A. fumigatus sensu stricto*.[72] *A. calidoustus* (section *Usti*) has been associated with intrinsic pan-azole resistance and is therefore encountered more frequently among patients receiving triazoles prophylaxis.[72,73] Reduced susceptibility to amphotericin is also described among several species notably *A. lentulus* and *A. terreus.*[74] Knowledge of the species may thus be helpful in guiding therapy, and advance in molecular diagnostics could help in this way. Previous guidelines did not suggest routine AFST for *Aspergillus* spp., however epidemiologic changes in immunocompromised patients, the increased use of antifungal prophylaxis, and emergence of resistance question whether AFST should be routinely performed.[75]

Historically, AmB was the agent of choice for treatment of IA. In 2002, a RCT by Herbrecht *et al.* demonstrated a survival advantage with voriconazole over AmBd among patients with IA [70.8% *versus* 57.9%; Hazard Ratio (HR) 0.59 (95% CI: 0.40, 0.88)].[76] Following this seminal trial, voriconazole became the first-line therapy for IA. More recently, the phase III SECURE study showed that ISA was non-inferior to voriconazole for all-cause mortality at 12 weeks [19 *versus* 20%; −1.0% (95% CI: −7.8, 5.7)] for the treatment of IMIs; encountered cases were mainly IA and half where proven/probable diagnoses. Significantly less adverse events were documented among patients treated with ISA compared to patients treated with voriconazole (42% *versus* 60% $p < 0.001$).[77] Similarly, posaconazole was non-inferior to voriconazole in all-cause mortality at 12 weeks [15% *versus* 21%; −5.3% (95% CI −11.6, 1.0)] while being associated with fewer drug discontinuation secondary to related adverse events.[78] As such, new triazoles are acceptable treatment options against IA and may be associated with fewer adverse events. Liposomal AmB remains an alternative for treatment of IA; however, its safety profile is less favorable due to risk of dose-dependent nephrotoxicity.[79] These recommendations are reflected in Table 1.

Combination therapy with voriconazole and anidulafungin has been compared to voriconazole monotherapy in a study by Marr *et al.*[80] and did not lead to difference in survival [mortality at 6 weeks 19.3% *versus* 27.5%; −8.2% (95% CI −19.0, 1.5); $p = 0.087$]. Of note, in the post-hoc sub-group analysis of patients with positive galactomannan, combination therapy was associated with a survival benefit [mortality at 6 weeks 15.7% *versus* 27.3%; −11.5% (95% CI −22.7, −0.4); $p = 0.037$]. As such, combination therapy is not routinely recommended; however, it may be considered for salvage therapy, refractory, or breakthrough IA or infection with known antifungal resistance.[75]

Surveillance of short- and long-term azoles associated toxicities is important during treatment as prolonged duration is expected. Azoles use can lead to hepatotoxicity, drug–drug interactions, and QTc prolongation; exceptionally, ISA appears to shorten the QTc and may be an alternative agent for patients with prolonged QT.[81,82] Voriconazole is also associated with a wide range of neurological, ocular, and cutaneous toxicities.[83,84] Long-term use is associated with development of skin cancers and periostitis.[84,85]

Posaconazole can cause dose-dependent pseudohyperaldosteronism and hypokalemia.[86] Therapeutic drug monitoring (TDM) has been shown to decrease risk of voriconazole discontinuation secondary to adverse events and should be measured 4–7 days after start of therapy.[87,88] However, it is unclear whether TDM correlated with clinical outcome as a recent prospective randomized study reported no difference in outcome when compared to standard dosing.[87,89] Although optimal concentration are not perfectly defined, a through between 1–2 and 6 µg/mL is aimed for voriconazole and above 0.5–1.5 µg/mL for posaconazole.[88]

Surgery, duration of therapy, and secondary prophylaxis. Surgical resection should be considered for locally invasive disease, infection in proximity to vital structures (e.g. heart, large vessels) or if further iatrogenic immunosuppression is expected.[90] Given the high propensity of *Aspergillus* spp. to disseminate, assessment of disseminated disease to the CNS and distant occult foci of infection should be considered.[91]

Antifungal therapy should be continued until resolution of radiological and clinical disease, which is usually expected to take a minimum of 6 to 12 weeks. Follow-up imaging has limited value in the first 2 weeks of therapy, but is generally recommended at 6–12 weeks to assess disease response and duration of therapy.[75] Decreased in bronchoalveolar lavage galactomannan (GM) value is generally expected on therapy, but heterogeneity of specimens and the invasive nature of procedure limits its value for treatment follow-up. Serum GM trend has been proposed as a prognostic marker for neutropenic patients, and when positive should be repeated to assess treatment response.[92,93]

Because of concern for relapse, secondary prophylaxis may be considered in specific patient population.[94,95] Most data supporting this strategy have been reported from retrospective studies where prophylaxis may decrease relapse among patients on chemotherapy or HSCT.[96,97] Despite lack of robust data, both American (IDSA) and European (ESCMID-ECMM-ERS) guidelines give consideration for secondary prophylaxis in cases of persistent or subsequent immunosuppression.[75,98] The American Society of Clinical Oncology and IDSA Clinical Practice Guideline update recommends prophylaxis with mold-active oral triazole (posaconazole, voriconazole, and ISA) or a parenteral echinocandin in patients experiencing extended periods of neutropenia and at >6% risk for IA.[99] When azoles are contraindicated due to toxicity or drug interactions, inhaled AmB or liposomal AmB may be considered.[100]

Future drug options for Aspergillus *spp.* New antifungals in the pipeline with activity against *Aspergillus* spp. include: olorofim, fosmanogepix, ibrexafungerp, and opelconazole (see Table 2). Olorofim is the first agent of the new antifungal class named Orotomides; it inhibits the fungal dihydroorotate dehydrogenase enzyme involved in pyrimidine biosynthesis.[40] It was developed for both intravenous and oral administration.[40] It has good activity against *Aspergillus* spp. including azole-resistant isolates, but lacks activity against Mucorales and yeasts.[40] The FORMULA-OLS phase IIb study (ClinicalTrials.gov identifier: NCT03583164) assessing olorofim for the treatment of difficult-to-treat IMIs reported encouraging interim results with 44% treatment success (complete or partial response) and 14% all-cause mortality at 6 weeks. Tolerance was good with abnormal liver enzyme being the most commonly reported adverse event (8%) (ClinicalTrials.gov identifier: NCT03583164). Successful overall response was seen in 47% of IA cases.[101] The OASIS phase III study is currently evaluating olorofim in comparison to LAmB among patients with refractory IA or intolerant to azole therapy (ClinicalTrials.gov identifier: NCT05101187).

Fosmanogepix is also studied for the treatment of difficult-to-treat IMI and IA (ClinicalTrials.gov identifier: NCT04240886; AEGIS study). The FURI trial is evaluating the efficacy and safety of ibrexafungerp in a non-comparator single arm study for the treatment of refractory IMI, IC, and IA (ClinicalTrials.gov identifier: NCT03059992). Interim results reported improved or stable clinical status among 50% (5/10) of IA cases.[102] Opelconazole (PC945) is a new triazole agent optimized for inhaled formulation, with very limited systemic absorption and few CYP3A4 interactions, that will target non-*Niger Aspergillus* spp.[103] A phase II study is ongoing to look at its safety in the preemptive therapy setting in lung transplant recipients (ClinicalTrials.gov identifier: NCT05037851). Like with the inhaled formulation of amphotericin, the use of inhaled opelconazole could limit systemic toxicities of alternative therapies among transplant recipients

with an indication for anti-mold prophylaxis and other non-neutropenic hosts with IA. Encochleated Amphotericin B (CamB; MAT2203) is a novel nanoparticle-based encochleated formulation of amphotericin that is protected from gastrointestinal degradation and therefore has higher oral availability and fewer systemic toxicities.[104] As such, CamB may become an interesting oral treatment option against IA; however, there are no clinical studies to supports its use for this indication to date.

Mucorales. Mucormycosis can cause life-threatening invasive rhinocerebral or pulmonary disease in both immunocompromised and immunocompetent hosts. Risk factors include diabetes, malignancy, bone marrow and organ transplantation, IV drug use, and deferoxamine therapy.[105] AFST are limited by the absence of recognized breakpoints or epidemiological cutoff values for Mucorales and when done, MIC/MEC correlation with clinical outcome is unclear. AmBd has the most favorable *in vitro* activity against *Mucorales*.[106] Available antifungal arsenal consists of AmB and newer triazoles. Early surgical debridement and prompt antifungal therapy are key elements in the management of this infection.

Antifungal arsenal. First-line therapy for mucormycosis is LAmB. Liposomal formulation is favored over the deoxycholate formulation due to its improved safety profile and similar efficacy.[105,107,108] Optimal dosing remains uncertain, but higher dose have been associated with better outcome.[109] The non-comparative pilot study AmBiZygo has assessed the efficacy and tolerability of higher dose of LAmB. Doses of 10 mg/kg were associated with improved outcome compared to the results of the DEFEAT Mucor study where lower doses of LAmB were used (7.5 mg/kg/day).[109,110] However, high-dose LAmB was associated with high rates of nephrotoxicity (40%).[109] Current guidelines recommend LAmB at a dose of at least 5 mg/kg per day for mucormycosis without CNS involvement, and 10 mg/kg/day in cases of CNS involvement.[111,112]

ISA and posaconazole are active against Mucorales. ISA was assessed in a phase III open-label non-comparative RCT for the treatment of mucormycosis (VITAL study). Outcomes were comparable to those of matched historical controls from the FungiScope registry treated with AmBd (mortality rate of 33.3% *versus* 41.3%, respectively).[113] Moreover, ISA has several advantage over LAmB including a good safety profile (most common side effects were gastrointestinal complaints), availability in both oral and intravenous formulations, fewer drug–drug interactions, and lack of need for TDM. Currently, there are no RCT comparing posaconazole to AmB for first-line therapy of mucormycosis. Data derived from cases prospectively included in international registries have documented a 40–67% survival rate among patients treated with posaconazole.[114,115] Posaconazole as salvage therapy has been associated with favorable response ranging from 63% to 80%.[115–117] As such, ISA and posaconazole are acceptable alternatives for treatment of mucormycosis, when LAmB is not tolerated, or in the setting of refractory disease.[111] Additionally, the oral formulations for both these triazoles make them suitable stepdown options. Caution should be exerted in the setting of ocular or CNS involvement due to concern of low penetration of these compartments of both posaconazole and ISA.[118–121] Voriconazole lacks activity for *Mucorales* and should not be used for treatment of mucormycosis.

Because of its potentially fulminant progression and high mortality, using combination of antifungals that may have synergistic effects is tempting when treating mucormycosis. Multiple combinations have been studied, generally with LAmB as a backbone with addition of an echinocandin or a triazole. Although echinocandins are considered ineffective against Mucorales, one retrospective study suggested improved survival among patients with cerebral mucormycosis treated with LAmB and CAS compared to patients treated with LAmB alone (100% *versus* 45%; $p = 0.02$).[122] In contrast, Abidi *et al.*[123] did not observe better outcome with this combination therapy. Combination of azoles with LAmB has also been attempted with conflicting results. A large cohort of hematologic patients with mucormycosis treated with different combination therapies reported no difference in outcome between combination therapy and monotherapy. Taken together, data supporting the use of combination therapy are scant and conflicting. Nevertheless, given the high mortality associated with mucormycosis, combination therapy with LAmB and posaconazole or an echinocandin may be considered in cases of progressive disease.[62,111,124]

Surgery, follow-up modalities, duration of therapy, and secondary prophylaxis. Prompt and aggressive surgical debridement with clear margins is crucial to cure mucormycosis, especially for cutaneous and rhinocerebral diseases.[111] Several surgical interventions are often necessary for optimal control. Extension work-up with a cerebral, sinus, and lung CT are recommended to evaluate disease extent and guide surgical management. Cerebral and orbital MRI should be performed in the presence of neurological symptoms.[111]

Correction of underlying risk factors or reduction of immunosuppression when feasible should be done (e.g. hyperglycemia in a diabetic patient). Hyperbaric oxygenation and granulocytes infusion in neutropenic patients have been proposed, but no evidence strongly supports their use.[125,126] Deferasirox is not recommended.[110]

Duration of therapy should be guided by clinical responses and continued until complete resolution of infection, based on clinical and radiological imaging.[111] Treatment is often prolonged to 6–12 months.[111,116] Follow-up imaging is advised during treatment and to guide surgical interventions. Evidence for secondary prophylaxis is limited, but prophylaxis may be considered for neutropenic patients, those treated for graft *versus* host disease and on a case-by-case basis based on immunosuppressive status.[111]

Future drug options for Mucor *spp.* There are few antifungals in development for treatment of mucormycosis. Oteseconazole and PC-1244 are two azoles that have showed *in vitro* or *in vivo* activity in animal models against *Mucorales* species.[127,128] Fosmanogepix is not active against Mucorales with the exception of *Mucor* spp.[44,129,130] Ibrexafungerp has no or weak activity against *Mucorales* spp.[131]

Scedosporium spp

Scedosporium spp. is an ubiquitous hyaline mold that can cause severe pulmonary or disseminated infections in SOT, HSCT recipients as well as in patients with chronic pulmonary diseases receiving immunomodulators.[132–134] Trauma in the setting of environmental disaster such as tsunami and near drowning incidents are risk factor among immunocompetent hosts.[134] Management of scedosporiosis is challenging because of antifungal resistance (see Table 2).[112] *Scedosporium* spp. is intrinsically resistant to AmB and variably resistant to echinocandins.[134] Voriconazole is the most active agent against *Scedosporium* spp., followed by posaconazole.[135–137] In contrast, higher MICs have been reported with ISA, and it should not be used against scedosporiosis.[138,139]

There is no RCT for the treatment of scedosporiosis, and most data are derived from *in vitro* and observational cohort studies. Several studies have reported better outcomes with voriconazole compared to AmB.[134,140,141] A recent observational cohort study of 209 cases of scedosporiosis showed a survival benefit at 42 days for voriconazole monotherapy compared to AmB (mortality 11.3% *versus* 58.8%; $p < 0.001$).[134] Combination therapy has only been reported anectodally.[134,142] As such, voriconazole monotherapy is the recommended treatment for scedosporiosis.[62,112,143,144]

Despite medical therapy, scedosporiosis can be refractory, and therapy is limited by toxicity or intolerance. In such circumstances, antifungals combination for salvage therapy have been used despite the lack of robust data. Various combinations have been used and include voriconazole backbone combined with either terbinafine, echinocandin, miltefosine or AmB with variable outcomes.[142,145–157] In case of intolerance or resistance to voriconazole, posaconazole has been used with anecdotal success.[158,159]

Lomentospora prolificans

Lomentospora prolificans (formerly *Scedosporium prolificans*) is closely related to *Scedosporium* spp. but is now recognized as phylogenetically distinct.[160] Clinical presentation and predisposing factors can be similar, but *L. prolificans* distinguished itself by its multidrug resistance (resistant to AmB, echinocandin, and azoles) and the lack of effective antifungal therapy (see Table 2).[136,157,161] Thus, it is associated with high mortality (47–78%), especially in cases of disseminated diseases (88%).[133,162] Current guidelines recommend using voriconazole in combination with terbinafine based on the retrospective analysis of a cohort of 41 patients with lomentosporiosis, where this combination therapy was associated with higher treatment success compared to other antifungal regimens (63% *versus* 29%; $p = 0.053$).[62,112,143,144,163,164] Other combinations with posaconazole, echinocandins or LAmB may be considered in case of refractory diseases.[62,143,144]

For both scedosporiosis and lomentosporiosis, surgical debridement should be considered when feasible, especially in case of CNS infection.[133,165] Optimal duration of therapy is unknown, but should be at least until clinical and radiological resolution of diseases and potentially until recovery of immunocompromised state if reversible.

Future drug options for Scedosporium *spp. and* L. prolificans. Olorofim has excellent activity against both *Scedosporium* spp. and *L. prolificans.*[40] *In vitro* and animal studies have reported encouraging results.[40,166] Successful cases of prolonged use (10–12 months) without adverse events have been reported.[167,168] Olorofim for treatment of difficult-to-treat IMI is currently studied in an RCT (FORMULA-OLS study) (ClinicalTrials.gov identifier: NCT03583164). Interim results reported successful overall response at 6 weeks in 55% and 53% of scedosporiosis and lomentosporiosis, respectively.[101] Fosmanogepix also appears promising in treating scedosporiosis and lomentosporiosis. *In vitro* data suggest potent activity of the drug against *Scedosporiosis* spp. and *L. prolificans*.[41,44,130,169] Murine models studies also show prolongation of survival in immunocompromised mice with scedosporiosis.[170] *In vitro* data for ibrexafungerp suggest only modest activity against both species.[131]

Fusarium spp

Fusarium spp. is the second non-Aspergillus mold causing human infections.[171] Cases of fusariosis are most commonly seen in the immunocompromised population with prolonged neutropenia or severe T-cell immunodeficiency.[172,173] The *Fusarium* genus encompasses three complexes: *Fusarium solani* complex, *F. oxysporum* complex, and *F. fujikuroi* complex.[172] Multidrug resistance is common and antifungals resistance patterns vary significantly between complexes.[174] *F. solani* complex, which accounts for more than half of clinical diseases, typically shows high MICs to all azoles but may retain lower MIC to AmB (see Table 2).[172,175–177] Thus, effort to make good speciation and perform antifungal susceptibility testing should be made, even in the absence of Clinical and Laboratory Standards Institute (CLSI) or European Committee on Antimicrobial Susceptibility Testing (EUCAST) criteria.

Optimal treatment of fusariosis remains uncertain given lack of clinical trials. Historically, AmB was the treatment of choice. Despite concerns of poor *in vitro* activity, clinical improvement with LAmB have been reported (partial or complete response in 46–82%).[178–180] Voriconazole appears to have similar clinical efficacy (overall response in 45–63%), making it a suitable treatment option.[180–182] In one of the largest retrospective cohort of fusariosis ($n = 233$), survival probability at 90 days was 60% for patients receiving voriconazole and 48% for patients receiving LAmB (2001–2011).[180] Recent guidelines therefore recommend using either agent as first-line therapy for fusariosis.[112,143,144] However, given the great variability of susceptibility to antifungals, some experts suggest starting an empirical treatment combining both LAmB and voriconazole.[62,112,144] In severe or refractory cases, combination therapy with voriconazole with either terbinafine or AmB may be considered based on *in vitro* and anecdotal reports.[180,183] *In vitro* data have shown more frequent synergy between voriconazole and terbinafine, but published clinical experience has only shown modest success compared to case reports treated with LAmB and voriconazole.[184–188] Posaconazole could be considered for refractory cases if susceptibilities are known.[112,176,189] The current experience with ISA is not encouraging as nine fusariosis cases treated with ISA in the SECURE and VITAL trials showed treatment failure in most.[190] Echinocandins should not be used as they lack activity against *Fusarium*.[112,176]

Surgical debridement, including that of the potential primary skin source, should be considered when feasible and effective therapy should be continued until resolution of disease.[62,112,143,144] Correction of underlying risk factors or reduction of immunosuppression should be attempted, including consideration of granulocytes infusion in neutropenic patients although data are limited.[112,143,173,191]

Future drug options for Fusarium spp. Among novel agents, olorofim and fosmanogepix are promising for the treatment of fusariosis. Olorofim demonstrates good *in vitro* activity against *Fusarium* spp., including more resistant strains of *F. solani* (MICs 0.25–1 mg/L and 1–4 mg/L at 50% and 100% inhibition).[192] *In vitro* and *in vivo* data from murine models with disseminated fusariosis have also shown encouraging results for the use of Fosmanogepix (survival 100% at day 14 with E1210 *versus* 20% for control; $p < 0.05$).[193] ibrexafungerp, like other glucan synthase inhibitors, lacks activity against *Fusarium* spp.[131]

Conclusion

We have reviewed the management of most important invasive yeast and mold infections focusing on available antifungals and the literature that supports their use. Significant changes in immunocompromised hosts, increase in international travel, and widespread use of antifungal prophylaxis are all contributing to the changing epidemiology of IFI, such that resistant species are more commonly encountered, and treatment is becoming more challenging. Ongoing studies evaluating novel antifungal agents should provide critical information on the roles of these new molecules in the management of resistant or refractory cases. Development of other new antifungal classes might be critical and should be supported by collective and coherent action plans on a global scale with WHO, IDSA, ESCMID, and Mycoses Study Groups.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Author contributions

Catherine-Audrey Boutin: Writing – original draft.

Me-linh Luong: Writing – review & editing.

Acknowledgements

None.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

Competing interests

The authors declare that there is no conflict of interest.

Availability of data and materials

Not applicable.

ORCID iD

Catherine-Audrey Boutin https://orcid.org/0000-0001-7661-0882

References

1. Arendrup MC, Sulim S, Holm A, *et al.* Diagnostic issues, clinical characteristics, and outcomes for patients with fungemia. *J Clin Microbiol* 2011; 49: 3300–3308.
2. Kullberg BJ and Arendrup MC. Invasive candidiasis. *N Eng J Med* 2015; 373: 1445–1456.
3. Pfaller MA, Diekema DJ, Turnidge JD, *et al.* Twenty years of the SENTRY antifungal surveillance program: results for candida species from 1997–2016. *Open Forum Infect Dis* 2019; 6(Suppl. 1): S79–S94.
4. Parslow BY and Thornton CR. Continuing shifts in epidemiology and antifungal susceptibility highlight the need for improved disease management of invasive candidiasis. *Microorganisms* 2022; 10: 1208.
5. Boan P and Gardam D. Epidemiology and antifungal susceptibility patterns of candidemia from a tertiary centre in Western Australia. *J Chemother* 2019; 31: 137–140.
6. Xiao M, Chen SC, Kong F, *et al.* Distribution and antifungal susceptibility of candida species causing candidemia in china: an update from the CHIF-NET study. *J Infect Dis* 16 2020; 221(Suppl. 2): S139–S147.
7. Toda M, Williams SR, Berkow EL, *et al.* Population-based active surveillance for culture-confirmed candidemia - four sites, United States, 2012–2016. *MMWR Surveill Summ* 2019; 68: 1–15.
8. Sfeir MM, Jiménez-Ortigosa C, Gamaletsou MN, *et al.* Breakthrough bloodstream infections caused by echinocandin-resistant candida tropicalis: an emerging threat to immunocompromised patients with hematological malignancies. *J Fungi (Basel)* 2020; 6: 20.
9. Donnelly JP, Chen SC, Kauffman CA, *et al.* Revision and update of the consensus definitions of invasive fungal disease from the european organization for research and treatment of cancer and the mycoses study group education and research consortium. *Clin Inf Dis* 2020; 71: 1367–1376.
10. Gamaletsou MN, Daikos GL, Walsh TJ, *et al.* Breakthrough candidaemia caused by phenotypically susceptible Candida spp. in patients with haematological malignancies does not correlate with established interpretive breakpoints. *Int J Antimicrob Agents* 2014; 44: 248–255.

11. Pappas PG, Kauffman CA, Andes DR, *et al.* Clinical practice guideline for the management of candidiasis: 2016 update by the infectious diseases society of America. *Clin Inf Dis* 2016; 62: e1-50.
12. Reboli AC, Rotstein C, Pappas PG, *et al.* Anidulafungin versus fluconazole for invasive candidiasis. *N Engl J Med* 2007; 356: 2472–2482.
13. Cornely OA, Bassetti M, Calandra T, *et al.* ESCMID* guideline for the diagnosis and management of Candida diseases 2012: non-neutropenic adult patients. *Clin Microbiol Infect* 2012; 18(Suppl. 7): 19–37.
14. Kullberg BJ, Viscoli C, Pappas PG, *et al.* Isavuconazole versus caspofungin in the treatment of candidemia and other invasive candida infections: the ACTIVE Trial. *Clin Inf Dis* 2019; 68: 1981–1989.
15. Thompson GR, Soriano A, Skoutelis A, *et al.* Rezafungin versus caspofungin in a phase 2, randomized, double-blind study for the treatment of candidemia and invasive candidiasis: the STRIVE trial. *Clin Inf Dis* 2021; 73: e3647–e3655.
16. Thompson GR III, Soriano A, Cornely OA, *et al.* Rezafungin versus caspofungin for treatment of candidaemia and invasive candidiasis (ReSTORE): a multicentre, double-blind, double-dummy, randomised phase 3 trial. *Lancet* 2023; 401: 49–59.
17. Spec A, Pullman J, Thompson GR, *et al.* MSG-10: a phase 2 study of oral ibrexafungerp (SCY-078) following initial echinocandin therapy in non-neutropenic patients with invasive candidiasis. *J Antimicrob Chemother* 2019; 74: 3056–3062.
18. Amplyx Pharmaceuticals. Amplyx announces positive top-line data in phase 2 clinical trial of novel antifungal fosmanogepix. 2023. https://www.prnewswire.com/news-releases/amplyx-announces-positive-top-line-data-in-phase-2-clinical-trial-of-novel-antifungal-fosmanogepix-301095944.html
19. Vazquez JA, Pappas PG, Boffard K, *et al.* Clinical efficacy and safety of a novel antifungal, fosmanogepix, in patients with candidemia caused by Candida auris: results from a phase 2 trial. *Antimicrob Agents Chemother* 2023; 67: e0141922.
20. Rex JH, Pfaller MA, Walsh TJ, *et al.* Antifungal susceptibility testing: practical aspects and current challenges. *Clin Microbiol Rev* 2001; 14: 643–658.
21. Eschenauer GA, Carver PL, Lin SW, *et al.* Fluconazole versus an echinocandin for Candida glabrata fungaemia: a retrospective cohort study. *J Antimicrob Chemother* 2013; 68: 922–926.
22. Janum S and Afshari A. Central venous catheter (CVC) removal for patients of all ages with candidaemia. *Cochrane Database Syst Rev* 2016; 7: Cd011195.
23. Kuhn DM, George T, Chandra J, *et al.* Antifungal susceptibility of Candida biofilms: unique efficacy of amphotericin B lipid formulations and echinocandins. *Antimicrob Agents Chemother* 2002; 46: 1773–1780.
24. Fernández-Cruz A, Cruz Menárguez M, Muñoz P, *et al.* The search for endocarditis in patients with candidemia: a systematic recommendation for echocardiography? a prospective cohort. *Eur J Clin Microbiol Infect Dis* 2015; 34: 1543–1549.
25. Keighley C, Chen SC, Marriott D, *et al.* Candidaemia and a risk predictive model for overall mortality: a prospective multicentre study. *BMC Inf Dis* 2019; 19: 445.
26. Nasser RM, Melgar GR, Longworth DL, *et al.* Incidence and risk of developing fungal prosthetic valve endocarditis after nosocomial candidemia. *Am J Med* 1997; 103: 25–32.
27. Keighley C, Cooley L, Morris AJ, *et al.* Consensus guidelines for the diagnosis and management of invasive candidiasis in haematology, oncology and intensive care settings, 2021. *Intern Med J* 2021; 51(Suppl. 7): 89–117.
28. Vinikoor MJ, Zoghby J, Cohen KL, *et al.* Do all candidemic patients need an ophthalmic examination? *Int J Inf Dis* 2013; 17: e146–e148.
29. Breazzano MP, Day HR Jr., Bloch KC, *et al.* Utility of ophthalmologic screening for patients with Candida bloodstream infections: a systematic review. *JAMA Ophthalmol* 2019; 137: 698–710.
30. Breazzano MP, Bond JB III, Bearelly S, *et al.* American academy of ophthalmology recommendations on screening for endogenous Candida Endophthalmitis. *Ophthalmology* 2022; 129: 73–76.
31. CDC. Candida auris. Online, www.cdc.gov/fungal/candida-auris/index.html (2022, accessed March 2023)
32. Vila T, Sultan AS, Montelongo-Jauregui D, *et al.* Candida auris: a fungus with identity crisis. *Pathog Dis* 2020; 78: ftaa034

33. Lockhart SR, Etienne KA, Vallabhaneni S, *et al*. Simultaneous emergence of multidrug-resistant Candida auris on 3 continents confirmed by whole-genome sequencing and epidemiological analyses. *Clin Inf Dis* 2017; 64: 134–140.

34. Rybak JM, Sharma C, Doorley LA, *et al*. Delineation of the direct contribution of Candida auris ERG11 mutations to clinical triazole resistance. *Microbiol Spectr* 2021; 9: e0158521.

35. Ademe M and Girma F. Candida auris: from multidrug resistance to pan-resistant strains. *Infect Drug Resist* 2020; 13: 1287–1294.

36. Sanyaolu A, Okorie C, Marinkovic A, *et al*. Candida auris: an overview of the emerging drug-resistant fungal infection. *Infect Chemother* 2022; 54: 236–246.

37. Maphanga TG, Naicker SD, Kwenda S, *et al*. In vitro antifungal resistance of *Candida auris* isolates from bloodstream infections, South Africa. *Antimicrob Agents Chemother* 2021; 65: e0051721.

38. Chowdhary A, Tarai B, Singh A, *et al*. Multidrug-resistant Candida auris infections in critically Ill coronavirus disease patients, India, April-July 2020. *Emerg Infect Dis* 2020; 26: 2694–2696.

39. Lamoth F, Lewis RE and Kontoyiannis DP. Investigational antifungal agents for invasive mycoses: a clinical perspective. *Clin Inf Dis* 2022; 75: 534–544.

40. Wiederhold NP. Review of the novel investigational antifungal olorofim. *J Fungi (Basel)* 2020; 6: 122.

41. Pfaller MA, Huband MD and Flamm RK. In vitro activity of APX001A (Manogepix) and comparator agents against 1,706 fungal isolates collected during an International Surveillance Program in 2017. *Antimicrob Agents Chemother* 2019; 63: e00840-19.

42. Wiederhold NP. Pharmacodynamics, mechanisms of action and resistance, and spectrum of activity of new antifungal agents. *J Fungi (Basel)* 2022; 8: 857.

43. Garcia-Effron G. Rezafungin-mechanisms of action, susceptibility and resistance: similarities and differences with the other echinocandins. *J Fungi (Basel)* 2020; 6: 262.

44. Shaw KJ and Ibrahim AS. Fosmanogepix: a review of the first-in-class broad spectrum agent for the treatment of invasive fungal infections. *J Fungi (Basel)* 2020; 6: 239.

45. Patel V, Desjardins M and Cowan J. Shift in epidemiology of cryptococcal infections in ottawa with high mortality in non-HIV immunocompromised patients. *J Fungi (Basel)* 2019; 5: 104.

46. Pappas PG, Alexander BD, Andes DR, *et al*. Invasive fungal infections among organ transplant recipients: results of the Transplant-Associated Infection Surveillance Network (TRANSNET). *Clin Inf Dis* 2010; 50: 1101–1111.

47. van der Horst CM, Saag MS, Cloud GA, *et al*. Treatment of cryptococcal meningitis associated with the acquired immunodeficiency syndrome. National Institute of Allergy and Infectious Diseases Mycoses Study Group and AIDS Clinical Trials Group. *N Engl J Med* 1997; 337: 15–21.

48. Perfect JR, Dismukes WE, Dromer F, *et al*. Clinical practice guidelines for the management of cryptococcal disease: 2010 update by the Infectious Diseases Society of America. *Clin Inf Dis* 2010; 50: 291–322.

49. Bennett JE, Dismukes WE, Duma RJ, *et al*. A comparison of amphotericin B alone and combined with flucytosine in the treatment of cryptoccal meningitis. *N Engl J Med* 1979; 301: 126–131.

50. Molloy SF, Kanyama C, Heyderman RS, *et al*. Antifungal combinations for treatment of cryptococcal meningitis in Africa. *N Engl J Med* 2018; 378: 1004–1017.

51. Jarvis JN, Lawrence DS, Meya DB, *et al*. Single-dose liposomal Amphotericin B treatment for cryptococcal meningitis. *N Engl J Med* 2022; 386: 1109–1120.

52. WHO Guidelines. *Guidelines for diagnosing, preventing and managing cryptococcal disease among adults, adolescents and children living with HIV*. Geneva: World Health Organization, 2022.

53. Gamaletsou MN, Sipsas NV, Kontoyiannis DP, *et al*. Successful salvage therapy of refractory HIV-related cryptococcal meningitis with the combination of liposomal amphotericin B, voriconazole, and recombinant interferon-γ. *Diag Microbiol Inf Dis* 2012; 74: 409–411.

54. Pappas PG, Bustamante B, Ticona E, *et al*. Recombinant interferon- gamma 1b as adjunctive therapy for AIDS-related acute cryptococcal meningitis. *J Infect Dis* 2004; 189: 2185–2191.

55. Pfaller MA, Huband MD, Flamm RK, *et al*. Antimicrobial activity of manogepix, a first-in-class antifungal, and comparator agents tested against contemporary invasive fungal isolates from an international surveillance programme (2018–2019). *J Glob Antimicrob Resist* 2021; 26: 117–127.

56. Lu R, Hollingsworth C, Qiu J, *et al*. Efficacy of oral encochleated Amphotericin B in a mouse model of cryptococcal meningoencephalitis. *mBio* 2019; 10: e00724-19.

57. Li H, Guo M, Wang C, *et al*. Epidemiological study of Trichosporon asahii infections over the past 23 years. *Epidemiol Infect* 2020; 148: e169.

58. Arendrup MC, Boekhout T, Akova M, *et al*. ESCMID and ECMM joint clinical guidelines for the diagnosis and management of rare invasive yeast infections. *Clin Microbiol Infect* 2014; 20(Suppl. 3): 76–98.

59. Ruan SY, Chien JY and Hsueh PR. Invasive trichosporonosis caused by Trichosporon asahii and other unusual Trichosporon species at a medical center in Taiwan. *Clin Inf Dis* 2009; 49: e11–e17.

60. Kuo SH, Lu PL, Chen YC, *et al*. The epidemiology, genotypes, antifungal susceptibility of Trichosporon species, and the impact of voriconazole on Trichosporon fungemia patients. *J Formos Med Assoc* 2021; 120: 1686–1694.

61. Rodriguez-Tudela JL, Diaz-Guerra TM, Mellado E, *et al*. Susceptibility patterns and molecular identification of Trichosporon species. *Antimicrob Agents Chemother* 2005; 49: 4026–4034.

62. Shoham S and Dominguez EA. Emerging fungal infections in solid organ transplant recipients: guidelines of the American Society of Transplantation infectious diseases community of practice. *Clin Transplant* 2019; 33: e13525.

63. Nettles RE, Nichols LS, Bell-McGuinn K, *et al*. Successful treatment of Trichosporon mucoides infection with fluconazole in a heart and kidney transplant recipient. *Clin Inf Dis* 2003; 36: E63–E66.

64. Feugray G, Krzisch D, Dehais M, *et al*. Successful treatment of Trichosporon asahii fungemia with isavuconazole in a patient with hematologic malignancies. *Infect Drug Resist* 2019; 12: 2015–2018.

65. Go SE, Lee KJ, Kim Y, *et al*. Catheter-related *Trichosporon asahii* bloodstream infection in a neutropenic patient with myelodysplastic syndrome. *Infect Chemother* 2018; 50: 138–143.

66. Pfaller MA, Huband MD, Rhomberg PR, *et al*. Activity of manogepix, the active moiety of fosmanogepix against infrequently encountered yeast and mould isolates from the SENTRY antimicrobial surveillance programme (2017–2019). Paper presented at 2020 ESCMID, Proceedings of the 30th European Congress of Clinical Microbiology and Infectious Diseases; Paris, France, 2020.

67. Jallow S and Govender NP. Ibrexafungerp: a first-in-class oral triterpenoid glucan synthase inhibitor. *J Fungi (Basel)* 2021; 7: 163.

68. Vallabhaneni S, Benedict K, Derado G, *et al*. Trends in hospitalizations related to invasive aspergillosis and mucormycosis in the United States, 2000–2013. *Open Forum Infect Dis* 2017; 4: ofw268.

69. Castro C, Galán-Sanchez F, Linares MJ, *et al*. A prospective survey of Aspergillus spp. in respiratory tract samples: species identification and susceptibility patterns. *Med Mycol* 2019; 57: 412–420.

70. Kontoyiannis DP, Marr KA, Park BJ, *et al*. Prospective surveillance for invasive fungal infections in hematopoietic stem cell transplant recipients, 2001–2006: overview of the Transplant-Associated Infection Surveillance Network (TRANSNET) Database. *Clin Inf Dis* 2010; 50: 1091–1100.

71. Rivero-Menendez O, Alastruey-Izquierdo A, Mellado E, *et al*. Triazole resistance in Aspergillus spp.: a worldwide problem? *J Fungi (Basel)* 2016; 2: 21.

72. Hagiwara D, Watanabe A, Kamei K, *et al*. Epidemiological and genomic landscape of azole resistance mechanisms in Aspergillus Fungi. *Front Microbiol* 2016; 7: 1382.

73. Egli A, Fuller J, Humar A, *et al*. Emergence of Aspergillus calidoustus infection in the era of posttransplantation azole prophylaxis. *Transplantation* 2012; 94: 403–410.

74. Van Der Linden JW, Warris A and Verweij PE. Aspergillus species intrinsically resistant to antifungal agents. *Med Mycol* 2011; 49(Suppl. 1): S82–S89.

75. Patterson TF, Thompson GR III, Denning DW, *et al*. Practice guidelines for the diagnosis and management of aspergillosis: 2016 update by the Infectious Diseases Society of America. *Clin Inf Dis* 2016; 63: e1–e60.

76. Herbrecht R, Denning DW, Patterson TF, *et al*. Voriconazole versus amphotericin B for primary therapy of invasive aspergillosis. *N Engl J Med* 2002; 347: 408–415.

77. Maertens JA, Raad II, Marr KA, *et al*. Isavuconazole versus voriconazole for primary treatment of invasive mould disease caused

by Aspergillus and other filamentous fungi (SECURE): a phase 3, randomised-controlled, non-inferiority trial. *Lancet* 2016; 387: 760–769.

78. Maertens JA, Rahav G, Lee DG, *et al.* Posaconazole versus voriconazole for primary treatment of invasive aspergillosis: a phase 3, randomised, controlled, non-inferiority trial. *Lancet* 2021; 397: 499–509.
79. Cornely OA, Maertens J, Bresnik M, *et al.* Liposomal amphotericin B as initial therapy for invasive mold infection: a randomized trial comparing a high-loading dose regimen with standard dosing (AmBiLoad trial). *Clin Inf Dis* 2007; 44: 1289–1297.
80. Marr KA, Schlamm HT, Herbrecht R, *et al.* Combination antifungal therapy for invasive aspergillosis: a randomized trial. *Ann Intern Med 20* 2015; 162: 81–89.
81. Mellinghoff SC, Bassetti M, Dörfel D, *et al.* Isavuconazole shortens the QTc interval. *Mycoses* 2018; 61: 256–260.
82. Yang YL, Xiang ZJ, Yang JH, *et al.* Adverse effects associated with currently commonly used antifungal agents: a network meta-analysis and systematic review. *Front Pharmacol* 2021; 12: 697330.
83. Yang L, Wang C, Zhang Y, *et al.* Central nervous system toxicity of voriconazole: risk factors and threshold - a Retrospective Cohort Study. *Infect Drug Resist* 2022; 15: 7475–7484.
84. Williams K, Mansh M, Chin-Hong P, *et al.* Voriconazole-associated cutaneous malignancy: a literature review on photocarcinogenesis in organ transplant recipients. *Clin Inf Dis* 2014; 58: 997–1002.
85. Wang TF, Wang T, Altman R, *et al.* Periostitis secondary to prolonged voriconazole therapy in lung transplant recipients. *Am J Transplant* 2009; 9: 2845–2850.
86. Nguyen MH, Davis MR, Wittenberg R, *et al.* Posaconazole serum drug levels associated with pseudohyperaldosteronism. *Clin Inf Dis* 2020; 70: 2593–2598.
87. Pascual A, Calandra T, Bolay S, *et al.* Voriconazole therapeutic drug monitoring in patients with invasive mycoses improves efficacy and safety outcomes. *Clin Inf Dis* 2008; 46: 201–211.
88. Andes D, Pascual A and Marchetti O. Antifungal therapeutic drug monitoring: established and emerging indications. *Antimicrob Agents Chemother* 2009; 53: 24–34.
89. Veringa A, Brüggemann RJ, Span LFR, *et al.* Therapeutic drug monitoring-guided treatment versus standard dosing of voriconazole for invasive aspergillosis in haematological patients: a multicentre, prospective, cluster randomised, crossover clinical trial. *Int J Antimicrob Agents* 2023; 61: 106711.
90. Panackal AA, Bennett JE and Williamson PR. Treatment options in Invasive Aspergillosis. *Curr Treat Options Infect Dis* 2014; 6: 309–325.
91. Miceli MH. Central nervous system infections due to Aspergillus and other hyaline molds. *J Fungi (Basel)* 2019; 5: 79.
92. Miceli MH, Grazziutti ML, Woods G, *et al.* Strong correlation between serum Aspergillus galactomannan index and outcome of aspergillosis in patients with hematological cancer: clinical and research implications. *Clin Inf Dis* 2008; 46: 1412–1422.
93. Maertens J, Buvé K, Theunissen K, *et al.* Galactomannan serves as a surrogate endpoint for outcome of pulmonary invasive aspergillosis in neutropenic hematology patients. *Cancer* 2009; 115: 355–362.
94. Offner F, Cordonnier C, Ljungman P, *et al.* Impact of previous aspergillosis on the outcome of bone marrow transplantation. *Clin Inf Dis* 1998; 26: 1098–1103.
95. Fukuda T, Boeckh M, Guthrie KA, *et al.* Invasive aspergillosis before allogeneic hematopoietic stem cell transplantation: 10-year experience at a single transplant center. *Biol Blood Marrow Transplant* 2004; 10: 494–503.
96. Sipsas NV and Kontoyiannis DP. Clinical issues regarding relapsing aspergillosis and the efficacy of secondary antifungal prophylaxis in patients with hematological malignancies. *Clin Inf Dis* 2006; 42: 1584–1591.
97. Cordonnier C, Rovira M, Maertens J, *et al.* Voriconazole for secondary prophylaxis of invasive fungal infections in allogeneic stem cell transplant recipients: results of the VOSIFI study. *Haematologica* 2010; 95: 1762–1768.
98. Ullmann AJ, Aguado JM, Arikan-Akdagli S, *et al.* Diagnosis and management of Aspergillus diseases: executive summary of the 2017 ESCMID-ECMM-ERS guideline. *Clin Microbiol Infect* 2018; 24(Suppl. 1): e1–e38.
99. Taplitz RA, Kennedy EB, Bow EJ, *et al.* Antimicrobial prophylaxis for adult patients with cancer-related immunosuppression: ASCO and IDSA clinical practice guideline update. *J Clin Oncol* 2018; 36: 3043–3054.

100. Duckwall MJ, Gales MA and Gales BJ. Inhaled Amphotericin B as Aspergillosis Prophylaxis in hematologic disease: an update. *Microbiol Insights* 2019; 12: 1178636119869937.

101. Maertens JA, Verweij PE, Lanuza EF, *et al*. 870. Olorofim for the treatment of invasive mould infections in patients with limited or no treatment options: comparison of interim results from a phase 2B open-label study with outcomes in historical control populations (NCT03583164, FORMULA-OLS, Study 32). *Open Forum Inf Dis* 2022; 9(Suppl. 2): ofac492.063.

102. Thompson GR, King T, Azie N, *et al*. 871. Oral ibrexafungerp outcomes by fungal disease in patients from an interim analysis of a phase 3 open-label study (FURI). *Open Forum Inf Dis* 2022; 9(Suppl. 2): ofac492.064.

103. Hoenigl M, Sprute R, Egger M, *et al*. The antifungal pipeline: fosmanogepix, ibrexafungerp, olorofim, opelconazole, and rezafungin. *Drugs* 2021; 81: 1703–1729.

104. Aigner M and Lass-Flörl C. Encochleated Amphotericin B: is the oral availability of Amphotericin B finally reached? *J Fungi (Basel)* 2020; 6: 66.

105. Roden MM, Zaoutis TE, Buchanan WL, *et al*. Epidemiology and outcome of zygomycosis: a review of 929 reported cases. *Clin Inf Dis* 2005; 41: 634–653.

106. Badali H, Cañete-Gibas C, McCarthy D, *et al*. Epidemiology and antifungal susceptibilities of mucoralean fungi in clinical samples from the United States. *J Clin Microb* 2021; 59: e0123021.

107. Ibrahim AS, Gebremariam T, Husseiny MI, *et al*. Comparison of lipid amphotericin B preparations in treating murine zygomycosis. *Antimicrob Agents Chemother* 2008; 52: 1573–1576.

108. Wingard JR, White MH, Anaissie E, *et al*. A randomized, double-blind comparative trial evaluating the safety of liposomal amphotericin B versus amphotericin B lipid complex in the empirical treatment of febrile neutropenia. L Amph/ABLC Collaborative Study Group. *Clin Inf Dis* 2000; 31: 1155–1163.

109. Lanternier F, Poiree S, Elie C, *et al*. Prospective pilot study of high-dose (10 mg/kg/day) liposomal amphotericin B (L-AMB) for the initial treatment of mucormycosis. *J Antimicrob Chemother* 2015; 70: 3116–3123.

110. Spellberg B, Ibrahim AS, Chin-Hong PV, *et al*. The Deferasirox-AmBisome Therapy for Mucormycosis (DEFEAT Mucor) study: a randomized, double-blinded, placebo-controlled trial. *J Antimicrob Chemother* 2012; 67: 715–722.

111. Cornely OA, Alastruey-Izquierdo A, Arenz D, *et al*. Global guideline for the diagnosis and management of mucormycosis: an initiative of the European Confederation of Medical Mycology in cooperation with the Mycoses Study Group Education and Research Consortium. *Lancet Infect Dis* 2019; 19: e405–e421.

112. Bupha-Intr O, Butters C, Reynolds G, *et al*. Consensus guidelines for the diagnosis and management of invasive fungal disease due to moulds other than Aspergillus in the haematology/oncology setting, 2021. *Intern Med J* 2021; 51(Suppl. 7): 177–219.

113. Marty FM, Ostrosky-Zeichner L, Cornely OA, *et al*. Isavuconazole treatment for mucormycosis: a single-arm open-label trial and case-control analysis. *Lancet Infect Dis* 2016; 16: 828–837.

114. Skiada A, Pagano L, Groll A, *et al*. Zygomycosis in Europe: analysis of 230 cases accrued by the registry of the European Confederation of Medical Mycology (ECMM) Working Group on Zygomycosis between 2005 and 2007. *Clin Microbiol Infect* 2011; 17: 1859–1867.

115. Rüping MJ, Heinz WJ, Kindo AJ, *et al*. Forty-one recent cases of invasive zygomycosis from a global clinical registry. *J Antimicrob Chemother* 2010; 65: 296–302.

116. Greenberg RN, Mullane K, van Burik JA, *et al*. Posaconazole as salvage therapy for zygomycosis. *Antimicrob Agents Chemother* 2006; 50: 126–133.

117. van Burik JA, Hare RS, Solomon HF, *et al*. Posaconazole is effective as salvage therapy in zygomycosis: a retrospective summary of 91 cases. *Clin Inf Dis* 2006; 42: e61-5.

118. Felton T, Troke PF and Hope WW. Tissue penetration of antifungal agents. *Clin Microbiol Rev* 2014; 27: 68–88.

119. Reinwald M, Uharek L, Lampe D, *et al*. Limited penetration of posaconazole into cerebrospinal fluid in an allogeneic stem cell recipient with invasive pulmonary aspergillosis. *Bone Marrow Transplant* 2009; 44: 269–270.

120. Ashley ED. Antifungal drugs: special problems treating central nervous system infections. *J Fungi (Basel)* 2019; 5: 97.

121. Schwartz S, Cornely OA, Hamed K, *et al*. Isavuconazole for the treatment of patients with

invasive fungal diseases involving the central nervous system. *Med Mycol* 2020; 58: 417–424.

122. Reed C, Bryant R, Ibrahim AS, *et al.* Combination polyene-caspofungin treatment of rhino-orbital-cerebral mucormycosis. *Clin Inf Dis* 2008; 47: 364–371.

123. Abidi MZ, Sohail MR, Cummins N, *et al.* Stability in the cumulative incidence, severity and mortality of 101 cases of invasive mucormycosis in high-risk patients from 1995 to 2011: a comparison of eras immediately before and after the availability of voriconazole and echinocandin-amphotericin combination therapies. *Mycoses* 2014; 57: 687–698.

124. Tissot F, Agrawal S, Pagano L, *et al.* ECIL-6 guidelines for the treatment of invasive candidiasis, aspergillosis and mucormycosis in leukemia and hematopoietic stem cell transplant patients. *Haematologica* 2017; 102: 433–444.

125. Ferguson BJ, Mitchell TG, Moon R, *et al.* Adjunctive hyperbaric oxygen for treatment of rhinocerebral mucormycosis. *Rev Infect Dis* 1988; 10: 551–559.

126. Sahin B, Paydaş S, Coşar E, *et al.* Role of granulocyte colony-stimulating factor in the treatment of mucormycosis *J Clin Microbiol Infect Dis* 1996; 15: 866–869.

127. Colley T, Sehra G, Chowdhary A, *et al. In vitro* and *in vivo* efficacy of a novel and long-acting fungicidal azole, PC1244, on Aspergillus fumigatus infection. *Antimicrob Agents Chemother* 2018; 62: e01941-17.

128. Gebremariam T, Alkhazraji S, Lin L, *et al.* Prophylactic treatment with VT-1161 protects immunosuppressed mice from rhizopus arrhizus var. arrhizus infection. *Antimicrob Agents Chemother* 2017; 61: 00390-17.

129. Gebremariam T, Alkhazraji S, Alqarihi A, *et al.* Fosmanogepix (APX001) is effective in the treatment of pulmonary murine mucormycosis due to rhizopus arrhizus. *Antimicrob Agents Chemother* 2020; 64: e00178-20.

130. Rivero-Menendez O, Cuenca-Estrella M and Alastruey-Izquierdo A. In vitro activity of APX001A against rare moulds using EUCAST and CLSI methodologies. *J Antimicrob Chemother* 2019; 74: 1295–1299.

131. Lamoth F and Alexander BD. Antifungal activities of SCY-078 (MK-3118) and standard antifungal agents against clinical non-Aspergillus mold isolates. *Antimicrob Agents Chemother* 2015; 59: 4308–4311.

132. Cobo F, Lara-Oya A, Rodríguez-Granger J, *et al.* Infections caused by Scedosporium/Lomentospora species: clinical and microbiological findings in 21 cases. *Med Mycol* 2018; 56: 917–925.

133. Husain S, Muñoz P, Forrest G, *et al.* Infections due to Scedosporium apiospermum and Scedosporium prolificans in transplant recipients: clinical characteristics and impact of antifungal agent therapy on outcome. *Clin Inf Dis* 2005; 40: 89–99.

134. Seidel D, Meißner A, Lackner M, *et al.* Prognostic factors in 264 adults with invasive Scedosporium spp. and Lomentospora prolificans infection reported in the literature and FungiScope(®). *Crit Rev Microbiol* 2019; 45: 1–21.

135. Meletiadis J, Meis JF, Mouton JW, *et al.* In vitro activities of new and conventional antifungal agents against clinical Scedosporium isolates. *Antimicrob Agents Chemother* 2002; 46: 62–68.

136. Carrillo AJ and Guarro J. *In vitro* activities of four novel triazoles against Scedosporium spp. *Antimicrob Agents Chemother* 2001; 45: 2151–2153.

137. Heath CH, Slavin MA, Sorrell TC, *et al.* Population-based surveillance for scedosporiosis in Australia: epidemiology, disease manifestations and emergence of Scedosporium aurantiacum infection. *Clin Microbiol Infect* 2009; 15: 689–693.

138. Messer SA, Carvalhaes CG, Castanheira M, *et al.* In vitro activity of isavuconazole versus opportunistic filamentous fungal pathogens from the SENTRY Antifungal Surveillance Program, 2017–2018. *Diagnostic Microbiol Inf Dis* 2020; 97: 115007.

139. Lackner M, de Hoog GS, Verweij PE, *et al.* Species-specific antifungal susceptibility patterns of Scedosporium and Pseudallescheria species. *Antimicrob Agents Chemother* 2012; 56: 2635–2642.

140. Troke P, Aguirrebengoa K, Arteaga C, *et al.* Treatment of scedosporiosis with voriconazole: clinical experience with 107 patients. *Antimicrob Agents Chemother* 2008; 52: 1743–1750.

141. Husain S, Bhaskaran A, Rotstein C, *et al.* A strategy for prevention of fungal infections in lung transplantation: role of bronchoalveolar lavage fluid galactomannan and fungal culture. *J Heart Lung Transplant* 2018; 37: 886–894.

142. Goldman C, Akiyama MJ, Torres J, *et al.* Scedosporium apiospermum infections and

the role of combination antifungal therapy and GM-CSF: a case report and review of the literature. *Med Mycol Case Rep* 2016; 11: 40–43.

143. Tortorano AM, Richardson M, Roilides E, *et al.* ESCMID and ECMM joint guidelines on diagnosis and management of hyalohyphomycosis: Fusarium spp., Scedosporium spp. and others. *Clin Microbiol Infect* 2014; 20(Suppl. 3): 27–46.

144. Hoenigl M, Salmanton-García J, Walsh TJ, *et al.* Global guideline for the diagnosis and management of rare mould infections: an initiative of the European Confederation of Medical Mycology in cooperation with the International Society for Human and Animal Mycology and the American Society for Microbiology. *Lancet Infect Dis* 2021; 21: e246–e257.

145. Musk M, Chambers D, Chin W, *et al.* Successful treatment of disseminated scedosporium infection in 2 lung transplant recipients: review of the literature and recommendations for management. *J Heart Lung Transplant* 2006; 25: 1268–1272.

146. Rolfe NE, Haddad TJ and Wills TS. Management of Scedosporium apiospermum in a pre- and post-lung transplant patient with cystic fibrosis. *Med Mycol Case Rep* 2013; 2: 37–39.

147. Steinbach WJ, Schell WA, Miller JL, *et al.* Scedosporium prolificans osteomyelitis in an immunocompetent child treated with voriconazole and caspofungin, as well as locally applied polyhexamethylene biguanide. *J Clin Microbiol* 2003; 41: 3981–3985.

148. Henao-Martínez AF, Castillo-Mancilla JR, Barron MA, *et al.* Combination antifungal therapy in the treatment of scedosporium apiospermum central nervous system infections. *Case Rep Infect Dis* 2013; 2013: 589490.

149. Jabr R and Hammoud K. Scedosporium apiospermum fungemia successfully treated with voriconazole and terbinafine. *IDCases* 2020; 22: e00928.

150. Kesson AM, Bellemore MC, O'Mara TJ, *et al.* Scedosporium prolificans osteomyelitis in an immunocompetent child treated with a novel agent, hexadecylphospocholine (miltefosine), in combination with terbinafine and voriconazole: a case report. *Clin Inf Dis* 2009; 48: 1257–1261.

151. Trubiano JA, Paratz E, Wolf M, *et al.* Disseminated Scedosporium prolificans infection in an 'extensive metaboliser': navigating the minefield of drug interactions and pharmacogenomics. *Mycoses* 2014; 57: 572–576.

152. Balandin B, Aguilar M, Sánchez I, *et al.* Scedosporium apiospermum and S. prolificans mixed disseminated infection in a lung transplant recipient: an unusual case of long-term survival with combined systemic and local antifungal therapy in intensive care unit. *Med Mycol Case Rep* 2016; 11: 53–56.

153. Quaesaet L, Stindel E, Lanternier F, *et al.* Miltefosine-based regimen as salvage therapy in Lomentospora prolificans bone and joint infection. *Med Mal Infect* 2018; 48: 63–65.

154. Paajanen J, Halme M, Palomäki M, *et al.* Disseminated Scedosporium apiospermum central nervous system infection after lung transplantation: a case report with successful recovery. *Med Mycol Case Rep* 2019; 24: 37–40.

155. Walsh TJ, Peter J, McGough DA, *et al.* Activities of amphotericin B and antifungal azoles alone and in combination against Pseudallescheria boydii. *Antimicrob Agents Chemother* 1995; 39: 1361–1364.

156. Yustes C and Guarro J. *In vitro* synergistic interaction between amphotericin B and micafungin against Scedosporium spp. *Antimicrob Agents Chemother* 2005; 49: 3498–3500.

157. Cuenca-Estrella M, Alastruey-Izquierdo A, Alcazar-Fuoli L, *et al.* In vitro activities of 35 double combinations of antifungal agents against Scedosporium apiospermum and Scedosporium prolificans. *Antimicrob Agents Chemother* 2008; 52: 1136–1139.

158. Solé A, García-Robles AA, Jordá C, *et al.* Salvage therapy with topical posaconazole in lung transplant recipients with invasive Scedosporium infection. *Am J Transplant* 2018; 18: 504–509.

159. Mellinghoff IK, Winston DJ, Mukwaya G, *et al.* Treatment of Scedosporium apiospermum brain abscesses with posaconazole. *Clin Inf Dis* 2002; 34: 1648–1650.

160. Lackner M, de Hoog GS, Yang L, *et al.* Proposed nomenclature for Pseudallescheria, Scedosporium and related genera. *Fungal Diversity* 2014; 67: 1–10.

161. Espinel-Ingroff A. In vitro fungicidal activities of voriconazole, itraconazole, and amphotericin B against opportunistic moniliaceous and dematiaceous fungi. *J Clin Microbiol* 2001; 39: 954–958.

162. Rodriguez-Tudela JL, Berenguer J, Guarro J, *et al*. Epidemiology and outcome of Scedosporium prolificans infection, a review of 162 cases. *Med Mycol* 2009; 47: 359–370.

163. Jenks JD, Seidel D, Cornely OA, *et al*. Voriconazole plus terbinafine combination antifungal therapy for invasive Lomentospora prolificans infections: analysis of 41 patients from the FungiScope® registry 2008–2019. *Clin Microbiol Infect* 2020; 26: 784.e1–784.e5.

164. Jenks JD, Reed SL, Seidel D, *et al*. Rare mould infections caused by Mucorales, Lomentospora prolificans and Fusarium, in San Diego, CA: the role of antifungal combination therapy. *Int J Antimicrob Agents* 2018; 52: 706–712.

165. Nesky MA, McDougal EC and Peacock JE Jr. Pseudallescheria boydii brain abscess successfully treated with voriconazole and surgical drainage: case report and literature review of central nervous system pseudallescheriasis. *Clin Inf Dis* 2000; 31: 673–677.

166. Seyedmousavi S, Chang YC, Youn JH, *et al*. *In vivo* efficacy of olorofim against systemic scedosporiosis and lomentosporiosis. *Antimicrob Agents Chemother* 2021; 65: e0043421.

167. Tio SY, Thursky K, Ng G, *et al*. *Olorofim for a case of severe disseminated Lomentospora prolificans infection*. Proceedings of the 30th European Congress of Clinical Microbiology and Infectious Diseases, Paris, France, 2020, pp. 18–21.

168. Chen S, Rai NJ, Cunneen S, *et al*. *A case of Lomentospora prolificans (LoPro) treated with the novel antifungal olorofim*, Proceedings of the 30th European Congress of Clinical Microbiology and Infectious Diseases, Paris, France, 2020.

169. Castanheira M, Duncanson FP, Diekema DJ, *et al*. Activities of E1210 and comparator agents tested by CLSI and EUCAST broth microdilution methods against Fusarium and Scedosporium species identified using molecular methods. *Antimicrob Agents Chemother* 2012; 56: 352–357.

170. Alkhazraji S, Gebremariam T, Alqarihi A, *et al*. Fosmanogepix (APX001) is effective in the treatment of immunocompromised mice infected with invasive pulmonary scedosporiosis or disseminated fusariosis. *Antimicrob Agents Chemother* 2020; 64: e01735-19.

171. Park BJ, Pappas PG, Wannemuehler KA, *et al*. Invasive non-Aspergillus mold infections in transplant recipients, United States, 2001–2006. *Emerg Infect Dis* 2011; 17: 1855–1864.

172. Nucci M and Anaissie E. Fusarium infections in immunocompromised patients. *Clin Microbiol Rev* 2007; 20: 695–704.

173. Boutati EI and Anaissie EJ. Fusarium, a significant emerging pathogen in patients with hematologic malignancy: ten years' experience at a cancer center and implications for management. *Blood* 1997; 90: 999–1008.

174. Alastruey-Izquierdo A, Cuenca-Estrella M, Monzón A, *et al*. Antifungal susceptibility profile of clinical Fusarium spp. isolates identified by molecular methods. *J Antimicrob Chemother* 2008; 61: 805–809.

175. Pfaller MA, Messer SA, Woosley LN, *et al*. Echinocandin and triazole antifungal susceptibility profiles for clinical opportunistic yeast and mold isolates collected from 2010 to 2011: application of new CLSI clinical breakpoints and epidemiological cutoff values for characterization of geographic and temporal trends of antifungal resistance. *J Clin Microbiol* 2013; 51: 2571–2581.

176. Al-Hatmi AMS, Curfs-Breuker I, de Hoog GS, *et al*. Antifungal susceptibility testing of Fusarium: a practical approach. *J Fungi (Basel)* 2017; 3: 19.

177. Lewis RE, Wiederhold NP and Klepser ME. *In vitro* pharmacodynamics of amphotericin B, itraconazole, and voriconazole against Aspergillus, Fusarium, and Scedosporium spp. *Antimicrob Agents Chemother* 2005; 49: 945–951.

178. Walsh TJ, Hiemenz JW, Seibel NL, *et al*. Amphotericin B lipid complex for invasive fungal infections: analysis of safety and efficacy in 556 cases. *Clin Inf Dis* 1998; 26: 1383–1396.

179. Perfect JR. Treatment of non-Aspergillus moulds in immunocompromised patients, with amphotericin B lipid complex. *Clin Inf Dis* 2005; 40(Suppl. 6): S401–S408.

180. Nucci M, Marr KA, Vehreschild MJ, *et al*. Improvement in the outcome of invasive fusariosis in the last decade. *Clin Microbiol Infect* 2014; 20: 580–585.

181. Perfect JR, Marr KA, Walsh TJ, *et al*. Voriconazole treatment for less-common, emerging, or refractory fungal infections. *Clin Inf Dis* 2003; 36: 1122–1131.

182. Stanzani M, Tumietto F, Vianelli N, *et al*. Update on the treatment of disseminated

fusariosis: focus on voriconazole. *Ther Clin Risk Manag* 2007; 3: 1165–1173.

183. Lortholary O, Obenga G, Biswas P, *et al.* International retrospective analysis of 73 cases of invasive fusariosis treated with voriconazole. *Antimicrob Agents Chemother* 2010; 54: 4446–4450.

184. Córdoba S, Rodero L, Vivot W, *et al.* In vitro interactions of antifungal agents against clinical isolates of Fusarium spp. *Int J Antimicrob Agents* 2008; 31: 171–174.

185. Stempel JM, Hammond SP, Sutton DA, *et al.* Invasive fusariosis in the voriconazole era: single-center 13-year experience. *Open Forum Infect Dis* 2015; 2: ofv099.

186. Durand-Joly I, Alfandari S, Benchikh Z, *et al.* Successful outcome of disseminated Fusarium infection with skin localization treated with voriconazole and amphotericin B-lipid complex in a patient with acute leukemia. *J Clin Microbiol* 2003; 41: 4898–4900.

187. Tezcan G, Ozhak-Baysan B, Alastruey-Izquierdo A, *et al.* Disseminated fusariosis caused by Fusarium verticillioides in an acute lymphoblastic leukemia patient after allogeneic hematopoietic stem cell transplantation. *J Clin Microbiol* 2009; 47: 278–281.

188. Ho DY, Lee JD, Rosso F, *et al.* Treating disseminated fusariosis: amphotericin B, voriconazole or both? *Mycoses* 2007; 50: 227–231.

189. Raad II, Hachem RY, Herbrecht R, *et al.* Posaconazole as salvage treatment for invasive fusariosis in patients with underlying hematologic malignancy and other conditions. *Clin Inf Dis* 2006; 42: 1398–1403.

190. Cornely OA, Rahav G, Maher R, *et al.* Outcomes in patients with invasive mould disease caused by Fusarium or Scedosporium spp. Treated with Isavuconazole: Experience from the VITAL and SECURE Trials, 54th Interscience Conference on Antimicrobial Agents and Chemotherapy [ICAAC], Washington, DC, 2014.

191. Dignani MC, Anaissie EJ, Hester JP, *et al.* Treatment of neutropenia-related fungal infections with granulocyte colony-stimulating factor-elicited white blood cell transfusions: a pilot study. *Leukemia* 1997; 11: 1621–1630.

192. Badali H, Cañete-Gibas C, Patterson H, *et al.* In vitro activity of olorofim against clinical isolates of the Fusarium oxysporum and Fusarium solani species complexes. *Mycoses* 2021; 64: 748–752.

193. Hata K, Horii T, Miyazaki M, *et al.* Efficacy of oral E1210, a new broad-spectrum antifungal with a novel mechanism of action, in murine models of candidiasis, aspergillosis, and fusariosis. *Antimicrob Agents Chemother* 2011; 55: 4543–4551.