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Themed Issue: New challenges in antifungal therapy

Current antifungal treatment of fusariosis

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ABSTRACT

Fungi of the genus *Fusarium* are well known as major plant pathogens and soil inhabitants, but also cause a broad spectrum of human infections. Fusariosis is the second most common mould infection after aspergillosis, and keratitis is the most encountered implantation infection in immunocompetent individuals. Natamycin is active against *Fusarium* species both in vitro and in vivo, and is used along with voriconazole as the mainstay of treatment for *Fusarium* keratitis. Onychomycosis is treated with terbinafine, voriconazole and sometimes itraconazole. Cure is possible despite high in vitro minimum inhibitory concentrations (MICs). Recently, disseminated infections have increased dramatically, mainly affecting severely immunocompromised patients. The remarkable intrinsic resistance of *Fusarium* species to most antifungal agents results in high mortality rates in this patient population. Recovery of neutropenia is essential for patient survival and treatment should include voriconazole or amphotericin B as first-line and posaconazole as salvage therapy.

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1. Introduction

The fungal genus *Fusarium* (order *Hypocreales*) contains numerous plant-pathogenic species, and also human opportunistic pathogens causing eye, skin, nail and disseminated infections. The first published human case of fusariosis was an eye infection in 1958, and soon thereafter other types of disease were reported [1,2]. The genus has been subjected to several radical taxonomic revisions. Older, morphological subdivisions of the genus into sections did not match with phylogeny. Modern, polyphasic taxonomy has led to narrow species concepts with numerous micro-species, which are aggregated into 20 species complexes [3]. In *Fusarium*, a species complex is defined as a cluster of closely related entities that exhibit similar physiological and molecular features, and serve

as an alternative to the subgeneric 'sections' currently in use in e.g. *Aspergillus* [4,5].

Of the more than 300 recognised species to date, about a quarter has been isolated from humans, mostly causing superficial infections, such as onychomycosis or keratitis in immunocompetent individuals [2]. *Fusarium* keratitis was originally observed mainly among farmers and outdoor workers, but the widespread use of contact lenses has dramatically increased the incidence of keratitis among urban populations [6,7]. Onychomycosis is a common condition in otherwise healthy humans, with up to 10% of cases caused by *Fusarium* [8]. Deep and disseminated fusariosis have occasionally been documented, exclusively in patients with haematological malignancies and other conditions associated with immunosuppression [9]. Agents of any type of fusariosis are mainly found in three species complexes: *F. solani* complex (FSSC), *F. oxysporum* complex (FOSC) and *F. fujikuroi* complex (FFSC). The *F. dimerum*, *F. incarnatum-equiseti*, and *F. chlamydosporum* species complexes are rare causes of human infections [10]. *Fusarium* shows a remarkably high degree of intrinsic resistance to a wide spectrum of commonly used antifungals. The objective of the present

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paper was to review the current status of antifungal therapy of fusariosis, highlighting the best options for infection management.

2. Methods

2.1. Literature

The majority of the literature we reviewed that was related to treatment was based on case reports and in vitro and in vivo studies of drug susceptibilities. We assessed and collected leading articles on drugs that are available and have been used successfully in patients with fusariosis. Phylogeny and resistance, treatment of different infections (onychomycosis, keratitis and deep and invasive infection), in vitro antifungal susceptibility patterns, drug interactions, dose, and duration of treatment were considered. We selected publications most useful for readers interested in the medical management of *Fusarium* infections.

2.2. Phylogeny

The partial sequence of 28S rRNA retrieved from the National Center for Biotechnology Information (NCBI) was used to construct a phylogenetic tree of the Ascomycota, Basidiomycota and some other ancestral lineages, mainly showing the members that have been implicated in human diseases. The tree was constructed based on 28S rDNA sequences (n = 414) aligned by MAFFT, using a neighbour-joining algorithm with Kimura correction (Fig. 1). Orders represented by blue boxes are those where nearly all members have high intrinsic resistance to a wide panel of antifungal drugs. These groups of fungi share a high degree of intrinsic resistance to most currently used antifungal agents and belong to different orders. *Fusarium* with *Acremonium* and *Trichoderma* belong to the order

Hypocreales, whereas *Microascus*, *Scopulariopsis*, *Scedosporium* and *Lomentospora* are in the adjacent order, *Microascales*.

3. Identity and resistance

A robust taxonomy of the fungi requires species validation with the inclusion of ex-type specimens and establishment of phylogenetic relationships [4]. Species redefinitions have uncovered numerous *Fusarium* species responsible for infections that were previously unrecognised in the older literature. The phylogenetic approach also enables comparison of susceptibility data at the species, genus, and family level, showing trends in intrinsic resistance over larger groups of organisms. *Fusarium* species share their high degree of intrinsic resistance to most currently used antifungal agents with *Acremonium* and *Trichoderma*, which belong to the same order *Hypocreales*, and with *Microascus*, *Scopulariopsis*, *Scedosporium* and *Lomentospora* in the adjacent order *Microascales* [2]. Intrinsic multiresistance of these fungi is unique among the *Ascomycota* (Fig. 1), and indicates that this property was acquired in a common ancestor of the two orders. However, knowledge is scant on resistance mechanisms in *Fusarium* and relatives, and evolutionary relationships have not been established. Intrinsic resistance interferes with antifungal therapy and is particularly difficult in patients with prolonged immunosuppression or failure to come into remission of their haematological disease [6]. Insufficient documentation is available on the correlation of in vitro susceptibility test results and in vivo outcome, so no clinical breakpoints have been determined, but epidemiological cut-off values have been recently established for several *Fusarium* species [11].

The spectrum of *Fusarium* species causing human infection is globally increasing [10]. Recent molecular phylogenetic studies provided support for the recognition of additional cryptic species [2,3].

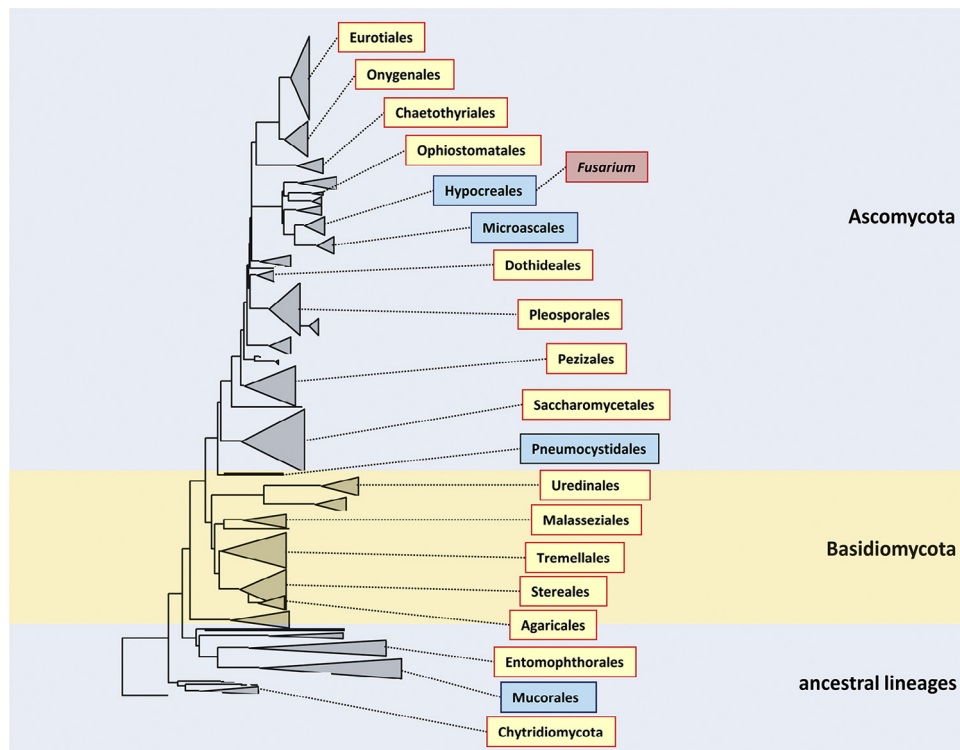


Fig. 1. Phylogenetic tree of the fungal kingdom based on 414 near-complete SSU rDNA sequences and constructed using a neighbour-joining algorithm with Kimura correction, and listing main orders that have been implicated in diseases of humans and animals. Orders in blue boxes are those where nearly all members have high intrinsic resistance to a wide panel of antifungal drugs.

Table 1
MIC ranges of amphotericin B, voriconazole, posaconazole, natamycin and terbinafine for the clinical *Fusarium* strains.^a

Species complex	<i>Fusarium</i> species (n)	MICs [range; µg/mL]					
		AMB	VRC	PSC	NATA	TBF	
<i>F. solani</i> complex (FSSC)	<i>F. keratoplasticum</i> (10)	1–2	4–16	8–16	2–4	8–16	
	<i>F. falciforme</i> (10)	0.5–2	4–16	1–16	2–4	1–8	
	<i>F. solani sensu stricto</i> (FSS5) (5)	1–2	16	16	4	-	
	<i>F. lichenicola</i> (5)	0.5	1–16	16	4	>2	
	<i>F. petroliphilum</i> (5)	1–2	8–16	8–16	4	-	
	<i>F. metavorans</i> (FSS6) (2)	1	16	16	4	-	
	<i>F. pseudoniforme</i> (1)	0.5	8	4	4	-	
	<i>F. oxysporum</i> complex (FOSC)	<i>F. oxysporum</i> (5)	0.5–2	2–8	0.5–16	4	2–8
	<i>F. fujikuroi</i> complex (FFSC)	<i>F. acutatum</i> (3)	1–2	1–16	1–16	4	-
		<i>F. ananatum</i> (5)	0.125–2	1–4	0.5–1	4	-
<i>F. andiyazi</i> (1)		1	2	1	4	-	
<i>F. anthropilum</i> (1)		0.5	1	0.5	4	-	
<i>F. fujikuroi</i> (5)		0.25–1	1–8	1–2	4	-	
<i>F. musae</i> (4)		4–8	1–8	8–> 16	-	2–4	
<i>F. napiforme</i> (4)		1–8	1–4	2–> 16	4	0.5–1	
<i>F. nygamai</i> (5)		1–4	1–16	8–> 16	4	0.125–2	
<i>F. proliferatum</i> (5)		0.5–2	2–8	1–> 16	4	0.25–1	
<i>F. sacchari</i> (5)		0.5–1	1–4	0.5–> 16	4	0.5–1	
<i>F. subglutinans</i> (2)		0.5–1	1–2	0.125–0.25	4	-	
<i>F. temperatum</i> (1)		0.25	1	0.25	4	-	
<i>F. thapsinum</i> (5)		1–2	1–4	2–> 16	4	0.25–1	
<i>F. verticillodes</i> (5)		1–2	1–4	0.25–1	4	0.25–0.5	
<i>F. dimerum</i> complex (FDSC)		<i>F. delphinoides</i> (3)	1–2	1–4	2–> 16	4	-
		<i>F. dimerum</i> (5)	0.5–1	2–4	2–> 16	4	1–2
<i>F. incarnatum-equiseti</i> complex (FIESC)		<i>F. incarnatum</i> (2)	0.5–2	2–4	4–8	4	1–2
	<i>F. equiseti</i> (2)	0.5–1	-	4–16	4	-	
<i>F. chlamydosporum</i> complex (FDSC)	<i>F. chlamydosporum</i> (1)	4	2	>16	4	0.25–1	

^a AMB, amphotericin B; VRC, voriconazole; PSC, posaconazole; NATA, natamycin; TBF, terbinafine; '-', no data available for the species.

Developments in taxonomy of *Fusarium* have had a major impact on our understanding of drug susceptibility profiles and species-specific differences between the newly recognised species [12]. For example, *Fusarium solani* complex exhibits in vitro susceptibility profiles that on average are higher than those of the *Fusarium fujikuroi* complex [13]. Minimum inhibitory concentrations (MICs) are generally >4 µg/mL for both posaconazole and voriconazole for most species. Despite these modest activities, both triazoles have been used successfully in patients with amphotericin B–refractory fusariosis (Table 1) [14–16]. There is an ongoing, prospective, multicentre study recruiting participants to evaluate the safety of voriconazole in the treatment of invasive aspergillosis and rare moulds, including *Fusarium* in children (ClinicalTrials.gov identifier: NCT00836875), but results have not yet been published.

Although resistance mechanisms in *Fusarium* are not entirely understood, amino acid alterations and/or overexpression of CYP51, the gene encoding sterol 14 α -demethylase, might be involved in azole resistance, similar to *Aspergillus* [17]. On the other hand, prolonged use of triazoles in the environment has raised concern about acquired resistance in *Sporothrix* spp., *Candida albicans*, *Cryptococcus neoformans* and *Aspergillus fumigatus* [18–21]. However, in the latter, fungi resistance develops among previously susceptible strains after exposure to the antifungal agent.

In most fungi, clinical isolates are thought to be more resistant to antifungals than environmental isolates, because of antimicrobial exposure during prolonged therapy in chronically-infected patients. As *Fusarium* is intrinsically resistant, i.e. strains are not susceptible even prior to confrontation with the antifungal, all isolates of a species show similar behaviour. Pujol et al compared 38 strains of clinical origin and 20 from environmental sources against different drugs and demonstrated similar activity against both groups of fungi [22]. The MIC values were generally high, with the only exceptions being amphotericin B and ketoconazole, which were more active against the environmental strains. However, many structurally similar antifungals, including azoles, are used in both hospitals

and agriculture, and show similar susceptibility profiles against both clinical and environmental isolates of *Fusarium* spp. [23].

4. Onychomycosis

Fusarium onychomycosis is one of the most common non-dermatophyte mould infections [24]. Frequencies vary between 1% and 16% [25,26]. Appropriate treatment is recommended because of the risk of dissemination from a local nail lesion upon increased immunosuppression [27]. The infections are clinically indistinguishable from onychomycosis by dermatophytes, and present as distal subungual, proximal subungual and total dystrophic infections [25,26]. *Fusarium* paronychia is often associated with onychomycosis and is characterised by periungual purulent inflammation, similar to that induced by *Candida* species [28,29]. The main species complexes responsible for onychomycosis are *F. oxysporum* and *F. solani*, with *F. fujikuroi* being less frequently involved [30]. Direct examination with KOH reveals thin, irregular hyphae, and confirmation of aetiology is by repeated culture and absence of growth of dermatophytes and yeasts [25]. Dermatophytes are susceptible to terbinafine and voriconazole, whereas *Fusarium* species show higher MICs, with large variability [2,23,31]. *Fusarium dimerum* is the complex with the lowest MIC ranges and is mostly susceptible to itraconazole (0.03–16 µg/mL), terbinafine (0.03–0.5 µg/mL) and voriconazole (0.5–8 µg/mL), whereas *F. oxysporum* is more susceptible to terbinafine (0.25–16 µg/mL) than to other antifungals. *Fusarium solani*, the most commonly isolated species complex, has high MICs for all antifungals, ranging from 16 to 64 µg/mL [32]. All species are resistant to fluconazole, and studies with posaconazole show large variations (range 0.5–16 µg/mL) [23,33,34].

Therapeutic outcome of *Fusarium* onychomycosis, particularly subungual cases, is variable. Itraconazole is usually applied at doses of 200 to 400 mg/d, either daily or intermittently (pulse therapy). A second commonly used drug is terbinafine at doses of 250 to 500 mg/d, sometimes combined with topical ciclopirox and

amorolfine lacquer, or with keratolytics, such as urea [28,29]. *Fusarium* paronychia can be treated with the drugs mentioned or with topical treatment, preferably occlusive to achieve better concentrations in skin and nails [35].

5. Keratitis

Fusarium keratitis is one of the most common causes of mycotic keratitis and can cause irreversible blindness. The infection usually develops from trauma, particularly with vegetable matter, contact lenses, foreign bodies, or surgery, and is favoured by empirical topical antibiotics and steroids [36]. It is characterised by inflammation, conjunctival erythema and an irregular central corneal ulcer (80%), with raised edges and growth in extension and depth, and there may be hypopyon, satellite lesions and corneal opacity [36]. Early diagnosis with direct microscopic examination, culture of the fungus and specific polymerase chain reaction (PCR) is essential. As in other fusariosis, keratitis is mainly caused by the *F. solani* and *F. oxysporum* complexes, and less frequently by *F. dimerum*, *F. chlamydosporum*, and *F. temperatum* [37,38]. In vitro susceptibility results show that variable MICs are obtained with amphotericin B and voriconazole [39].

Multiresistance limits the antifungal treatment options for *Fusarium* keratitis. Amphotericin B is usually very irritating to the corneal epithelium. It can be used intercamerally and intrastromally, but in randomised controlled trials this drug did not show greater efficacy than topical application (eye drops). However, it is mostly active after endophthalmitis has developed, and it is the compound that reduces hypopyon quickly [40,41]. A recent in vivo study in rabbits showed that amphotericin B combined with a chitosan-modified nanostructure lipid carrier decreases ophthalmic irritation and promotes drug penetration, with chitosan being an effective transport vehicle in keratin [42].

Natamycin 5% has been the most widely used topical polyene for keratitis, and although in vitro results show relatively high MICs in most *Fusarium* strains, it proved to be effective in clinical trials [23,36,43]. For example, Sharma et al concluded that it is more effective than voriconazole (1%), and considered it the best antifungal for use as monotherapy, particularly in incipient cases [44]. O'Day et al recommended natamycin 5% (50 mg/mL) solution as first choice for treatment of filamentous fungal keratitis, including *Fusarium*, particularly in superficial infections [45]. Lalitha et al reported that natamycin has a lower relative MIC than amphotericin B in a comparative study of different antifungal agents [46]. In another clinical trial comparing the efficacy of natamycin vs. voriconazole, there was no difference between the two drugs in terms of healing time and final visual acuity [47]. Voriconazole 1% has a good penetration and tolerability, although its activity was lower than natamycin against *Fusarium* keratitis in comparative studies [48]. Voriconazole has been used in regimens combining topical (10 mg/mL eye drops) and oral (400 mg/d) administration, with good results, particularly when a hypopyon is present. This regimen is considered useful to prevent dissemination and development of endophthalmitis [48]. Al-Hatmi et al recently observed a significant in vitro synergy of natamycin with voriconazole, itraconazole or micafungin [49]. Prajna et al reported equal or inferior efficacy of 1% voriconazole compared with 5% natamycin eye drops in a clinical trial, although in cases of *Fusarium* keratitis natamycin is known to be significantly more active than voriconazole [44,50,51].

In vitro and in vivo studies show that posaconazole has a broad spectrum against many fungi, including *Fusarium* spp., and is effective against most agents that are resistant to itraconazole and fluconazole [52,53]. Experience with its use in ocular infections is still limited, but initial results are encouraging. In one case report, *F. solani* did not respond to treatment with natamycin and amphotericin B, but responded to posaconazole with 200 mg 4 times daily

associated with topical use (100 mg/mL prepared from an oral solution), and the patient completely recovered [54]. Tu et al described three cases of keratitis due to *F. solani* that were progressing to endophthalmitis and unresponsive to treatment with oral and topical voriconazole, and a rapid therapeutic response to posaconazole was achieved [55].

Other drugs that have been tested for *Fusarium* include topical miconazole, which proved effective in an experimental study with less frequent dosing (1.2 to 10 mg) and can be used for topical administration as a 1% (10 mg/mL) solution mainly for superficial infections [56]. Further comparative controlled studies are needed to demonstrate the real benefits of this drug.

6. Deep infections

Over the last two decades there has been a progressive increase in the incidence of invasive *Fusarium* infections in severely compromised patients. Patients with the highest risk are those with haematological malignancy, intensive chemotherapy and/or a corticosteroid regimen, recipients of solid organ or stem cell transplant leading to prolonged and profound neutropenia of <500 cells/mm³ and/or severe T-cell immunodeficiency [57]. Environmental factors also play a role, e.g. contamination of water reservoirs has been the cause of hospital outbreaks with *Fusarium* [58,59]. Patients with disseminated fusariosis frequently present with lung involvement, positive blood cultures, metastatic skin lesions, and cellulitis [60]. Notably, positive serum galactomannan antigen testing has been reported in some patients with documented invasive fusariosis [61]. Despite advances in therapy and early diagnosis, invasive fusariosis remains associated with high morbidity and up to 70% mortality [7].

Prior to the voriconazole era, the initial approach to treating invasive fusariosis was to administer high-dose (>5 mg/kg/d) liposomal amphotericin B [7,62]. Some retrospective studies involving patients with invasive fusariosis and haematological malignancies treated with amphotericin B (either deoxycholate or lipid formulations) showed improvement in 32–46% of patients, and of those patients, only 13–21% were still alive 90 days after diagnosis [63–65]. However, the overall response rates in immunocompromised hosts were dismal. In addition, few animal studies have been conducted to evaluate the effectiveness of amphotericin B, which did not prove to be effective either in neutropenic or immunocompetent animals [7,66–68]. After FDA approval in 2002, voriconazole became the first-line treatment [69]. Voriconazole is preferred to amphotericin B because of its lower toxicity and higher clinical efficacy against fusariosis [70]. Muhammed et al reported that voriconazole is effective in treating fusariosis, particularly when intolerance to, or failure of, the amphotericin B formulation warrants the use of voriconazole [24]. Nucci et al suggested using liposomal AMB (3 mg/kg/d) as first-line therapy, while intravenous voriconazole is used at a loading dose of 6 mg/kg every 12 h for two doses [71]. For some patients, this combination is used as first-line therapy before antifungal susceptibility testing results are available because of the variable susceptibility of *Fusarium* spp. to antifungal agents.

Perfect et al reported that voriconazole resulted in a favourable response in 5 (45%) of 11 patients with fusariosis who were refractory to standard therapy [65]. Nucci et al reviewed 233 published cases from 11 countries, of which 92% had a haematological disease [57]. Treatment of systemic fusariosis was evaluated in two periods: 1985–2000 (period 1, n = 121) and 2001–2011 (period 2, n = 112). During period 1, 63% (76/121) of patients were treated with deoxycholate amphotericin B, 18% (22/121) with lipid formulations of amphotericin B and 2% (2/110) with voriconazole. In contrast, voriconazole (36/112, 32%) was more frequently used in period 2 compared with deoxycholate amphotericin B (34/121, 30%), and lipid formulations of amphotericin B (12/112, 11%). The 90-day

probability of survival in periods 1 and 2 was 22% and 43%, respectively. Combination therapy of voriconazole plus a lipid formulation of amphotericin B was used in 21 patients. In period 2, the 90-day probability of survival was 60% in patients treated with voriconazole, 53% in those treated with a lipid formulation of amphotericin B, and 28% in those treated with deoxycholate amphotericin B. Open-label and compassionate clinical trials have demonstrated that voriconazole shows excellent activity against the majority of *Fusarium* species [72]. Voriconazole treatment is associated with a survival rate of approximately 40% compared with the historical 10% success rate of amphotericin B [73]. In addition, voriconazole is available in both oral (tablet and suspension) and intravenous formulations, with a bioavailability of greater than 90% with the oral drugs.

Posaconazole has been recommended for prophylaxis against fungal infections in neutropenic patients [74]. It proved to be effective in animal models of invasive fusariosis caused by isolates with reduced in vitro susceptibility [75]. A study of 21 patients with haematological malignancies initially treated with amphotericin B, which was associated with severe infusion-related toxicity and nephrotoxicity, showed a 50% overall response to posaconazole [15]. Several studies showed that patients responded favourably to posaconazole, which has been proposed for salvage therapy of disseminated fusariosis in patients who were refractory to conventional therapy or with intolerance to amphotericin B [16,76–79]. Notably, breakthrough *Fusarium solani* infection in a patient with acute myeloid leukaemia on posaconazole prophylaxis has been reported [78].

Isavuconazole has MICs equivalent to, or higher than, other triazoles against *Fusarium* species [23]. In two clinical trials (SECURE and VITAL), 7 patients with fusariosis were treated with isavuconazole as primary therapy, resulting in 44% 90-day survival [80]. *Fusarium* species are intrinsically resistant to echinocandins (casposfungin, micafungin, and anidulafungin) with MICs of >16 mg/L [2]. Surprisingly, casposfungin was recently reported to cure a breakthrough *Fusarium* fungaemia in a patient with acute leukaemia treated with amphotericin B [81]. Recently, Hassler et al reported on treatment of 10 patients with prolonged neutropenia and invasive fusariosis [82]. The treatment consisted of voriconazole as monotherapy (n = 2) and combination therapy of voriconazole, either with a lipid formulation of amphotericin B (n = 5) or an echinocandin (n = 3), with an overall 50% survival.

Antifungal combinations for fusariosis have not been evaluated using animal models or in clinical trial settings. Data on combination therapy for fusariosis are limited to a few case reports with amphotericin B deoxycholate plus voriconazole, casposfungin plus amphotericin B deoxycholate, and amphotericin B deoxycholate plus terbinafine [83–87]. In vitro combination of amphotericin B and ravuconazole has synergistic interaction against clinical isolates of *Fusarium* [88]. Spader et al reported synergy for the combinations of amphotericin B with casposfungin (68.7%), amphotericin B with rifampin (68.7%), amphotericin B with 5-flucytosine (59.3%), and amphotericin B with voriconazole (37.5%) [89]. However, in one study, the majority of *Fusarium* isolates tested using the combination of amphotericin B and voriconazole displayed neither a synergistic nor an antagonistic interaction between these two antifungal agents [90]. Recently, Martin-Vicente et al reported on double and triple in vitro combinations for strains belonging to the *Fusarium solani* complex [91]. All of the double combinations showed a high percentage of synergy against this species, with anidulafungin/voriconazole and amphotericin/anidulafungin being the most active (87.5% synergy). Amphotericin/voriconazole showed 62.5% synergy. The triple combination (voriconazole/amphotericin/anidulafungin) showed 87.5% synergy.

When possible, antifungal treatment should be combined with surgery and reversal of immunosuppression. In 2014, the European

Fungal Infection Study Group and the European Confederation of Medical Mycology recommended voriconazole or a lipid formulation of amphotericin B with strong (AII) and moderate (BII) support, respectively, as optimal management for invasive fusariosis [92]. Nucci et al demonstrated a 21% increase in survival rate of invasive fusariosis during the last decade, associated with the use of voriconazole, either alone or in combination with other therapies [57].

Novel identification tools, such as MALDI-TOF MS, or non-culture diagnostic assays, enable both accurate and fast identification of *Fusarium* species in the clinical laboratory: further insight into antifungal susceptibility profiles associated with each species should help to choose an adequate first-line antifungal treatment and thus improve the prognosis of invasive fusariosis patients [93]. Susceptibility testing of clinical isolates is highly recommended in the clinical setting, not only because there are significant strain- and species-specific differences in antifungal susceptibility, but also for epidemiological studies to detect emergence of resistant strains [94]. Further data from animal models and clinical trials evaluating the optimal treatment strategy against *Fusarium* infections are needed to refine and improve treatment guidelines, which are currently based on data from relatively large, but uncontrolled case series.

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