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REVIEW

Fusariosis, a complex infection caused by a high diversity of fungal species refractory to treatment

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Abstract In recent years the number of opportunistic invasive fusariosis has increased significantly, the main factors involved in these infections being reviewed here. In spite of the extensive literature published the advances in the management of disseminated fusariosis have been very poor and it remains a severe infection, refractory to treatment and with a high mortality rate. There are no ideal therapies and the presence of neutropenia has a critical part to play in the outcome of the infection. At least 70 species have been involved in fusariosis. *Fusarium solani* species complex is responsible for nearly 60 % of the cases and *F. oxysporum* species complex for approximately 20 % of them. Most of the infections are caused by four species, i.e. *F. petroliphilum, F. keratoplasticum* and other two unnamed phylogenetic species. The efficacy of amphotericin B and voriconazole, the most used antifungal drugs, for treating invasive fusariosis are controversial but in general the percentage of patients cured in the different clinical trials is low. Infections by *Fusarium verticillioides* seem to have the best prognosis. The recent release of complete genome sequences of the most clinically relevant species and the emergence of fungal genomics offer excellent opportunities for examining the multifactorial processes of *Fusarium* pathogenicity. Using knockout mutants of genes encoding sequence-specific proteins, several virulence factors have been characterized.

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Introduction

Fusariosis is, after aspergillosis, the second most common mould infection in humans. Up until the 1980s, the cases of fusariosis reported were mainly superficial, such as keratitis and onychomycosis, or locally invasive, but since then disseminated infections have increased substantially, mainly affecting patients with haematological malignancies [1–6]. Disseminated fusariosis, the main topic of this review, is particularly frequent in patients with allogeneic hematopoietic stem cell transplantation (HSCT) due to greater immunosuppression and profound and prolonged neutropenia. Outcome is worse in patients receiving corticosteroids than in those not receiving such therapy [3]. Probably, and similarly to aspergillosis, most of the disseminated fusarioses are acquired by inhalation of airborne microconidia. However, the bigger size of those in comparison to the conidia of *Aspergillus* (8–16 x 2–4 μm in *F. solani* versus 2.5–3 μm in *A. fumigatus*) makes infection by inhalation less likely than in aspergillosis. Most of the pathogenic species of *Fusarium* have been found in environmental samples, including plumbing systems of hospitals [7]; however, in a study that investigated the environmental sources of *Fusarium* infections in a tertiary-care centre it was demonstrated that the most likely source of infection was the external environment rather than nosocomial sources, such as water [8]. Disseminated infection is characterized by persistent fever, which is refractory to broad-spectrum antibiotic treatment, and by skin lesions with a central necrosis. Although not completely elucidated, the role of the innate immunity and particularly the Toll-like receptors and T-cell defences seems to be crucial in the progression of fusariosis [5]. Considering the erratic and poor response of the antifungal treatment to disseminated fusariosis, the presence of infections involving skin or nail should be carefully investigated before initiating immunosuppressive therapy since it has been shown that such lesions can be a focus for fungal

dissemination. Treatment can be complemented by putting neutropenic patients in rooms protected with HEPA filters and positive pressure [5]. Regardless the treatment, successful outcome of disseminated infection depends on the degree and persistence of immunosuppression, with practically a 100 % death rate for persistent neutropenic patients [5].

Virulence

Data on murine infections seems to demonstrate that *Fusarium solani* is the most virulent species complex, since under those experimental conditions five *F. solani* strains were able to kill all animals tested, as opposed to the 100 % survival of animals infected with *F. proliferatum, F. oxysporum* or *F. verticillioides* [9]. The complete genome sequences of representative strains of the human pathogenic species *F. oxysporum*, *F. solani* and *F. verticillioides* are already available [10, 11] and, although defining virulence factors in opportunistic agents is always challenging, the use of comparative genomic tools will allow one to identify potential virulence factors and increase knowledge of the pathogenesis mechanisms of these important opportunistic fungi. In recent years, di Pietro et al., using a well-characterized tomato-pathogenic isolate of *F. oxysporum* f.sp. *lycopersici*, whose complete genome has recently sequenced [10], and molecular disruption techniques on selected genes encoding sequence-specific proteins, have been able to characterize some important virulence determinants of that fungus in mammals. They have tested a single fungal isolate to study virulence mechanisms in plant and mammalian pathogenesis. Using this multihost model, they demonstrated that some virulence factors are specific for plants, some for animals and others common to both [12]. Using a disseminated infection in mice by that fungal isolate, Ortoneda et al. [12] demonstrated that mutations in the chitin synthase encoding gene caused alterations in the cell wall of the conidia, inducing important deformations in their surface. The resulting swollen conidia were retained in the pulmonary blood vessels, causing the death of the animals within 24 h by respiratory insufficiency. At the same time, mice infected with the wild-type strain survived 5–12 days. Knockout mutants of *wc1* that encode white collar 1, a photoreceptor that perceives light and generates signals that stimulate cellular responses, such as carotenoid biosynthesis, spore formation, and phototropism, among others, showed a marked reduction in virulence in mice. However, the mechanisms involved in such loss of virulence are unclear since they might not be attributable to its defects in carotene accumulation and hydrophobicity, because both alterations were light dependent and the fungus remained in the dark during the infection. The reduced virulence of the knockout mutants might be explained by the existence of Wc-1-dependent signal transduction pathways in *F. oxysporum* that control the production of other secondary metabolites in dark conditions [13]. While individual virulence determinants may vary between different pathogen-host systems, the signalling pathways that control fungal pathogenicity are remarkably conserved. Prados-Rosales et al. [14] demonstrated that a mitogen-activated protein kinase, Fmk1, and a G protein β subunit, Fgb1, are components of distinct signalling pathways that collectively control the virulence of *F. oxysporum* in mice. PacC is part of an intracellular signalling system in several filamentous fungi that responds to ambient pH, which is needed to establish invasive fusariosis [12]. Using explanted donor corneas, it was demonstrated that PacC-regulated genes appear to be involved in fungal adaptation to the corneal microenvironment and in filamentous growth into stromal tissue. The PacC-regulated phenotype could thereby affect adaptive filamentous growth at the ocular surface and facilitate opportunistic fungal invasion into the traumatized human cornea [15].

Other proteins necessary for virulence mechanisms of *F. oxysporum* in mammals are Fpr1, a pathogenesis-related PR-1-like protein that is secreted and proteolytically processed by the fungus and whose function depends on the integrity of the proposed active site of PR-1-like proteins [16], and also some members of the velvet protein complex (VeA, VelB and LaeA), which regulates hyphal growth, conidiogenesis and secondary metabolism [17]. It was demonstrated that they promote chromatin accessibility and transcription of gene clusters encoding biosynthesis of the siderophore ferricrocin as well as the mycotoxin beauvericin, which both function as virulence determinants in this fungus [17]. As occurs in other human fungal pathogens, such as *Aspergillus fumigatus, Candida albicans*, and *Cryptococcus neoformans,* the bZIP protein HapX functions in *F. oxysporum* as a key regulator of iron homeostasis and virulence. Deletion of *hapx* does not affect iron uptake but causes derepression of genes involved in iron-consuming pathways, leading to impaired growth under iron-depleted conditions [18].

The clinically relevant *Fusarium* spp.

The genus *Fusarium* comprises at least 200 species, grouped into approximately ten phylogenetic species complexes [19], most of them being plant pathogens or soil inhabitants. Species of *Fusarium* (anamorphs) have been associated with different ascomycete teleomorphs, i.e. *Gibberella, Nectria, Neocosmospora, Haematonectria, Cyanonectria, Geejayessia* and *Albonectria.* Two different names have been used to refer to the anamorph or to the teleomorph of a single species. However, on January 1, 2013 the International Code of Nomenclature for algae, fungi and plants prohibited the use of the dual nomenclature [20]. Therefore, for pleomorphic fungi, i.e. those that have asexual and sexual stages, such as *Fusarium,* one name must now be chosen. Concerning *Fusarium,* a

number of experts in the study of this fungus recently proposed that the genus *Fusarium* be recognized as the unique name for a group of species of importance in plant and animal pathology and mycotoxicology [21]. Approximately 70 species of *Fusarium* have been involved in infections in humans and other animals, most of them grouped into several species complexes (Table 1). Although some of the morphospecies of *Fusarium* involved in human infections can be identified by using microscopy and cultures (Tables 2 and 3), it requires a high degree of expertise. Important references for the morphological identification of *Fusarium* are the classical works of Gerlach and Nirenberg [23], Booth [24] and Leslie and Summerell [25]. However, most of the pathogenic species of *Fusarium* remain unnamed and can only be identified by multilocus sequence typing (MLST) approaches. It has been demonstrated that approximately 60 % of all human infections are caused by members of the *Fusarium solani* species complex (FSSC) and 20 % by the *F. oxysporum* species complex (FOSC). However, not all the isolates of *F. oxyxporum* are capable of growing at 35–37 °C and thus of causing invasive infections, since thermotolerance is a prerequisite for virulence. The rest of mostly human infections are mainly produced by members of the *Fusarium incarnatum equiseti* species complex (FIESC), *Giberella fujikuroi* species complex (GFSC), *Fusarium chlamydosporum* species complex (FCSC) and *Fusarium dimerum* species complex (FDSC) [7].

Most human infections are caused by only four species: *F. petroliphilum, F. keratoplasticum* and two unnamed phylogenetic species belonging to the FOSC and FDSC complexes [26] (Table 4). The ribosomal RNA genes sequences, especially those of the ITS region, widely used in fungal phylogeny, identification and bar-coding, possess small phylogenetic signals within *Fusarium*, and the presence of duplicated divergent alleles in that region complicates the usefulness of this marker with these fungi [19, 27]. For molecular identification of fusaria three different loci have been recommended: the translation elongation factor 1α (*EF-1α*), the largest subunit of RNA polymerase (*RPB1*) and the second largest subunit of RNA polymerase (*RPB2*). Based on these loci, DNA sequence databases have been constructed, which are Web-accessible at FUSARIUM-ID (http://isolate.fusariumdb.org/guide.php) and CBS-KNAW (http://www.cbs.knaw.nl/fusarium/) and can be used for reliable identification of clinical isolates.

Table 1 *Fusarium* species involved in human infections grouped into species complexes

F. incarnatum - F. equiseti species complex (FIESC)
F. lacertarum
F. equiseti
18 unnamed species
F. sambucinum species complex (FSAMSC)
F. armeniacum
F. brachygibbosum
F. sporotrichioides
F. tricinctum species complex (FTSC)
F. acuminatum
F. flocciferum
2 unnamed species
Gibberella fujikuroi species complex (GFSC)
F. napiforme
F. guttiforme
F. verticillioides
F. thapsinum
F. nygamai
F. acutatum
F. fujikuroi
F. proliferatum
F. sacchari
F. ananatum
F. subglutinans
F. oxysporum species complex (FOSC)
3 unnamed species
F. chlamydosporum species complex (FCSC)
3 unnamed species
F. concolor
F. cf. lateritium
F. solani species complex (FSSC)
F. falciforme
F. lichenicola
F. keratoplasticum
F. petroliphilum
17 unnamed species
F. dimerum species complex (FDSC)
F. delphinoides
F. penzigii
F. dimerum
2 unnamed species

Diagnosis

In the clinical diagnosis of disseminated fusariosis in severely neutropenic patients, skin lesions and positive blood cultures are very important [5]. In contrast to aspergillosis, here blood cultures are of particular help because they are positive in nearly 50 % of disseminated fusariosis [5, 28]. In general, fungemia must be considered an important predictor of fatal outcome, since its presence usually represents dissemination and high tissue burden with fast progression [29]. However, the definitive identification usually relies on time-consuming culturing methods of the appropriate samples and microscopy. A critical point for the correct diagnosis of fusariosis is the sampling procedure. Considering the fact that mixed

Table 2 Relevant morphological characteristics of *Fusarium* spp. involved in human infections (morphological terms described in [22])

Fusarium dimerum species complex
- Colonies growing slowly, less than 2–3 cm diameter in 10 days
- Only monophialides are produced
- Macroconidia short, generally 1–2 septate, with non-distinct foot-shaped cells
- Microconidia absent or scarce
- Chlamydospores, single or in pairs, can be present

Fusarium concolor
- Colonies growing rapidly, aerial mycelium whitish to incarnadine sometimes tinged cherry by the substrate mycelium
- Mono- and polyphialides are present
- Microconidia abundant
- Chlamydospores abundant in pairs, chains or clusters.

Fusarium chlamydosporum species complex, *Fusarium sambucinum* species complex, *Fusarium tricinctum* species complex
- Colonies growing rapidly, aerial mycelium white or tan, never light purple
- Mono- and polyphialides are present
- Macroconidia with no distinct foot-shaped cell
- Microconidia abundant
- Chlamydospores single or in long chains

Fusarium incarnatum equiseti species complex
- Colonies growing rapidly, aerial mycelium white or tan, never light purple
- Mono- and polyphialides are present
- Macroconidia with the apical cell extended and whip-like
- Microconidia absent or sparse
- Chlamydospores in long chains or large clumps

Fusarium lateritium
- Colonies growing moderately slow; aerial mycelium white
- Only monophialides are produced
- Microconidia absent or sparse
- Chlamydospores in long chains or large clumps

Gibberella fujikuroi species complex
- Colonies growing moderately slow; aerial mycelium white or light purple
- Mono- and polyphialides
- Macroconidia very thin, needle-like with thin walls
- Microconidia abundant in chains and false heads
- Sporodochia orange to yellow to tan
- Chlamydospores usually absent, but with few exceptions (F. napiforme)

Fusarium oxysporum species complex
- Colonies growing rapidly; aerial mycelium white or light purple
- Only monophialides are present
- Macroconidia very thin, needle-like with thin walls
- Microconidia abundant, in false heads only
- Sporodochia cream or orange to yellow or tan
- Chlamydospores single or in chains

Fusarium solani species complex
- Colonies growing rapidly; aerial mycelium white, never purple
- Only monophialides are present
- Microconidia abundant, in false heads only
- Sporodochia cream or blue-green to blue
- Chlamydospores single or in chains

fusarial infections exist and that more than one species could be involved, diagnosis should not rely on the identification of a single colony and a unique sampling site [30, 31]. Guarro et al. identified a strain of *F. verticillioides* from a blood culture and a strain of *F. solani* from skin biopsy, both samples from the same HIV positive patient [30]. Detection of only one species when more species are present may result in erroneous treatment.

Histopathology and radiology methods can be of help in the diagnosis but neither are specific and can be confused with other fungal infections like aspergillosis, which requires different management. In a recent study on pulmonary fusariosis involving patients with haematological malignancies, chest CTs revealed the presence of nodules and masses suggestive of the infection by an angioinvasive mould in 82 % of patients versus only 45 % with chest radiography [32]. The identification of clinical isolates of *Fusarium* at genus level is not difficult when the characteristic sickle, boat-shaped, multiseptate macroconidia are present [22]. However, the identification of the species is challenging and although some species can be identified by morphological criteria (Tables 2 and 3), the use of molecular methods is recommended for confirmation. A promising approach for the identification of clinical isolates of *Fusarium* is

Table 3 Key to the identification of the *Fusarium* species of the *Gibberella fujikuroi* species complex

1. Macroconidia with an acute apical cell	*F. acutatum*
1′. Macroconidia without acute apical cell	2
2. Chlamydospores present	3
2′. Chlamydospores lacking	4
3. Presence of polyphialides; microconidia oval or club-shaped	*F. nygamai*
3′. Polyphialides lacking; microconidia lemon-shaped or napiform	*F. napiforme*
4. Microconidia in false heads	*F. subglutinans,* *F. guttiforme,* *F. sacchari,* *F. ananatum,*
4′. Microconidia on chains	5
5. Chains of microconidia produced on polyphialides	*F. proliferatum* *F. fujikuroi*
5′. Chains of microconidia produced on monophialides	6
6. Colonies commonly showing yellow pigment	*F. thapsinum*
6′. Colonies not yellow	*F. verticillioides*

Table 4 The four species and sequence types of *Fusarium* most common in human infections [26]

Species (sequence type)	Species complex
Fusarium oxysporum species complex (ST 33)	FOSC
Fusarium keratoplasticum (ST a)	FSSC
Fusarium keratoplasticum (ST b)	FSSC
Fusarium petroliphilum (ST d)	FSSC
Fusarium petroliphilum (ST k)	FSSC
Fusarium dimerum species complex (ST a)	FDSC

the mass spectroscopy using matrix-assisted laser desorption ionization-time-of-flight (MALDI-TOF) [33]. This is a cost-effective technique that can generate results within 1 h and in a recent study was able to identify correctly 57 strains belonging to five species of *Fusarium* [34].

There is some controversy about the usefulness of the galactomannan test in the diagnosis of fusariosis. Nucci and Anaissie [5] pointed out that the test is negative in *Fusarium* infections and this together with a positive 1,3-β-D-glucan test in a high-risk patient with mould infection is highly suggestive of fusariosis. Conversely, other studies have demonstrated that a positive galactomannan test is a useful criterion in early diagnosis of fusariosis [35, 36].

Using a murine model, a duplex real time PCR (RT-PCR) assay has been shown to successfully quantify the DNA of *Fusarium* spp in lung tissue (sensitivity 87–93.9 %) and serum (sensitivity 42.8–86.7 %) of animals infected with those fungi [37].

In vitro antifungal susceptibility

Although up to now no breakpoints have been defined for *Fusarium* spp., in general, all the drugs have shown poor in vitro activity against these fungi [38–42] (Table 5), amphotericin B usually being the drug that shows the lowest MICs [42, 43]. The only drugs that have shown some activity in vitro are posaconazole against *F. verticillioides*, and terbinafine also against this and a few other species. Combinations do not generally offer better protection. In various studies the combination of terbinafine plus voriconazole showed synergy against different species of *Fusarium* [44–46], and although caspofungin alone has shown very high MECs against several species of *Fusarium*, that drug combined with other antifungals showed a strongly synergistic effect [47].

Treatment

Since there are no formal clinical trials for the evaluation of fusariosis treatment, the efficacy of the different therapies is based on the results of a few clinical cases or retrospective studies and the optimal treatment strategy remains unclear. In those diseases where clinical data on the different therapies is scarce the results obtained with animal studies can play an important role in guiding new treatments; however, in fusariosis the results obtained with animal models have been inconclusive, too [48]. In recent years numerous animal studies have evaluated different therapeutic strategies for the treatment of systemic fusariosis but the results have usually been discouraging [48]. In addition, *Fusarium* spp. show low virulence for mice, which implies the use of very high inocula, and are not pathogenic for guinea pigs [49], which are the most suitable animals for testing some drugs like voriconazole.

Unfortunately, the clinical response to the antifungals of the different *Fusarium* species is unknown since in numerous cases the species was not identified or its identity was doubtful. Although some authors recommend identifying clinical isolates of *Fusarium* at species level for optimal treatment [50], evidence seems to demonstrate that this practice may be very important for epidemiological studies but less useful for establishing the most suitable treatment. In vitro and experimental studies have shown that the different species of *Fusarium* are resistant to practically all the available antifungal drugs, with only irrelevant differences among the species.

The drugs that have been more effective against fusariosis are voriconazole, amphotericin B and posaconazole, although in general the clinical response to them must be considered only modest. Colony-stimulating factors or donor granulocyte transfusions have been added on several occasions to the antifungal therapy for neutropenic patients that responded to treatment but their particular role in the resolution of the infection is unknown.

Amphotericin B

In a study reported in 1998 [51] on the safety and efficacy of amphotericin B lipid complex in patients refractory to or intolerant of conventional antifungal therapy, 9 of 11 patients (82 %) with fusariosis showed a partial or complete response to treatment. However, in later studies the results were considerably poorer. Three retrospective studies involving patients with invasive fusariosis and haematological malignancies treated with amphotericin B (deoxycholate or lipid formulations) have shown efficacy (cure or improvement) in 32–46 % of patients, although only 13–21 % of them were still alive 90 days after diagnosis [3, 4, 50].

In murine studies the efficacy of amphotericin B, even at high doses, against several strains of *F. oxysporum* and *F. solani* was very poor, either testing neutropenic [52–54] or immunocompetent animals [55]. In one study, liposomal amphotericin B showed some efficacy in prolonging survival

but not in reducing fungal load in kidney [54], and in another study there was a contrary effect when that drug was administered as a prophylaxis, i.e. treatment was initiated before infection [56].

Voriconazole

Voriconazole has generally shown poor in vitro activity against *Fusarium* spp. (mean MICs=9 μg/ml against *F. solani*) (Table 5), which precludes in vivo efficacy. However, this drug has been effective in several cases of localized infections like peritonitis, pneumonia, cutaneous infection, disseminated in a solid tumour, etc. [reviewed in 57]; in neutropenic patients with disseminated infection the benefit of this drug is less clear; and in the clinical trials conducted so far the results of the therapy have been only modest. In three clinical studies that included a relatively high number of patients with fusariosis (11–73), complete or partial response to voriconazole was achieved in 45–47 % of patients [29, 58, 59]; however, in neutropenic patients the response rates were considerably lower, being only 5 % in Campo et al. [29]. In general, no significant differences in the outcome of patients treated with the drug were obtained, either as salvage or primary therapy [59]. A negative aspect related to the prolonged use of voriconazole is its reported association with breakthrough fusariosis. An association was present in at least two cases that involved leukemia patients, in one after the use of voriconazole as a prophylaxis [60] and in the other after the treatment of pulmonary aspergillosis [61].

In two experimental studies that evaluated the use of voriconazole in the treatment of murine infections by *F. oxysporum* or *F. solani,* its efficacy was very poor [52, 53].

Posaconazole

There has been less clinical experience with the use of posaconazole in the treatment of fusariosis than with amphotericin B and voriconazole. An important limitation of the use of this drug as first line therapy is the lack of currently available intravenous formulation. In a retrospective analysis of three independent, multicenter, open-label trials, Raad et al. [62] evaluated the outcome of 21 patients with fusariosis, 38 % of them being neutropenic, treated with posaconazole as salvage therapy. The study showed positive results (complete or partial response) in 48 % of patients. However, all but one patient had been treated initially with a lipid-based formulation of amphotericin B.

In experimental studies the results have been controversial. In two studies, posaconazole at high doses (50 and 100 mg/kg/day) showed efficacy against *F. solani* [63, 64] and in another this drug, even at high doses, exerted very poor efficacy against mice infected by each of two strains of *F. oxysporum* [53]. Such results are difficult to explain because there is no other experimental evidence that demonstrates whether *F. solani* responds better to the antifungal therapies than *F. oxysporum.* In addition, in one of those studies where posaconazole showed efficacy, the authors mention that results obtained with this drug were comparable to those of amphotericin B [63].

The lower efficacy of amphotericin B in comparison with the clinical trials that used voriconazole or posaconazole has been explained by the fact that the patients treated with salvage therapies survived long enough to receive a second treatment [5].

Table 5 Activities of conventional and new antifungal drugs against different species of clinical interest of the genus *Fusarium*

Species (nº isolates)	MIC (mg/L)[a]							
	TBF	AMB	*VRC*	PSC	ABC	KTC	RVC	ITC
F. solani (27)	>16	2.39	9.82	>16	>16	>16	>16	>16
F. oxysporum (28)	2.69	2.32	6.09	28.98	16.40	12.19	10.77	>16
F. verticillioides (24)	0.24	2.33	2.19	0.83	3.34	3.24	1.77	>16
F. proliferatum (9)	0.29	3.70	9.39	20.16	9.75	21.53	8.83	>16
F. incarnatum (9)	10.08	0.93	3.70	2.94	16	2.72	9.33	>16
F. chlamydosporum (8)	0.27	1.54	2.83	2.38	11.31	8.72	7.34	>16
F. nygamai (7)	0.34	3.28	6.56	32	9.75	21.53	8.83	>16
F. dimerum (7)	0.91	1.64	4	32	8.83	3.62	8.83	>16
F. sacchari (5)	0.14	1.52	3.03	2	6.06	18.38	5.28	>16
F. thapsinum (5)	0.44	2.64	2.64	>16	18.38	>16	18.38	>16
F. napiforme (3)	0.12	3.18	1.59	32	4	8	3.18	>16

[a] Determined according to the CLSI methods, after 48 h of incubation at 35 °C

ABC albaconazole, *AMB* amphotericin B, *ITC* itraconazole, *KTC* ketoconazole, *PSC* posaconazole, *RVC* ravuconazole, *TBF* terbinafine, *VRC* voriconazole

Echinocandins

Data concerning the use of echinocandins in fusariosis treatment is very scarce. These drugs are inactive in vitro and have shown poor efficacy in experimental studies. In one murine study, micafungin did not work for animals infected with *F. solani* [53], and in another, caspofungin at 1 but not 5 mg/kg/day improved survival but did not reduce tissue burden [56].

Does *F. verticilioides* respond better than other species to antifungals?

In most of the reported clinical cases of fusariosis and even in clinical trials the identification of the fungal isolates to species level was not usually carried out. Regarding that, and considering the high number of unnamed phylogenetic species involved in cases of fusariosis revealed in recent studies, it is difficult to assess whether successful outcomes depend on the species that cause the infection. However, data mainly based on experimental studies seems to indicate that the species that responds best to treatment is *F. verticillioides*. This species is generally the most susceptible to antifungal drugs, at least to posaconazole (mean MICs of 0.83 μg/ml), terbinafine (mean MICs of 0.24 μg/ml) and voriconazole. Although voriconazole usually shows high MICs against *Fusarium* spp., in the case of *F. verticillioides* MICs are only relatively high (mean MICs=2.19 μg/ml). The fact that at least two drugs showed high in vitro activity together with the results shown in animals where *F. verticillioides* was less virulent than *F. solani* [9] would suggest a better prognosis for those infections caused by *F. verticillioides* than for those caused by *F. solani*. However, in animal models some results have been controversial too. Monotherapies and combinations of voriconazole, amphotericin B and posaconazole showed poor efficacy in experimental murine infections by two strains of *F. verticillioides* [65], while the combination of liposomal amphotericin B and terbinafine showed good results [66]. In humans, the results of different therapies against *F. verticillioides* infections have been variable. The association of amphotericin B with caspofungin resolved a disseminated infection in a leukemia patient [67] and voriconazole resolved a fungemia in a liver transplantation patient [68]. More clinical studies are needed to confirm if there actually are significant differences in outcomes in the infections produced by different species of *Fusarium.*

Combined therapy

The poor, and in some cases only modest, activity shown in general by the monotherapies for patients against invasive fusariosis has prompted the use of different combination regimens. However, the clinical experience is only based on anecdotal observations and to ascertain the value of combination versus monotherapy. In deep-seated and disseminated fusariosis further studies are required with a much larger sample of patients [29].

The results of several clinical cases can be found in the literature where various combination regimens, including echinocandins-polyene, azole-polyene and polyenes or azoles plus terbinafine were tested to treat fusariosis. However, no statistical studies have been published that have evaluated whether or not combination therapy is more effective than monotherapy.

Amphotericin B plus voriconazole

Although in vitro and experimental studies do not support the use of the combination of amphotericin B plus voriconazole in treating fusariosis, such combination is the most commonly used in clinical practice with generally poor efficacy [69]. The in vitro interactions of the combination of those drugs have proven to be additive or subadditive but not synergistic [44]. In murine models the combination of voriconazole with amphotericin B against *F. oxysporum* showed the same very poor results as the respective monotherapies [53] while the use of such combined therapy against *F. solani* prolonged mice survival for the two strains tested, but only reduced tissue burden in mice infected by one strain [52].

Of the 20 reported cases of disseminated fusariosis treated with a combined therapy in the last 10 years, 14 responded positively, and in seven of those the clinical response was achieved before resolution of neutropenia. The best results were achieved with amphotericin B plus voriconazole (7 cases) followed by liposomal amphotericin B plus terbinafine (2 cases) [70]. In another recent study of six lung transplant patients with fusariosis treated with different therapies, including liposomal amphotericin B plus caspofungin or voriconazole, voriconazole alone and amphotericin B plus voriconazole, the only survivor was the patient treated with the latter combination [69]. The clinical evidence on the use of such combination is controversial. In the retrospective study of Lortholary et al. [59], the outcome shown by the patients treated with a combination of voriconazole plus any other drug, including amphotericin B, and those treated with only voriconazole was not significantly different.

Amphotericin B plus posaconazole

There is little clinical experience with the use of the combination of amphotericin and posaconazole. Based on a case that reported poor efficacy using such combination [71] it has been argued that its use should be avoided in disseminated fusariosis due to potential treatment failures. Nevertheless, the authors themselves recognized that the level of posaconazole was subtherapeutic due to the patient's poor

diet. This combination probably warrants further research because in experimental studies using murine models of disseminated infection by *F. oxysporum* where several drug combinations were tested, posaconazole combined with amphotericin B gave the best results [53].

Amphotericin B plus caspofungin

The combination of amphotericin B plus caspofungin has shown synergistic or synergistic to additive in in vitro interactions against *Fusarium* isolates [72]. In the clinical setting, two cases of disseminated fusariosis in ALL patients have been improved with the use of such combination. In both cases, suppressive therapy with voriconazole was continued; in one, the infection was resolved [73] and in the other the patient died [67]. In two clinical cases of invasive infections caspofungin showed usefulness with clinical and microbiological improvement when it was added to amphotericin B as a salvage therapy when amphotericin B alone failed [73, 74]. In a murine study, the combination of liposomal amphotericin B plus caspofungin did not improve the results of the respective monotherapies [56].

Voriconazole plus echinocandins

There is very little clinical experience with the combination of voriconazole plus an echinocandin. Labois et al. [75] described an infection by *F. solani* refractory to caspofungin as empirical therapy in a ALL patients, which improved with the addition of voriconazole to the treatment. A neutropenic patient with refractory biphenotypic lymphoblastic leukemia was successfully treated with the combination of voriconazole plus micafungin and the addition of donor granulocyte transfusions, recombinant interferon gamma-1b and GM-CSF. A previous treatment with posaconazole and amphotericin B had failed, although the antifungal dosages were subtherapeutic [71]. In an in vitro study the interaction of these two drugs against a strain of *F. solani* showed indifference [76] and in a murine model of disseminated infection by this species the combination was not able to resolve the infection [52].

Adjunctive therapies, such as surgical debridement of localized infections or removal of catheters, have been recommended by different authors.

Conclusions

Most of the cases of fusariosis are caused by species of the complex FSSC, some unnamed, which can only be identified by molecular methods. In vitro data demonstrates general resistance of *Fusarium* to practically all the available antifungal drugs, *Fusarium verticillioides* being the most susceptible species. Due to the universal antifungal resistance of these fungi the MIC determination is of poor value. This poor in vitro activity correlates with the lack of efficacy in animal models. Mortality remains high in spite of the availability of new antifungals. Clinical studies have shown modest efficacy of posaconazole and voriconazole, being considerably lower in neutropenic patients. Recuperation of neutropenia continues to be the most important determinant of outcome in these patients. There is little quality information on the real efficacy of combined therapies, amphotericin B plus voriconazole being the most used.

Conflict of interest The author declares no conflict of interest.

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