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Invasive fusariosis

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SUMMARY Invasive fusariosis is a serious invasive fungal disease, affecting immunocompetent and, more frequently, immunocompromised patients. Localized disease is the typical clinical form in immunocompetent patients. Immunocompromised hosts at elevated risk of developing invasive fusariosis are patients with acute leukemia receiving chemotherapeutic regimens for remission induction, and those undergoing allogeneic hematopoietic cell transplant. In this setting, the infection is usually disseminated with positive blood cultures, multiple painful metastatic skin lesions, and lung involvement. Currently available antifungal agents have poor *in vitro* activity against *Fusarium* species, but a clear-cut correlation between *in vitro* activity and clinical effectiveness does not exist. The outcome of invasive fusariosis is largely dependent on the resolution of immunosuppression, especially neutrophil recovery in neutropenic patients.

KEYWORDS *Fusarium*, fusariosis, immunocompromised, fungal infection

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INTRODUCTION

Fusarium species are ubiquitous fungi, widely distributed in the air, soil, and water, including seawater and community and hospital water distribution systems (1, 2). *Fusarium* is considered one of the five most important plant pathogens, with outbreaks of disease in cereals, resulting in significant agricultural losses (3). *Fusarium* species also cause disease in animals, especially aquatic animals such as dolphins, seahorses, and turtles (4). In humans, the most frequent diseases caused by *Fusarium* species are superficial: onychomycosis and keratitis (5, 6). Onychomycosis caused by *Fusarium* species is increasingly reported worldwide. It is difficult to treat superficial mycosis, with negative health consequences such as pain and impaired quality of life. In addition, in severely immunocompromised patients, onychomycosis may serve as a portal of entry for invasive disease, either locally invasive such as cellulitis and lymphangitis, or disseminated disease (7). *Fusarium* is the most frequent agent of fungal keratitis. Trauma and the use of contact lenses are common predisposing factors. Severe cases may evolve into corneal perforation and endophthalmitis (8).

In addition to onychomycosis and keratitis, *Fusarium* species cause invasive disease, which may be localized or, more frequently, disseminated. The latter occurs almost exclusively in severely immunosuppressed patients, particularly patients with acute myeloid leukemia (AML), acute lymphoid leukemia (ALL), and hematopoietic cell transplant (HCT) recipients (9). Finally, *Fusarium* species may cause allergic sinusitis, allergic bronchopulmonary disease, and mycotoxicosis (10–15).

PATHOGENESIS OF INVASIVE FUSARIOSIS

The main portal of entry of *Fusarium* species in cases of invasive disease is the airways, followed by the skin at sites of breakdown. As with invasive aspergillosis, after the inhalation of conidia, hyphae are formed in the alveoli, resulting in inflammation and bronchial dissemination. Subsequently, hyphae invade blood vessels, causing thrombosis and tissue infarction. The innate and adaptative immune responses are important in containing infections by *Fusarium* species and other filamentous fungi (16), with alveolar macrophages and neutrophils playing a major role in preventing hyphal formation and angioinvasion (17). Interferon-gamma and granulocyte colony-stimulating factor can enhance the phagocytic activity of monocytes and neutrophils (18, 19).

A remarkable difference between invasive fusariosis and aspergillosis is the frequent occurrence of positive blood cultures and metastatic skin lesions in the former (20). *Fusarium* microconidia produce yeast-like structures (adventitious sporulation). These small structures called aleuroconidia invade blood vessels causing fungemia and dissemination to various organs including the skin (21).

Animal models of invasive fusariosis in neutropenic mice showed a very high fungal burden, with no cell infiltration, whereas infection in non-neutropenic mice was characterized by necrosis, hemorrhage, macrophagic and neutrophilic infiltration, and a lower fungal burden (22). In addition to neutropenia, the inoculum size is an important predictor of outcome. In an animal model of non-neutropenic mice, intratracheal inoculation of 1×10^6 microconidia resulted in pulmonary infection, with a neutrophilic infiltrate and alveolar hemorrhage but no deaths. By contrast, the inoculation of 1×10^8 microconidia resulted in the rapid death—within 24 hours—of all mice (23).

FUSARIUM CHARACTERSITICS AND TAXONOMY

More than 300 phylogenetically different species of *Fusarium* grouped in more than 20 species complexes have been described, most of which are found in the environment (24). Most medically important *Fusarium* species belong to seven species complexes: *Fusarium solani* species complex (FSSC), *Fusarium oxysporum* species complex (FOSC), *Fusarium fujikuroi* species complex (FFSC), *Fusarium incarnatum-equiseti* species complex (FIESC), *Fusarium chlamidosporum* species complex (FCSC), *Fusarium dimerum* species complex (FDSC), and *Fusarium sporotrichoides* species complex (FSAMSC) (Table 1) (25).

TABLE 1 The most common *Fusarium* species complexes causing disease in humans and their respective species

Fusarium solani species complex	*Fusarium oxysporum* species complex	*Fusarium fujikuroi* species complex	*Fusarium incarnatum-equiseti* species complex	*Fusarium chlamidosporum* species complex	*Fusarium dimerum* species complex	*Fusarium sporotrichoides* species complex
F. falciforme	*F. oxysporum*	*F. acutatum*	*F. incarnatum*	*F. chlamydosporum*	*F. dimerum*	*F. aermeniacum*
F. keratoplasticum	Unnamed	*F. anthophilum*	*F. equiseti*		*F. delphinoides*	*F. brachygibbosum*
F. lichenicola		*F. andiyazi*	Unnamed		*F. penzigii*	*F. langsethiae*
F. petroliphilum		*F. fujikuroi*				*F.sporotrichioides*
F. pseudensiforme		*F. nygamai*				
		F. proliferatum				
		F. verticillioides				

Species belonging to FSSC account for approximately 50% of cases of invasive fusariosis (especially *F. falciforme* and *F. keratoplasticum*) with 20% of infections caused by FOSC. A few studies suggest geographic clustering of *Fusarium* species causing invasive disease. For example, most cases reported in Brazil belonged to the FSSC and FOSC species complexes (26, 27), while FFSC (mostly *F. verticillioides*, and *F. proliferatum*) were the most common agents reported from Europe (28). By contrast, a study evaluating 127 isolates from 26 countries (including isolates from the environment and from cases of superficial infection) did not show a clustering of species in a particular region of the globe (25).

Fusarium species grow easily and rapidly on different media without cycloheximide. On potato dextrose agar, the colonies have velvety to cottony surfaces and may present diverse colors: pink, yellow, red, gray, or white (Fig. 1). A distinguishing characteristic of the genus *Fusarium* is the production of hyaline banana-shaped macroconidia from phialides, with several transverse septa and foot cells at the base (Fig. 2). Ovoid microconidia may also be present, sometimes arranged in the apex of a conidiophore. In direct examnation of biological materials, the hyphae are irregular, hyaline, septate branched, with swollen cells. Hyaline, thick-walled chlamydospores may be present, intercalary or in terminal position. Species identification requires molecular methods (29–32) or matrix-assisted laser desorption/ionization flight time (MALDI-TOF) (33–38).

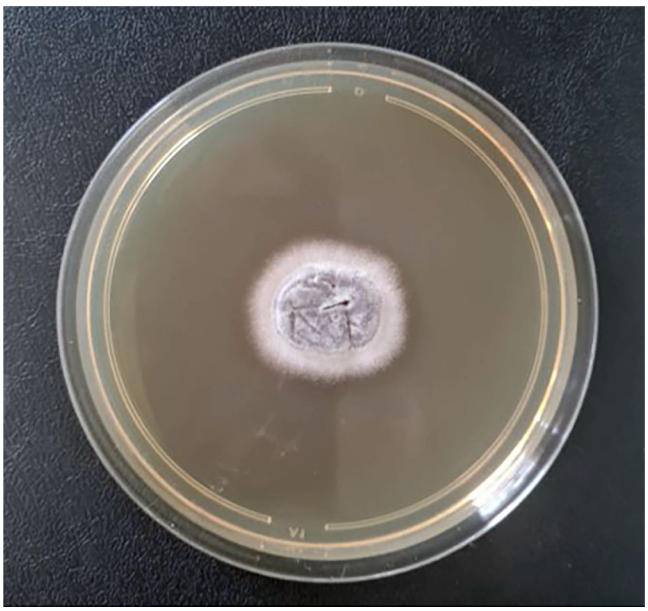

FIG 1 Culture of *Fusarium* species on potato dextrose agar after 7 days showing colony with white cottony margins and velvety center with shades of gray. (Courtesy of Dr. Geovanni Breda, reproduced with permission.)

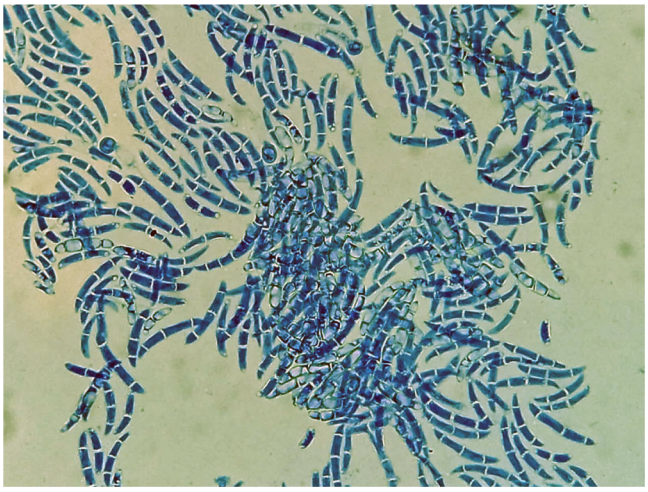

FIG 2 Microscopic morphology (×400) showing hyaline septate hyphae with banana-shaped macroconidia. (Courtesy of Dr. Geovanni Breda, reproduced with permission.)

EPIDEMIOLOGY AND CLINICAL SPECTRUM OF INVASIVE FUSARIOSIS

The clinical spectrum of invasive fusariosis is broad, and the clinical form depends on the portal of entry and the immune status of the host (Table 2). Immunocompromised patients are more likely to present with disseminated disease and immunocompetent patients usually have localized disease. In nonimmunocompromised patients with localized disease, skin breakdown may be present. This is the case of skin and soft tissue infection in burn patients (39–41) or after trauma (42), including combat-related injuries (43); skin ulcers in the setting of vascular insufficiency such as diabetes mellitus (44–47), venous insufficiency (48) and sickle cell disease (49); osteomyelitis after trauma (50–53) or surgery (54); arthritis after trauma (55, 56); endophthalmitis following eye injury (57), ocular surgery (58–60), or complicating keratitis (61, 62); peritonitis associated with peritoneal dialysis (63–66); and endocarditis following cardiac surgery (67, 68). *Fusarium* species may also be occasional agents of eumycetoma (69, 70). Immunocompetent patients may also develop sinusitis (71, 72), pneumonia (73, 74), fungemia (75), and rarely disseminated disease (76).

In immunocompromised patients, the most frequent clinical form of invasive fusariosis is that of disseminated disease with pneumonia, multiple skin lesions, and positive blood cultures. Most cases of invasive fusariosis in such patients occur in the context of remission induction of de novo or relapsed acute leukemia, or after allogeneic HCT (20). Occasional cases of disseminated disease have been reported in patients without classical immunosuppression, such as in a patient with acute respiratory distress syndrome and extracorporeal membrane oxygenation (77), and following multiple traumas (78, 79). Immunocompromised patients may also develop localized disease, including brain abscesses (80–82), endocarditis (83, 84), osteomyelitis (85, 86), sinusitis (87), and pneumonia (88).

Epidemiology of invasive fusariosis in patients with hematologic malignancies

The first case series of disseminated invasive fusariosis was reported in 1988. Nine cases of invasive fusariosis occurred over a 10-year period at a cancer center in the United States. Eight of these patients had hematologic malignancies, and four presented with positive blood cultures and metastatic skin lesions (89). In 1999, 43 cases of invasive fusariosis from the same institution were reported, with detailed characteristics of 54 additional published cases. The most frequent underlying disease was AML (53%), followed by ALL (16%) and most leukemic patients (83%) had relapsed disease. Fusariosis

TABLE 2 Clinical spectrum of invasive fusariosis

Immunocompetent patients	Immunocompromised patients
Skin and soft tissue infection	Disseminated disease
Osteomyelitis	Pneumonia
Arthritis	Fungemia
Endophthalmitis	Sinusitis
Peritonitis	Brain abscess
Endocarditis	Endocarditis
Eumycetoma	Osteomyelitis
Sinusitis	Arthritis
Pneumonia	Endophthalmitis
Fungemia	
Disseminated disease	

occurred after HCT in 12 patients (28%) and the diagnoses were made after engraftment in seven of those. Neutropenia was present in 84% of the 43 patients and 32% were receiving corticosteroids at the diagnosis of fusariosis (20).

In a multicenter retrospective study of 84 cases of invasive fusariosis in hematologic patients, AML and ALL were the most frequent underlying diseases (35% and 21%, respectively), followed by chronic myeloid leukemia (15%, all allogeneic HCT recipients). Fusariosis occurred in the context of HCT in 39% (33 cases, 29 of which were after allogeneic HCT). Among 79 patients with hematologic malignancies, 67 had active cancer at diagnosis of fusariosis and 40 were receiving treatment for relapsed disease. Neutropenia and corticosteroid therapy were present in 83% and 46%, respectively. The median duration of neutropenia before the diagnosis of fusariosis was 16 days (range 2–93) (90).

Detailed epidemiologic information regarding invasive fusariosis in HCT recipients was provided in a multicenter retrospective study of 61 cases (54 allogeneic and 7 autologous) (Table 3). The types of allogeneic HCT reflected the usual population of patients during the study period (1985–2001), with 48% of cases after receipt of HLA-matched related, 31% matched unrelated, and 10% mismatched related. The overall incidence of invasive fusariosis was 5.97 cases per 1,000 HCT, with a wide variation across centers (5.00–11.33 cases per 1,000 HCT), and the type of HCT: 4.21–5.0 after HLA matched related, 2.28 after HLA-compatible matched unrelated, 20.19 among mismatched related, and 1.4–2.0 among autologous HCTs (91).

Between 2007 and 2009, we conducted a prospective multicenter (eight sites) evaluation of the incidence of invasive fusariosis in Brazil among HCT recipients and patients with AML or myelodysplasia (MDS) receiving chemotherapy for remission induction. The 1-year cumulative incidence of invasive fusariosis among 237 patients with AML or MDS, 378 allogeneic HCT recipients, and 322 autologous HCT recipients was 5.2%, 3.8%, and 0.6% respectively (92).

In a recent prospective study evaluating the epidemiology of invasive fungal diseases (IFD) in four Brazilian centers between 2015 and 2016, the incidence of invasive fusariosis was 4.3% and 2%, respectively, in patients with AML and autologous HCT recipients, for an overall incidence of 1.6%. No case of fusariosis were diagnosed among allogeneic HCT recipients (93).

Two single-center studies confirmed the high frequency of invasive fusariosis in Brazil. The first was a retrospective study evaluating the etiologic agents of invasive mold disease (IMD) in patients with hematologic malignancies between 2004 and 2006. Among 29 cases of IMD, invasive fusariosis was the second most frequent (6 cases, 20.7%) (94). In the other study, 94 cases of IFD were diagnosed in 664 hematologic patients and 316 HCT recipients in a 10-year period. Invasive fusariosis was the second most frequent IFD (17 cases, 18.1%). The incidence of invasive fusariosis in patients with AML and allogeneic HCT recipients was 3.1%, for an overall incidence of 1.7% (95).

TABLE 3 Characteristics of 54 cases of invasive fusariosis in allogeneic hematopoietic cell transplant recipients

Time (days) of diagnosis after transplant	Neutropenia	Receipt of corticosteroids	GVHD[a]	Disseminated disease
0–30 (*n* = 20)	17 (85%)	12 (50%)	4 (20%)	18 (90%)
31–60 (*n* = 16)	5 (31%)	12 (75%)	14 (87%)	12 (75%)
100–365 (*n* = 10)	3 (30%)	5 (50%)	5 (50%)	4 (40%)
>365 (*n* = 8)	0	3 (38%)	8 (100%)	6 (75%)

[a]GVHD = graft versus host disease.

In Italy, a retrospective multicenter study reported all cases of mold infections diagnosed in hematologic patients in 14 hospitals between 1988 and 1997. Six cases of invasive fusariosis were diagnosed in 2 of the 14 hospitals (one case in one hospital and five in another). The incidence of invasive fusariosis in patients with acute leukemia was 0.06% (0.08% in AML and no case in ALL) (96). In a subsequent study from the same group, 15 cases of invasive fusariosis were diagnosed among 11,802 patients with hematologic malignancies treated in 18 centers (0.1%), with 13 cases among 3012 patients with AML (0.4%), one case in 1173 patients with ALL (0.08%), and one case in 3457 patients with non-Hodgkin's lymphoma (0.03%) (97). In another study, only three cases of invasive fusariosis developed among 1,249 allogeneic HCT (0.2%) (98).

A surveillance study evaluated the epidemiology of IFD in HCT recipients from 23 transplant centers in the United States. The investigators identified invasive fusariosis in 53 of 1514 HCTs (3.5%). The 1-year cumulative incidence of IFD caused by rare molds (including *Fusarium* species) was <0.3% (99).

A retrospective single-center study in a hospital in Israel described the characteristics of 87 cases of non-*Aspergillus* mold infections occurring in patients with hematologic malignancies and in allogeneic HCT recipients. Invasive fusariosis was the leading infection, accounting for 35% of cases, followed by mucormycosis (25%). As reported in other studies, most cases of fusariosis occurred in patients with acute myeloid leukemia and disseminated disease was the most frequent clinical presentation (100).

In Spain, a retrospective multicenter study evaluated the incidence and epidemiology of invasive fusariosis in neutropenic and non-neutropenic patients. Between 2000 and 2015, all cases of invasive fusariosis diagnosed in 18 centers were reviewed. A total of 58 cases were diagnosed, 44 in neutropenic and 14 in non-neutropenic patients. Most cases occurred in patients with hematologic malignancies (79%). The incidence of invasive fusariosis increased from 0.40 cases per 100,000 admissions during 2000–2009 to 0.79 cases per 100,000 admissions during 2010–2015 ($P < 0.01$), for an overall incidence of 0.55 cases per 100,000 admissions (101).

Investigators assessed the risk factors for invasive fusariosis in a multicenter prospective cohort of 237 patients with AML or MDS receiving induction remission chemotherapy and in 663 HCT recipients. There were eight cases of invasive fusariosis in the AML/MDS cohort (3.4%). The only significant variable associated with invasive fusariosis was active smoking, with a hazard ratio (HR) of 9.11 [95% confidence interval (CI) 2.04–40.71). In all, 17 cases (2.6%) developed in the HCT cohort, two among 318 autologous (0.6%) and 15 among 345 allogeneic HCTs (4.3%). Variables associated with invasive fusariosis in the early post-transplant period of allogeneic HCT (until day +40) were AML as underlying disease (HR: 4.38, 95% CI: 1.39–13.81), one of the eight centers (HR: 5.15, 95% CI: 1.66–15.97), and receipt of anti-thymocyte globulin in the conditioning regimen (HR: 22.17, 95% CI: 4.86–101.34). Factors associated with invasive fusariosis occurring after day +40 post-allogeneic HCT were a history of IMD before HCT (HR: 10.65, 95% CI: 1.19–95.39), non-myeloablative conditioning regimen (HR: 35.08, 95% CI: 3.90–315.27), and grade III/IV acute graft versus host disease (GVHD; HR: 16.50, 95% CI: 2.67–102.28). Cytomegalovirus (CMV) reactivation was also associated with invasive fusariosis (HR 5.99), but the *P* value was marginally significant ($P = 0.05$) (102).

Other studies evaluated risk factors for non-*Aspergillus* IMD following allogeneic HCT. Using data from the CIBMTR (Center for International Blood and Marrow Transplant Research) database, 52 cases of invasive fusariosis were identified between 1995 and 2008. Variables associated with invasive fusariosis occurring in the first-year post-transplant were umbilical cord blood as a stem cell source, with a relative risk (RR) of 3.11 (95% CI: 1.14–6.81) and prior CMV infection (RR: 2.72, 95% CI 1.24–5.97) (103).

As pointed out, most cases of invasive fusariosis occur in patients with hematologic malignancies, particularly in patients with acute leukemia. In the largest series of invasive fusariosis, 215 of 233 cases (92%) occurred in patients with hematologic diseases, and 150 of the 215 (69.8%) patients had AML, ALL, or MDS as an underlying disease. Other hematologic diseases included aplastic anemia, non-Hodgkin's lymphoma, multiple myeloma, and myelofibrosis. In most of these cases, invasive fusariosis occurred in the context of HCT (9).

Patients receiving ibrutinib and other Bruton kinase inhibitors are at increased risk of developing IDF, especially invasive aspergillosis (104). Recently, two cases of invasive fusariosis occurred in patients with chronic lymphocytic leukemia (CLL) receiving ibrutinib (105, 106). The first patient started ibrutinib as the fourth line of therapy and developed disseminated fusariosis 6 weeks after ibrutinib initiation. The second patient received ibrutinib as the sixth line of therapy and developed fusarial sinusitis after 4 years of ibrutinib.

Recently, chimeric antigen receptor T (CAR-T) cell therapy has been approved for the treatment of various hematologic malignancies including ALL, lymphoma, and multiple myeloma (107). Patients receiving CAR-T cell therapy are at increased risk of infection for various reasons including the cumulative immunosuppression associated with the underlying disease and prior therapies, the lymphodepleting chemotherapy, lymphopenia, hypogammaglobulinemia, and prolonged neutropenia (108). Bacteria and viruses account for most infections with only a minority caused by fungi (109). A case of invasive fusariosis was reported in a patient with refractory ALL who received CAR-T cell therapy, with a skin nodule and sinusitis (110).

Epidemiology of invasive fusariosis in other immunosuppressed patients

In contrast with the higher frequency of invasive fusariosis in patients with hematologic malignancies, including HCT recipients, invasive fusariosis is uncommon in solid organ transplant (SOT) recipients. For example, in a prospective survey of IFD in SOT recipients from 15 centers in the United States, 1,208 cases of IFD were diagnosed in a 5-year period, with only six cases of invasive fusariosis (111).

Cases of invasive fusariosis (either localized or disseminated) have been reported after liver (88, 112–117), kidney (118–124), lung (125–128), and multi-organ transplant (85, 129). Most cases of invasive fusariosis in liver transplant recipients occurred early after re-transplantation or rejection in the context of severe immunosuppression, with disseminated disease. By contrast, most cases in renal transplant recipients occurred years after transplant, with skin and subcutaneous nodules that evolved over weeks to months.

Sporadic cases of invasive fusariosis have been reported in other immunosuppressive conditions including patients with solid tumors (9, 130), chronic granulomatous disease (81, 131), AIDS (132, 133), hemophagocytic lymphohistiocytosis (134), chronic corticosteroid exposure (86), end-stage renal disease (84), primary immunodeficiency syndromes (135, 136) and, more recently, COVID-19 (137, 138).

Nosocomial acquisition of fusariosis, outbreaks, and pseudo-outbreaks

Since *Fusarium* species are widely encountered in the environment, invasive fusariosis may be acquired in the community. However, except for cases of localized disease associated with trauma in which the disease is community-acquired, it is difficult to identify whether the patient acquired fusariosis in the community or the hospital.

In the hospital, patients may acquire invasive fusariosis by airborne transmission, as shown in an outbreak in the hematology unit of a Brazilian hospital. Molecular typing was performed in 104 *Fusarium* species isolates recovered from the air of the unit and 15 isolates recovered from blood cultures. Genotypic relatedness was present in five isolates from the blood and seven from the air, belonging to FSSC, and in one FFSC bloodstream isolates and in one isolate recovered from the air of the same room occupied by the patient. A reduction in the incidence of invasive fusariosis coincided with the installation of water filters at the exit of faucets and showers in patients' rooms (139).

Fusarium species are frequently recovered from hospital water systems worldwide (140–142). In a prospective study conducted in a hospital in the United States, *Fusarium* species were present in the hospital water tanks and water-related structures such as shower heads, drains, and aerators. In addition, aerosolization of *Fusarium* species occurred after running the showers. Molecular methods of patients' and environmental isolates showed close relatedness, indicating the nosocomial source of invasive fusariosis (2).

In another study, an outbreak of 10 cases of invasive fusariosis diagnosed in a 2-year period in a children's cancer hospital was investigated. *Fusarium* species grew from the water of six patients' rooms, and from the air and other environmental sources in three rooms. Molecular typing showed relatedness between all *Fusarium oxysporum* isolates from the environment and two patients (143).

An outbreak of seven cases of fungemia due to *Fusarium verticillioides* (FFSC) was reported in a hospital in Greece. None of the patients had hematologic disease. An environmental source was not found, and the outbreak was resolved after the implementation of infection control measures consisting of intensive disinfection of patients' medication preparation and storage rooms (144). In another study, seven cases of catheter-related fungemia due to FOSC were diagnosed in a 5-month period at a pediatric cancer center. No environmental source was found, and the outbreak was controlled after the implementation of a multidisciplinary central line insertion care bundle (145).

An increase in the incidence of invasive fusariosis was observed in the hematology unit of a Brazilian hospital. Between 2001 and 2004, no cases of invasive fusariosis were diagnosed. In 2005, there were two cases, with an incidence of 2.47 cases per 1,000 admissions. The incidence increased to 4.95 in 2006, 16.78 in 2007, and 13.6 cases in 2008. A distinguishing feature of this outbreak was that in 17 of 20 cases (85%), a cutaneous portal of entry was present, either onychomycosis or interdigital intertrigo (7). In a review of skin lesions, 259 cases of invasive fusariosis were reported, and a cutaneous portal of entry was present in 11% of cases only (146). This prompted an environmental investigation, with the hypothesis that the hospital water was the source of infection. *Fusarium* species grew from 14 air samples, 44 swab samples of water-related structures, and 10 water samples. Molecular typing of these environmental isolates and 98 clinical isolates (55 from the hematologic patients and 43 from patients with superficial infections diagnosed in the dermatology outpatient clinic). Most clinical isolates belonged to the FSSC while most environmental isolates belonged to the FOSC. Furthermore, the predominant FSSC strains in patients were rarely found in the environment (147). The incidence of invasive fusariosis in the unit reduced in subsequent years without any intervention in the environment.

Interestingly, the incidence of superficial infections diagnosed in the dermatology outpatient unit caused by *Fusarium* species increased in the same period, suggesting that hematologic patients who developed invasive fusariosis were admitted with skin lesions that were overlooked at admission (7). Subsequently, a prospective study was conducted to investigate the frequency of skin lesions with positive culture for *Fusarium* species on admission of high-risk hematologic patients. Among 61 patients screened, alterations in the skin and/or nails were present in 32 patients (mostly interdigital intertrigo and onychomycosis) and 4 of these 32 patients had *Fusarium* species recovered

from their lesions. The presence of fusarial intertrigo or onychomycosis on admission was associated with the subsequent development of invasive fusariosis (148).

Pseudo-outbreaks of fusariosis have also been reported; three were associated with contamination of bronchoscopes by FOSC (149) and FSSC (150, 151). In a third pseudo-outbreak, sterile containers used to store and transport biologic materials for culture were contaminated by FFSC (152).

CLINICAL MANIFESTATIONS OF INVASIVE FUSARIOSIS

Clinical presentation of invasive fusariosis

The four most frequent clinical presentations of invasive fusariosis in immunosuppressed patients are as follows: (a) disseminated disease, (b) pneumonia, (c) fungemia, and (d) cellulitis or lymphangitis at sites of skin breakdown. Disseminated disease is the most frequent clinical presentation, and manifests as persistent or recurrent fever in the context of febrile neutropenia (20), with the concomitant or subsequent appearance of skin lesions (90), and involvement of other organs such as lungs, sinuses, and central nervous system. Blood cultures are frequently positive. Less frequently, the disease presents with persistent or recurrent fever and pneumonia (153).

Skin lesions

The skin is a frequent organ involved in invasive fusariosis, either as a primary infection or by hematogenous spread. The characteristics of skin involvement by *Fusarium* species were described in a study that evaluated 43 new cases of invasive fusariosis and 216 published cases. Among 232 immunocompromised and 27 immunocompetent patients, skin involvement was present in 70% of patients and was more frequent in immunocompromised patients (72% versus 52%) (146). Among 14 immunocompetent patients with skin lesions, 13 presented with localized infection, usually with a history of recent skin breakdown because of trauma, or onychomycosis. All patients with skin lesions associated with onychomycosis presented as cellulitis. By contrast, various patterns of lesions were present in patients with a history of trauma, including necrotic lesions, cellulitis, ulcers, and subcutaneous abscesses. Among 167 immunocompromised patients with skin lesions, 20 (12%) presented with localized lesions. Cellulitis at the site of preexisting onychomycosis (Fig. 3 and 4) was present in 8 of the 20 patients with localized skin lesions. Various patterns of skin lesions occurred in the other patients including necrotic lesions, abscesses, ulcers, and papular lesions. The most frequent skin lesions in immunocompromised patients were multiple disseminated painful erythematous papular or nodular lesions, with or without central necrosis (ecthyma gangrenosum-like) (Fig. 5). The necrosis is the result of invasion of the blood vessels of the dermis by hyphae, with subsequent thrombosis. Myalgia may occur in the context of disseminated metastatic skin lesions (20).

In addition to metastatic skin lesions, immunocompromised patients may present with localized skin involvement that subsequently disseminates to other organs. Among 14 patients with invasive fusariosis with a cutaneous portal of entry, the most frequent lesion was periungueal cellulitis with preexisting onychomycosis (6 cases), followed by interdigital intertrigo (6 patients) with or without lymphangitis (Fig. 6 to 8) (7).

Pneumonia

Lung involvement in fusariosis has many common features with aspergillosis, including the spectrum of clinical forms, similar clinical presentation, images, and fungal biomarkers (154). In a literature review of 357 cases of fusariosis diagnosed in immunocompetent and immunocompromised patients, pneumonia was reported in 152 cases (42%) and was more frequent in immunocompromised patients (46% versus 17.5%) (153). Among seven cases of pneumonia in immunocompromised patients identified in that study, lung involvement was part of disseminated disease in four. Bilateral lung involvement

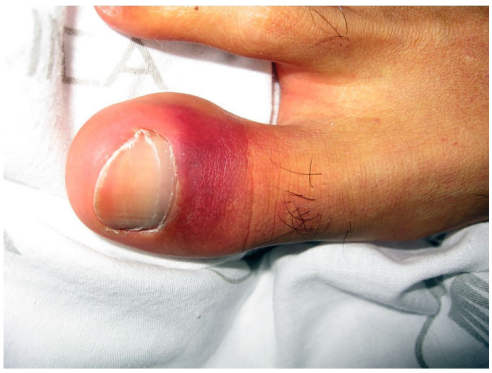

FIG 3 Periungueal cellulitis. (Courtesy of Dr. Marcia Matos, reproduced with permission.)

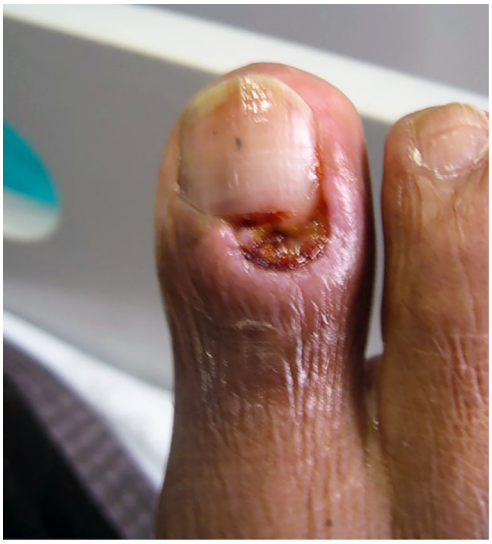

FIG 4 Periungueal cellulitis with tissue destruction. (Courtesy of Dr. Marcia Matos, reproduced with permission.)

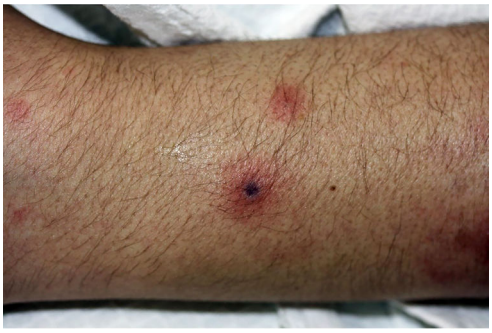

FIG 5 Nodular skin lesion with an area of central necrosis, with a typical appearance of ecthyma gangrenosum. (Courtesy of Dr. Marcia Matos, reproduced with permission.)

was present in five cases. More recently, another case of pneumonia occurred in an immunocompetent patient, with a right lung cavitary lesion (74).

In the literature review of 357 cases of invasive fusariosis, 24 cases occurred in SOT recipients. Pneumonia was reported in 10 cases, all in lung transplant recipients. Images

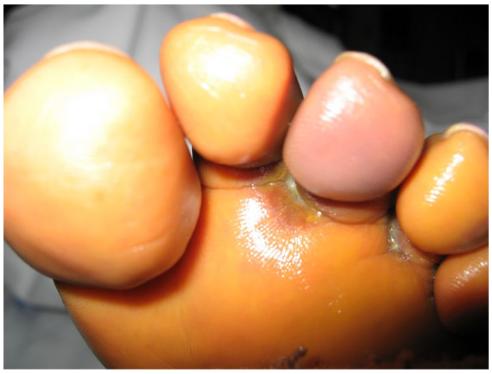

FIG 6 Interdigital intertrigo with cellulitis. (Courtesy of Dr. Marcia Matos, reproduced with permission.)

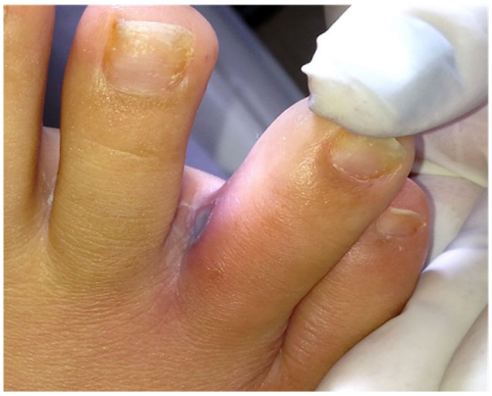

FIG 7 Interdigital intertrigo with cellulitis. (Courtesy of Dr. Hugo Morales, reproduced with permission.)

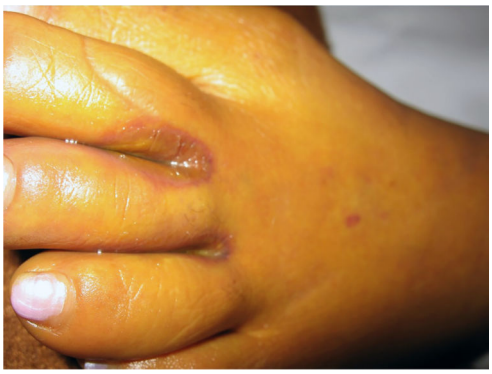

FIG 8 Interdigital intertrigo with cellulitis. (Courtesy of Dr. Marcia Matos, reproduced with permission.)

in the lungs included ground-grass infiltrates, nodules, alveolar infiltrates, bronchiectasis, and pleural effusion (153).

Lung involvement is frequent in patients with hematologic malignancies and HCT recipients: 54% and 84% in a series of 84 (90) and 43 cases, respectively (20). In a series of 233 cases (92% with hematologic diseases), lung involvement occurred in 49% of cases, with a higher frequency among neutropenic patients (55% versus 32% in non-neutropenic patients). Interestingly, patients with a cutaneous portal of entry were more likely to have bilateral lung involvement (88%) compared with patients with a presumed airborne portal of entry (68%), suggesting hematogenous spread to the lungs in patients with a cutaneous portal of entry (9).

Imaging of pulmonary fusariosis in patients with hematologic malignancies was characterized in 20 patients. Pulmonary symptoms were present in 95% of cases, and the most frequent manifestation was shortness of breath (14 patients). Chest CT scans of 11 patients were available for review. Nodules in nine (82%) patients, with sizes ranging from 0.3 to 2.7 cm, and a lung mass was present in six patients (size range: 3.0–6.7 cm). Mass or nodule was present in 9 of the 11 patients. No patient presented with a halo sign or tree-in-bud infiltrates (155).

Another study characterized the pattern of lung images in neutropenic patients with invasive fusariosis. Among nine cases, lung infiltrates were present in eight. The most frequent patterns of the image were ground-grass opacities and/or centrilobular micronodules and peribronchial consolidations with air bronchogram (5 cases each), followed by macronodules (4 cases). No patient presented with a halo sign. Compared with 11 cases of invasive aspergillosis, patients with invasive fusariosis were more likely to have small airway involvement and less likely to have macronodules with a halo sign (156).

In another study, 26 cases of invasive fusariosis were compared with 36 cases of invasive aspergillosis. Lung involvement was more frequent in aspergillosis (88.9% versus 50%, $P = 0.001$). The most frequent pattern of the image in cases of invasive fusariosis were macronodules (8 cases, 61.5%) (Fig. 9) and centrilobular micronodules and ground-grass infiltrates (7 cases each). The halo sign was present in three cases (Fig. 10). The only significant difference between cases of fusariosis and aspergillosis was a higher proportion of a halo sign in aspergillosis (62.5% versus 23.1%, $P = 0.02$) (154).

Sinusitis

Sinusitis is a frequent manifestation of invasive fusariosis, either occurring as a localized disease or, more commonly, as part of a disseminated disease. In a review of 294 cases of invasive fusariosis, sinusitis was reported in 54 cases (18%), with only two cases occurring in immunocompetent individuals (157). These patients presented with chronic infection. Among immunocompromised patients, in 70% sinusitis was part of disseminated disease. In a series of 233 cases of invasive fusariosis (92% occurring in patients with hematologic diseases), sinusitis was reported in 72 cases (31%).

Sinusitis may present as a radiologic finding with sinus opacities in a febrile neutropenic patient, or with nasal discharge and obstruction, with or without necrosis of mucosal surfaces and periorbital and nasal cellulitis. In patients with suspected fusarial sinusitis, nasal endoscopy with biopsy may yield the diagnosis (157).

Fungemia

Fungemia is frequent in invasive fusariosis, alone or (more frequently) as part of a disseminated disease. Indeed, *Fusarium* species are the leading agents of fungemia caused by molds in patients with hematologic malignancies (157). Among 84 patients with hematologic disease and a diagnosis of invasive fusariosis, fungemia was reported in 46 (55%), with 37 cases as part of disseminated disease and nine without apparent involvement of other organs (90). Occasional cases of catheter-related fungemia have been reported, including immunocompetent individuals (75, 112, 145). Typically, fungemia is the sole clinical manifestation of infection, the patient is in good general clinical conditions, and catheter removal plus a short course of antifungal therapy results in control of the disease.

Disseminated fusariosis

Disseminated disease is by far the most frequent clinical presentation of invasive fusariosis in severely immunocompromised patients such as those with profound neutropenia. In a series of 233 cases of invasive fusariosis, disseminated disease was present in 72% (9). In another study, disseminated disease occurred in 39 of 58 patients

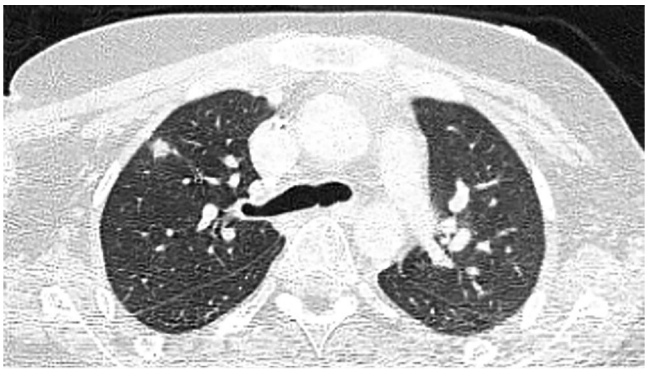

FIG 9 Chest computed tomography showing macronodules in both lungs.

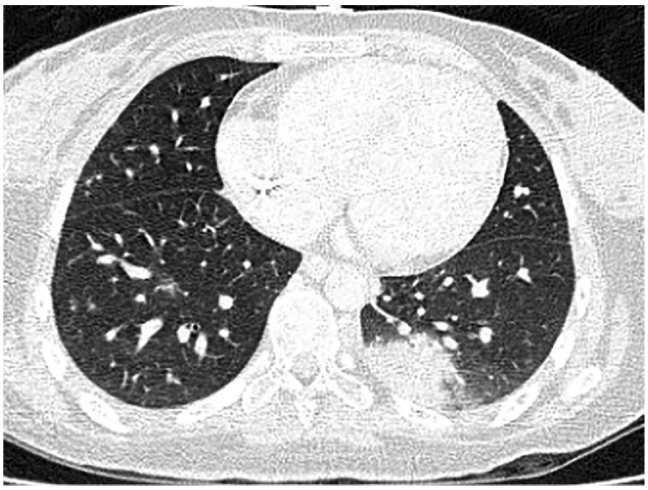

FIG 10 Chest computed tomography showing a large nodule with a halo sign in the left lung.

with invasive fusariosis (67.2%), with a higher incidence in neutropenic patients (79.5% versus 28.6% in non-neutropenic patients (101).

The typical presentation of disseminated fusariosis is that of the sudden appearance of various painful skin lesions in a persistently febrile neutropenic patient. Myalgia is frequent and the patients usually present with a toxic appearance (Fig. 11 and 12). In addition to lungs and sinus involvement, other organs affected include the liver, spleen (Fig. 13), eyes (endophthalmitis) (Fig. 14 to 16), and joints (55, 158).

DIAGNOSIS OF INVASIVE FUSARIOSIS

Apart from the clinical presentation, the diagnosis of invasive fusariosis relies on direct examination, culture, and/or histopathology of different biologic materials. In a series of 84 hematologic patients with invasive fusariosis, culture alone was the source of diagnosis in 65 patients (77%), and culture + histopathology in the remaining 19 patients. The most frequent sources of diagnosis by culture were the blood and the skin (90). In another study of 233 cases of invasive fusariosis, the diagnosis was made by culture alone in 138 cases (59%), culture plus histopathology in 83, and histopathology alone in 3 cases. The most frequent sources of diagnosis were the skin (100 cases) and the blood (85 cases) (9).

In a neutropenic patient who presents with typical skin lesions of invasive fusariosis (erythematous painful nodules), the fastest way of establishing a preliminary diagnosis of invasive fusariosis is by performing the direct examination of a fragment of skin biopsy.

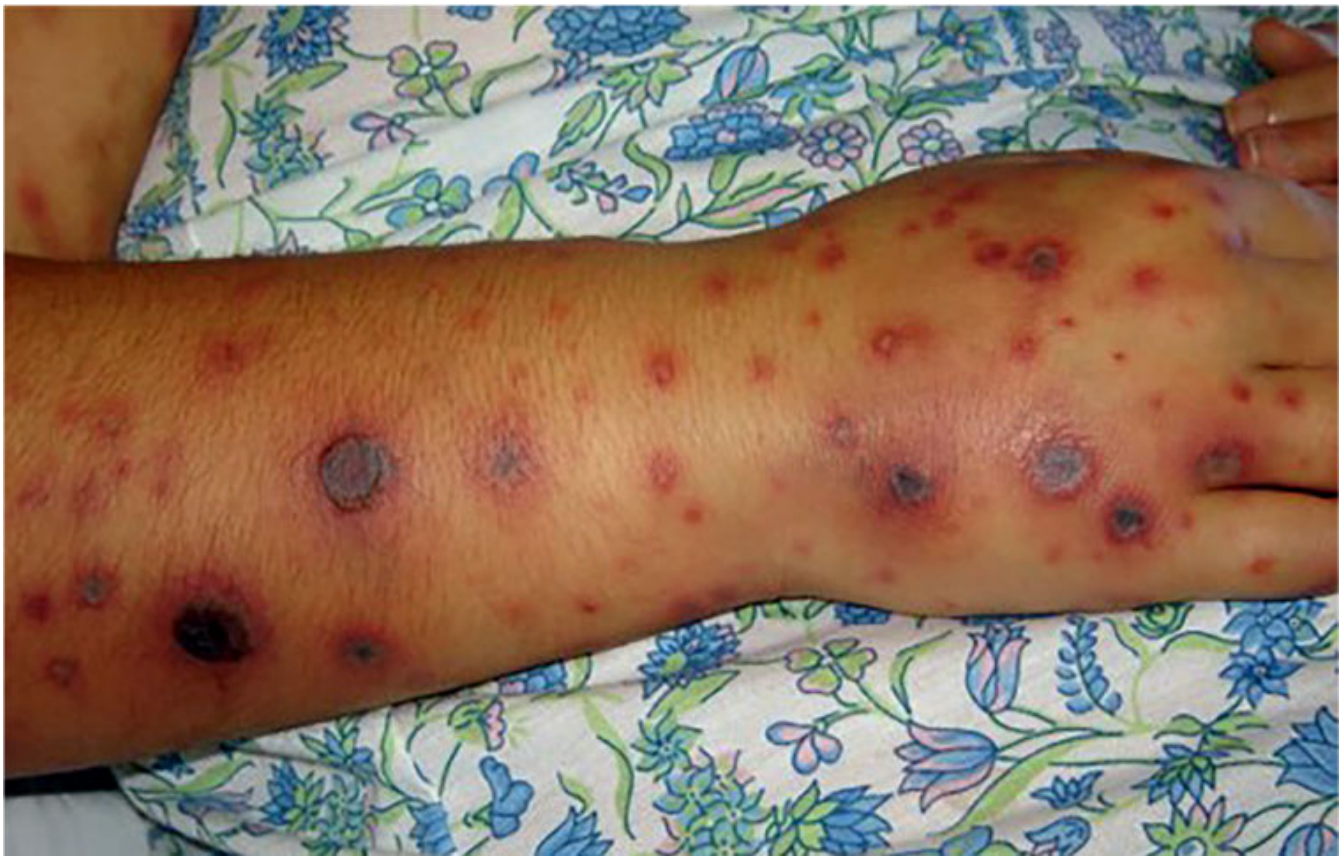

FIG 11 Disseminated skin lesions and toxemic appearance. Lesions at various stages of evolution: papular and nodular lesions with and without central necrosis. (Courtesy of Dr. Marilza Campos Magalhães, reproduced with permission.)

In this context, a direct examination showing septate acute branching hyaline hyphae is highly suggestive of invasive fusariosis and should prompt the immediate start of appropriate antifungal therapy. The biopsy must be deep enough to identify hyphae invading blood vessels of the dermis in the histopathologic examination of the skin. In addition, one fragment of the biopsy should be placed in formalin for histopathology and another in sterile saline for direct examination and culture. This combination of culture and histopathology is crucial to establish a confirmatory diagnosis of invasive fusariosis because in tissue various hyaline fungi have the same picture. Therefore, in the absence of culture showing the growth of *Fusarium* species, the histopathologic diagnosis should be of hyalohyphomycosis, unless the fungus is identified in paraffin-embedded tissue by *in situ* hybridization (159) or real-time quantitative PCR (160).

As mentioned before, fungemia is a frequent manifestation of invasive fusariosis. Two studies evaluated the performance of fungal media in growing *Fusarium* species. In the first study, the authors compared the performance of selective fungal medium with that of standard aerobic media. For lower inocula, fungal growth was detected faster in the fungal bottle (161). The other study evaluated the performance of fungal media versus bacterial media with concomitant bacterial and fungal infection and concluded that blood culture bottles with fungal media should be preferred for optimal fungal growth (162).

Until recently, species identification was only achieved by molecular methods, generally available only in reference laboratories (29–32). More recently, MALDI-TOF has become available in routine laboratories and has been an efficient method for the early identification of fungi at the species level, including *Fusarium* (33–38). In one study

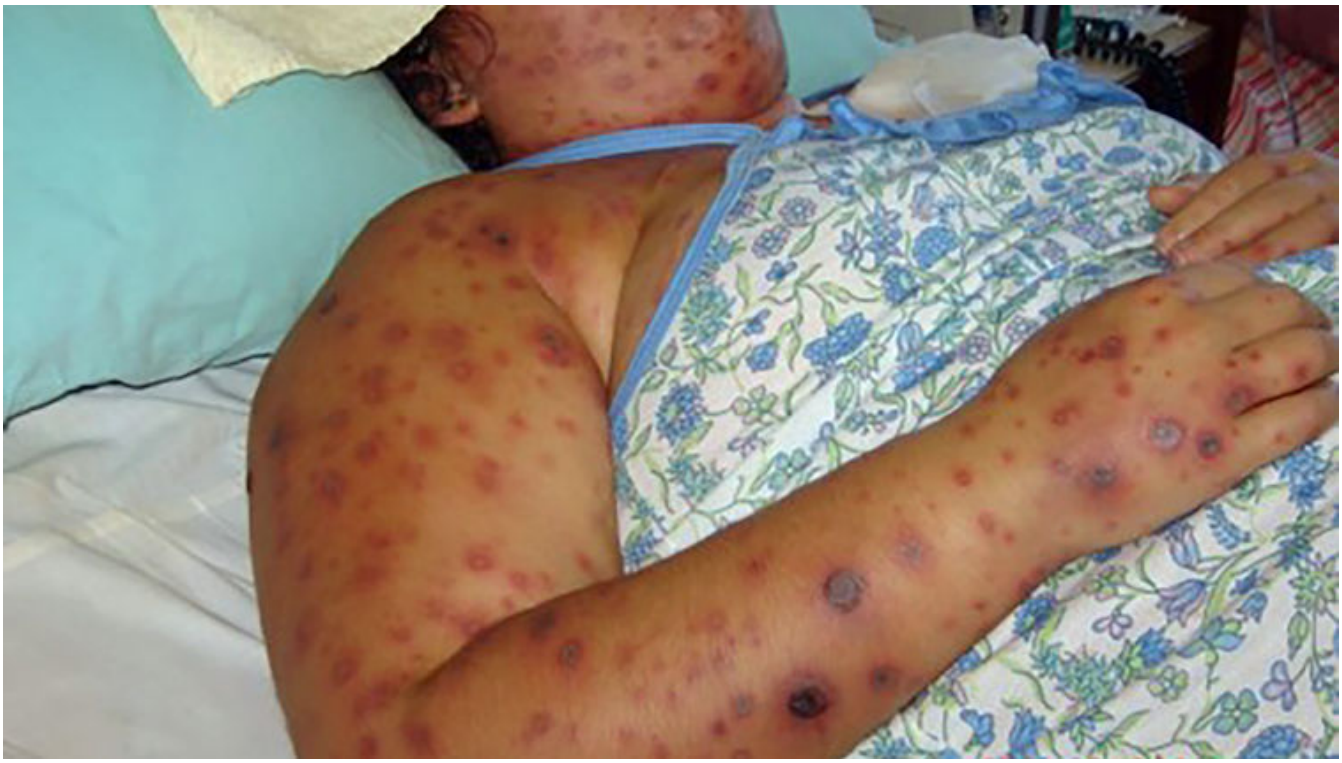

FIG 12 Disseminated skin lesions and toxemic appearance. Lesions at various stages of evolution: papular and nodular lesions with and without central necrosis. (Courtesy of Dr. Marilza Campos Magalhães, reproduced with permission.)

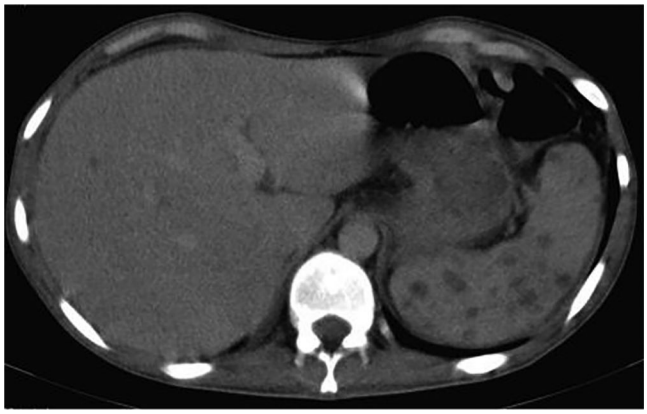

FIG 13 Nodules in the spleen.

evaluating 289 *Fusarium* isolates, MALDI-TOF correctly identified all species complexes and 82.8% of isolates at the species level (34).

Patients with invasive fusariosis may have a positive *Aspergillus* galactomannan (GMI) test in the serum. In a study, 11 patients with invasive fusariosis caused by distinct species had at least two GMI tests performed per week. Nine of these 11 patients had repeated positive GMI results, with an index ranging from 0.5 to 7.7, in the absence of isolation of *Aspergillus* species in the culture of bronchial secretions or of other respiratory specimens (163). In another study, 18 hematologic patients with invasive fusariosis and at least one GMI test performed within 2 days before or after the diagnosis were evaluated. In total, 15 (83%) had at least one positive GMI test, with sensitivity and specificity of 83% and 67%, respectively. The test was positive before the diagnosis of invasive fusariosis in 11 of the 15 cases (73%), at a median of 10 days (range 3–39) (164).

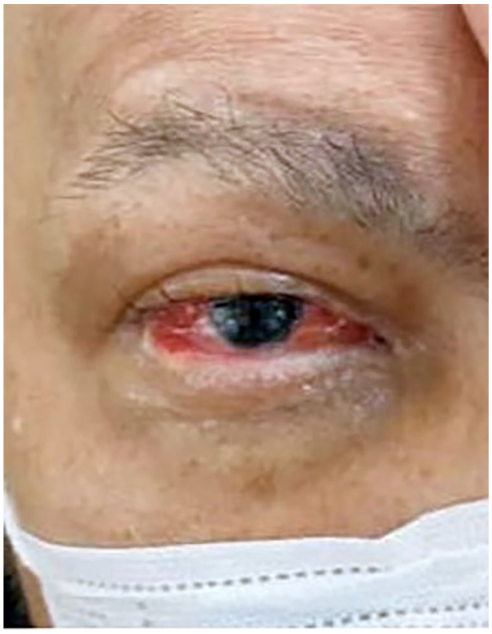

FIG 14 Endophthalmitis with periorbital cellulitis. (Courtesy of Dr. Clara Rosemberg, reproduced with permission.)

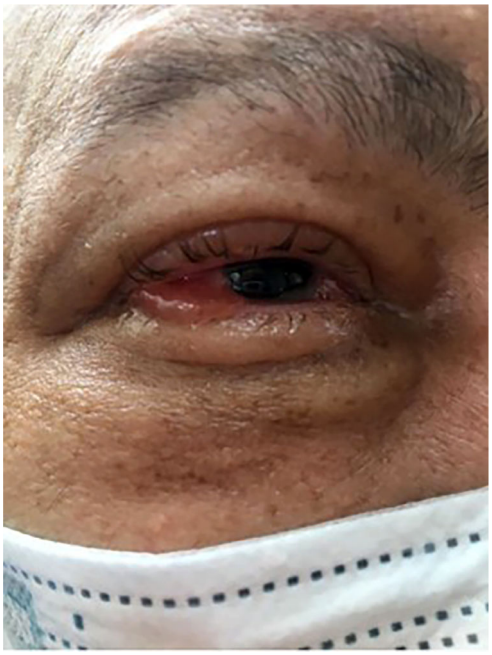

FIG 15 Endophthalmitis with periorbital cellulitis. (Courtesy of Dr. Clara Rosemberg, reproduced with permission.)

In another study reporting the characteristics of 65 cases of invasive fusariosis diagnosed in a multicenter prospective surveillance study, 10 had positive GMI tests. Three of these 10 patients had positive cultures for *Aspergillus*, suggesting that the positive tests represented mixed infection (165). More recently, investigators compared the cases of invasive aspergillosis to those with invasive fusariosis diagnosed in a Brazilian center. All patients were followed with serial (2–3×/week) serum GMI, with a median of 12 tests among 35 patients with aspergillosis and 13 tests among 26 patients with fusariosis.

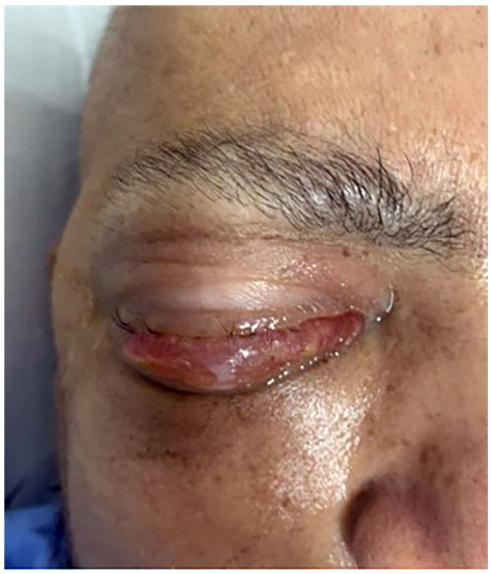

FIG 16 Endophthalmitis with periorbital cellulitis. (Courtesy of Dr. Clara Rosemberg, reproduced with permission.)

Serum GMI was positive in 89% of patients with aspergillosis and 73% of patients with fusariosis. The authors did not observe differences in the median number of positive tests, value of the first positive, or the peak GMI (154). Taken together, one should be cautious in interpreting a positive GMI in high-risk hematologic patients cared in areas with high incidence of invasive fusariosis.

Patients with invasive fusariosis may also have a positive 1,3-beta-D-glucan (BDG) test in the serum. In a study, serum samples of 13 patients with invasive fusariosis were tested for BDG. In all, 12 patients (92%) had at least one positive BDG test in the serum. Interestingly, the test was positive before the diagnosis of fusariosis in 11 patients, at a median of 10 days. However, given the high sensitivity and false-positive rates of the test (166), the positive predictive value was 7% only, considering two positive tests, suggesting that BDG is more useful to rule out rather than to confirm the diagnosis of invasive fusariosis (167). In another study, 81 blood samples from 15 patients with invasive fusariosis were tested for BDG. The rate of positivity was 58.3% (168).

In a study using a quantitative PCR assay as fungal biomarkers for the earlier diagnosis of invasive hematogenous fusariosis, the investigators detected *Fusarium* species in the blood in 14 of 15 patients with invasive fusariosis, at a median of 6 days before the diagnosis was confirmed by positive cultures or biopsy. The test was negative in all control samples, including patients with other IFD or those without IFD (168).

MANAGEMENT OF INVASIVE FUSARIOSIS

The management of invasive fusariosis depends on the immune status of the host and the form of the disease. We consider surgical debridement with or without systemic antifungal therapy in most cases of disease limited to the skin and soft tissues. By contrast, we always apply systemic antifungal therapy for infections in deeper organs and/or homogeneously disseminated with or without surgical debridement.

Antifungal susceptibility

Fusarium species typically exhibit high minimum inhibitory concentrations (MICs) to most antifungal agents, with higher MICs against azoles such as voriconazole, posaconazole, and isavuconazole, compared with amphotericin B. Fluconazole and the echinocandins have no activity against *Fusarium* species. In general, *Fusarium solani* and *Fusarium verticillioides* (FFSC) have higher MICs for azoles compared with other species.

Investigators evaluated 1,150 *Fusarium* species isolates belonging to various species complexes and established epidemiologic cutoff values (the highest MIC that would categorize an isolate as wild type, that is, without known mechanisms of resistance) (169). Among 608 FSSC isolates, the epidemiologic cutoff values (μg/mL) for amphotericin, voriconazole, and posaconazole were 4, 16, and 32, respectively. For FOSC, the epidemiologic cutoff for amphotericin B, voriconazole, and posaconazole was 4, 8 and 8 μg/mL, respectively (170).

Among 14 *Fusarium* species isolates tested, the MIC of isavuconazole was 16 μg/mL in one isolate, and >16 μg/mL in the remaining 13 isolates (171). In another study, the MIC50 of 14 isolates was >8 μg/mL for isavuconazole (172).

The *in vitro* activity of olorofim, an antifungal agent under development, was evaluated against 45 FOSC and 16 FSSC clinical isolates. Olorofim exhibited good *in vitro* activity for FOSC. When a 50% inhibition was considered, the MIC ranges were between 0.03 and 0.5 μg/mL and 0.06 and >4 μg/mL when a 100% inhibition was the endpoint. For FSSC, the activity was lower, with MIC ranges of 0.25–1 μg/mL and 1–>4 μg/mL at 50% and 100% inhibition, respectively. The authors concluded that since olorofim is a new class of agent with a novel mechanism of action, the endpoint for *in vitro* activity that correlates with *in vivo* activity is yet to be determined (173).

The activity of manogepix, a new antifungal drug with a new mechanism of action, was tested against 49 FOSC and 19 FSSC isolates and exhibited good *in vitro* activity. For FOSC, the MIC_{50} range was ≤0.015 to 0.125 μg/mL, and for FSSC the MIC_{50} range was ≤0.015 to 0.25 μg/mL. The same FSSC isolates exhibited MIC ranges of 0.25 to 2 μg/mL for amphotericin B, 4 to >16 μg/mL for posaconazole, 2 to >16 μg/mL to voriconazole, and >16 μg/mL for isavuconazole (174). Table 4 summarizes the susceptibility of *Fusarium* species to different antifungal agents.

Antifungal susceptibility tests are meant to help clinicians choose the most appropriate antimicrobial agent to treat their patients. An important question when we evaluate the results of antifungal susceptibility tests in invasive fusariosis is the apparent lack of correlation between *in vitro* data and clinical outcomes. This is illustrated by the high MICs exhibited by different *Fusarium* species against voriconazole and the good clinical response to this agent (9, 176). A multicenter study evaluated the correlation between MIC and outcome in 88 patients with invasive fusariosis (74 with hematologic disease). The most frequent treatment was voriconazole monotherapy (30.7%), followed by liposomal amphotericin B plus voriconazole (26.1%). A correlation between MIC and outcomes (survival or death) was not observed (177). The results of this study reflect on the recommendations of recently published global guidelines for the management of rare mold infections: strong recommendations for epidemiologic purposes but weak recommendations for the choice of primary therapy (178).

Prophylaxis

Mold-active prophylaxis with agents that may have activity against *Fusarium* species is considered standard of care in high-risk patients such as HCT recipients with GVHD and AML patients receiving intensive induction remission chemotherapy (179). Primary prophylaxis specifically for invasive fusariosis was evaluated in one study. In a previous publication, high-risk hematologic patients with superficial skin lesions in the feet (onychomycosis and/or interdigital intertrigo) at hospital admission with positive culture for *Fusarium* species were at an increased risk for invasive fusariosis (148). Subsequently, in a non-randomized trial, anti-mold prophylaxis (voriconazole or posaconazole) was given to 20 episodes at elevated risk (neutropenia or graft versus host disease) and compared with 219 episodes where fluconazole or no prophylaxis was given. Overall, anti-mold prophylaxis did not decrease the incidence of invasive fusariosis: 5.9% without versus 5% with anti-mold prophylaxis. However, 4 of 5 patients with superficial skin lesions with positive cultures for *Fusarium* species who did not receive anti-mold prophylaxis developed invasive fusariosis versus none of the six with anti-mold prophylaxis ($P = 0.01$)(180). Based on these data, primary anti-mold prophylaxis

TABLE 4 Antifungal susceptibility of *Fusarium* species to different antifungal agents

Drug	Reference	Method	No. isolates	MIC range (μg/mL)	MIC_{50} (μg/mL)[a]	MIC_{90} (μg/mL)	Mode (μg/mL)	GM (μg/mL)
				Fusarium solani species complex				
Amphotericin B	(169)	CLSI	608	≤0.25 to 16	-	-	2	-
Itraconazole	(169)	CLSI	608	0.5 to ≥16	-	-	16	-
Posaconazole	(169)	CLSI	608	1 to ≥16	-	-	8	-
Voriconazole	(169)	CLSI	608	0.5 to ≥16	-	-	8	-
Isavuconazole	(175)	EUCAST	22	4 to ≥16	>16	>16	-	14.02
Olorofim	(173)	CLSI	16	1 to >4	>4	>4	>4	>4
Manogepix	(174)	CLSI	19	≤0.015*	-	-	-	≤0.015**
				Fusarium oxysporum species complex				
Amphotericin B	(169)	CLSI	226	≤0.25 to 16	-	-	2	-
Itraconazole	(169)	CLSI	226	1 to ≥16	-	-	16	-
Posaconazole	(169)	CLSI	226	0.5–16	-	-	2	-
Voriconazole	(169)	CLSI	226	0.5 to ≥16	-	-	4	-
Isavuconazole	(175)	EUCAST	17	2 to ≥16	8	>16	-	9.41
Olorofim	(173)	CLSI	45	0.06 to >4	0.5	4	0.25	0.515
Manogepix	(174)	CLSI	49	≤0.015 to 0.03*	-	-	-	≤0.015**
				Fusarium fujikuroi species complex				
Amphotericin B	(169)	CLSI	151	0.5–16	-	-	2	-
Itraconazole	(169)	CLSI	151	1 to ≥16	-	-	16	-
Posaconazole	(169)	CLSI	151	≤0.25 to ≥16	-	-	0.5	-
Voriconazole	(169)	CLSI	151	0.5 to ≥16	-	-	2	-
Isavuconazole	(175)	EUCAST	31	4 to ≥16	>16	>16	-	13.68

[a]MIC = minimum inhibitory concentration; GM = geometric mean; *, minimal effective concentration; geometric mean MEC/MIC.

is recommended in high-risk hematologic patients who present on admission with superficial skin lesions with positive cultures for *Fusarium* species (178).

Secondary prophylaxis for patients who had a history of invasive fusariosis and underwent subsequent periods at risk (GVHD or neutropenia) was evaluated in a multicenter retrospective study of forty patients. Relapse of invasive fusariosis occurred in two of eight patients (25%) not receiving secondary prophylaxis and in 3 of 32 (9.4%) on prophylaxis. Among patients with a history of disseminated fusariosis, relapse occurred in two of two (100%) patients who were not on secondary prophylaxis and in 3 of 26 (11.5%) who were receiving secondary prophylaxis ($P = 0.03$) (181). Therefore, we recommend that patients with prior invasive fusariosis who will undergo additional immunosuppressive therapies receive secondary prophylaxis (mold-active azole or a lipid formulation of amphotericin B).

In addition to antifungal prophylaxis, measures to reduce patient exposure to *Fusarium* should be attempted, including the treatment of high-risk neutropenic patients in rooms with HEPA filter and positive pressure, and avoiding contact with reservoirs of *Fusarium*, including cleaning showers prior to use by high-risk patients and avoiding contact with contaminated tap water (2).

Prognostic factors

As with other IFDs, recovery of immunosuppression is an important prognostic factor. Prognostic factors in invasive fusariosis were evaluated in 84 patients with hematologic diseases. Multivariate analysis revealed two factors negatively impacting survival: persistent neutropenia (HR: 5.43) and receipt of corticosteroids (HR: 2.18). The 90-day probability of survival was 67% when both factors were absent and zero with both factors. Survival was 30% in patients recovering from neutropenia but receiving corticosteroids, and 4% in persistently neutropenic patients without corticosteroids (90). In another study, among 54 allogeneic HCT recipients with invasive fusariosis, univariate predictors of death were acute GVHD (HR: 2.05) and persistent neutropenia (HR: 3.64). By

multivariate analysis, only persistent neutropenia was significant (HR: 3.65) (91), a finding also reported by others (9, 99, 101).

Primary therapy

There are no randomized studies evaluating different treatment regimens for the treatment of invasive fusariosis. The largest series of invasive fusariosis ever published involved 44 centers from 11 countries in a retrospective study of 236 patients diagnosed between 1985 and 2011. Among the 206 patients who received treatment, the most frequent agent was deoxycholate amphotericin B (110 patients), followed by voriconazole (38 patients), and a lipid formulation of amphotericin B (liposomal 20, lipid complex 8, and colloidal dispersion 6). Combination therapy was given to 21 patients, mainly voriconazole plus amphotericin B. The 90-day probability of survival was not significantly different among patients receiving voriconazole or lipid amphotericin B (53% and 48%, respectively). By contrast, the 90-day probability of survival of patients receiving deoxycholate amphotericin B was poor (27%). There was no difference in the outcome of patients receiving monotherapy or combination therapy. Improved outcome was observed between patients treated between 2001 and 2010 and those treated before 2000 (9). Based on these results, recently published guidelines recommend either voriconazole (6 mg/kg twice daily on day 1, followed by 4 mg/kg twice daily subsequently) or a lipid formulation of amphotericin B (liposomal amphotericin B—3 mg/kg daily; amphotericin B lipid complex—5 mg/kg daily) as primary therapy. Combination therapy can also be considered, with a potential for early step-down to monotherapy (178).

The treatment of invasive fusariosis may be challenging because of the poor penetration of antifungal agents in infected tissues, such as endophthalmitis and arthritis. For endophthalmitis, we recommend systemic and intravitreal antifungal, sometimes with vitrectomy (158).

Evaluation of response to treatment

Assessing response to treatment relies on physical examination and laboratory studies. Signs of progression of fusariosis include the appearance of new skin lesions, signs of infection in new organs as well as persistent fungemia and elevated serum GMI and/or BDG. In patients with extensive disease, positron-emission tomography/computed tomography (PET/CT) can assist in response assessment (182–184).

Adjunctive therapies

Patients with necrotic lesions that are prone may benefit from surgical debridement of necrotic tissue (185). For the occasional cases of catheter-related fungemia, catheter removal and a short course of antifungal treatment result in a cure of infection (186).

The use of granulocyte transfusions as adjuvant treatment was evaluated in 11 neutropenic patients with invasive fusariosis. Clinical response was observed in 10 patients. The authors performed a literature review of 23 published cases, with a response rate of 30% (187). It is important to note that granulocyte transfusions represent a transient measure to allow time for neutrophil recovery.

Other ancillary measures include the use of granulocyte or granulocyte-monocyte colony-stimulating factors (G-CSF and GM-CSF), and interferon-gamma (16). More recently, the checkpoint inhibitor nivolumab was used as adjuvant treatment of patient with AML who developed invasive fusariosis in the lungs that subsequently disseminated to the liver and spleen, with marked improvement after four doses (188).

TABLE 5 Approach to the diagnosis and management of invasive fusariosis in high-risk hematologic patients[a]

Action
Identify patients at elevated risk
Acute leukemia receiving induction chemotherapy for newly diagnosed or relapsed disease with profound (<100/mm^3) neutropenia; active smoking
Allogeneic HCT recipient
Pre-engraftment period: profound (<100/mm^3) neutropenia, cord blood HCT, ATG in the conditioning regimen
Post-engraftment period: receipt of corticosteroids or other immunosuppressive agents for the treatment of severe GVHD, CMV reactivation
The presence of skin breakdowns at sites of onychomycosis and/or interdigital intertrigo should increase the alertness
Consider the diagnosis of invasive fusariosis if
Skin lesions or unexplained myalgia
New pulmonary infiltrates
Sinusitis
Endophthalmitis
Positive blood culture for mold
Diagnostic workup
Prompt biopsy of a skin lesion, with direct examination, culture, and histopathology
Treat immediately if
Presence of hyaline hyphae on the direct exam of a fragment of skin biopsy
Positive blood culture for a mold

[a]HCT = hematopoietic cell transplantation; ATG = anti-thymocyte globulin; GVDH = graft versus host disease; CMV = cytomegalovirus.

Approach to the diagnosis and treatment of invasive fusariosis in hematologic patients

The first step in the approach to the diagnosis of invasive fusariosis is to identify the typical scenario/patient at risk: patients with AML or ALL receiving induction chemotherapy for newly diagnosed or relapsed disease, and allogeneic HCT recipients with profound (<100/mm^3) neutropenia or, in non-neutropenic HCT recipients, receipt of corticosteroids or other immunosuppressive agents for the treatment of severe GVHD. The presence of skin breakdowns (onychomycosis and/or interdigital intertrigo) should increase alertness, as well as the presence of risk factors such as active smoking in AML, and receipt of anti-thymocyte globulin, cord blood as a source of stem cells or CMV reactivation in allogeneic HCT. In these scenarios, clinicians should strongly consider the diagnosis of invasive fusariosis in the presence of skin lesions, new pulmonary infiltrates, sinusitis, endophthalmitis, or a positive blood culture for mold or elevation of serially obtained serum markers of IFD. In the presence of skin lesions, it is important to promptly obtain a biopsy with direct examination, culture, and histopathology; direct examination is the fastest way of achieving a presumptive diagnosis of invasive fusariosis. Anti-mold-active antifungal therapy should be immediately started if direct examination shows hyaline hyphae, or in the presence of positive blood culture for a mold and/or increasing serum markers of IFD (Table 5).

CONCLUSIONS

Invasive fusariosis is a serious IFD, affecting both immunocompetent and, more frequently, immunocompromised patients. In immunocompetent individuals, the disease is usually localized. Immunocompromised patients more prone to develop invasive fusariosis are patients with acute leukemia receiving chemotherapeutic regimens for induction remission and allogeneic HCT recipients. The disease is usually disseminated with multiple painful metastatic skin lesions, positive blood cultures, and lung involvement. Currently available antifungal agents have poor *in vitro* activity

against *Fusarium* species, but a clear-cut correlation between *in vitro* activity and clinical effectiveness does not exist. The outcome of invasive fusariosis is largely dependent on the recovery of immunosuppression, especially neutrophil recovery in neutropenic patients.

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