Human fusariosis

M. C. Dignani[1] *and E. Anaissie*[2]

[1]FUNDALEU (Foundation for the Fight against Leukemia), Uriburu 1450, Buenos Aires, Argentina and [2]The Myeloma Institute for Research and Therapy, The University of Arkansas for Medical Sciences, Slot 776, 4301West Markham, Little Rock, AR 72205, USA

ABSTRACT

Fusarium species frequently implicated in human infections include *F. solani*, *F. oxysporum* and *F. moniliforme*. Among immunocompetent patients, tissue breakdown (as caused by trauma, severe burns or foreign body) is the risk factor for fusariosis. Infections include keratitis, onychomycosis and occasionally peritonitis and cellulitis. Treatment is usually successful and requires removal of the foreign body as well as antifungal therapy. Among immunocompromised patients, mainly patients with haematological malignancies, *Fusarium* spp. are the second most common pathogenic mould. Risk factors for disseminated fusariosis include severe immunosuppression (neutropenia, lymphopenia, graft-versus-host disease, corticosteroids), colonisation, tissue damage, and receipt of a graft from an HLA-mismatched or unrelated donor. Clinical presentation includes refractory fever (> 90%), skin lesions and sino-pulmonary infections (~75%). Type of skin lesions includes ecthyma-like, target, and multiple subcutaneous nodules. Skin lesions lead to diagnosis in > 50% of patients and precede fungemia by ~5 days. In contrast to disseminated aspergillosis, disseminated fusariosis can be diagnosed by blood cultures in 40% of patients. Histopathology reveals hyaline acute-branching septate hyphae similar to those found in aspergillosis. Mortality from fusarial infections in immunocompromised patients ranges from 50% to 80%. Host immune status is the single most important factor predicting outcome. Persistent neutropenia and corticosteroid therapy significantly affect survival. Optimal treatment has not been established. Anecdotal successes have been reported with various agents (high-dose amphotericin B, lipid-based amphotericin B formulations, itraconazole, voriconazole) and with cytokine-stimulated granulocyte transfusions. Preventing fusariosis relies on detection and treatment of cutaneous damage prior to commencing immunosuppression and decreasing environmental exposure to Fusaria (via air and water).

Keywords Fusarium, review, fungi

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INTRODUCTION

The genus *Fusarium* is a common soil saprophyte and an important plant pathogen. The organism causes a broad spectrum of human disease, including mycotoxicosis and infections which can be locally invasive or disseminated.

Corresponding author and reprint requests: E. Anaissie, The Myeloma Institute for Research and Therapy, The University of Arkansas for Medical Sciences, Slot 776, 4301West Markham, Little Rock, AR 72205, USA
Tel: +1 501 296 1503, ext 1454
Fax: +1 501 686 6442
E-mail: AnaissieElias@uams.edu

MICROBIOLOGY

Fusarium spp. are agents of hyalohyphomycosis along with other fungi such as *Penicillium* spp., *Scedosporium* spp., *Acremonium* spp., *Paecilomyces* spp., *Aspergillus* spp., *Scopulariopsis* spp. and others [1]. 'Hyalohyphomycosis' is a term that describes fungal infections caused by moulds whose basic tissue form is in the nature of hyaline, light-coloured, hyphal elements that are branched or unbranched, occasionally toruloid, and without pigment in their wall [2].

Fusarium spp. grow rapidly on many media (without cycloheximide which is inhibitory). On potato dextrose agar, *Fusarium* spp. produce white, lavender, pink, salmon, or grey colonies

(which readily change colour) with velvety to cottony surfaces [3].

Microscopically, the hyphae of *Fusarium* in tissue resemble those of *Aspergillus* spp.; the filaments are hyaline, septate and 3–8 μm in diameter. They typically branch at acute or right angles. The production of both fusoid macroconidia (hyaline, multicellular, banana-like clusters with foot cells at the base of the macroconidium) and microconidia (hyaline, unicellular, ovoid to cylindrical in slimy head or chains) are characteristic of the genus *Fusarium.* If microconidia are present, the shape, number of cells (usually one to three), and mode of cell formation (chains or false heads) are important in identification. Chlamydospores are sometimes present and appear singly, in clumps or in chains, and their walls may be rough or smooth [3].

Fusarium can be distinguished from *Acremonium* by its curved, multicellular macroconidia, while *Cylindrocarpon* is distinguished from *Fusarium* by its straight to curved macroconidia that lack foot cells [3]. The identification of *Fusarium* spp. may be difficult and is well described by Nelson *et al.* [4].

Fusarium spp. possess several virulence factors including the production of tricothecene and other mycotoxins. These mycotoxins can suppress humoral and cellular immunity, and cause tissue breakdown. *Fusarium* spp. also have the ability to adhere to prosthetic material (contact lenses, catheters), and to produce proteases and collagenases [4].

EPIDEMIOLOGY

Fusarium spp. are widely distributed in soil, plants and air. They are common in tropical and temperate regions but are also found in desert, alpine and arctic areas [4]. In a survey of airborne fungi conducted in the USA, *Fusarium* spp. were more commonly recovered from air samples than were *Aspergillus* spp. [5]. *Fusarium* spp. colonised 17% of throat specimens of 27 nonhospitalised healthy adults [6]. These organisms can also colonise the conjunctival sac, especially in diseased eyes [7]. Wind and rain effectively *Fusarium* disperse [8].

Fusarium spp. are the most common cause of fungal keratitis world-wide. In a series of 391 incidences of infectious keratitis in Thailand, 34 (12%) were fungal and *Fusarium* was the most common fungus recovered [9]. Another series of 1352 fungal keratitis cases in India confirmed this finding (37%).

In severely immunocompromised patients, this fungus can cause disseminated disease and has recently emerged as the second most common pathogenic mould (after *Aspergillus*) in high-risk patients with haematological cancer, and in recipients of solid organ [10] and allogeneic bone marrow or stem cell transplants [11–13]. In the latter patient population, the distribution of fusariosis is bimodal, with peaks observed before and several weeks after engraftment. At one US institution, the incidence of fusarial infection was 1.2% among 750 allogeneic and 0.2% among 1537 autologous marrow transplant recipients during a 10-year period [11]. A review of fusarial infections in patients with acute leukaemia in Italy showed an incidence of 0.06% [14]. While the incidence in Europe has remained stable over the past 20 years, it has significantly increased at one US institution from 0.5 to 3.8 cases per year from 1975 to 1995 [11]. In this institution, the hospital water system was found to be a reservoir for *Fusarium* spp. [15]. In another US institution, 31 cases of invasive fusariosis were documented among 5589 stem cell transplant recipients (0.55%) during a 14-year period, with an increase in the number of these patients during the late 1990s [13].

RISK FACTORS

Tissue breakdown from direct trauma or the presence of a foreign body in a colonised patient are the usual risk factors for infections in non-immunosuppressed patients. These infections are mainly localised and include keratitis after trauma or among contact lens wearers [16], onychomycosis among individuals who walk barefooted and, rarely, peritonitis in patients undergoing continuous ambulatory peritoneal dialysis, cellulitis after injury [17] and others.

Disseminated fusariosis among previously healthy individuals can develop in the setting of a severe burn injury [18,19].

Risk factors for disseminated fusariosis include severe immunosuppression (mainly patients with haematological malignancies) in addition to colonisation and tissue damage. More specifically, neutropenia, lymphopenia, graft-versus-host disease, corticosteroid therapy or any other immunosuppressive treatment, are considered risk factors for disseminated fusariosis [11,20–22]. In

a recent review of invasive fungal infections among stem cell transplant recipients, multiple myeloma, and receipt of a graft from an HLA-mismatched or unrelated donor were significantly associated with fusarium infections [13].

CLINICAL MANIFESTATIONS

Infections by *Fusarium* spp. can be divided into foreign-body associated, single organ invasion and disseminated fusariosis [4]. Mycotoxicosis caused by *Fusarium* spp. will not be included in this review.

Single organ invasion

Keratitis

Fusarium spp. are a frequent cause of corneal damage in developing countries in the tropics [23], and are the most frequent cause of fungal keratitis in the USA [24]. The main predisposing factor is ocular trauma due to the implantation of vegetable or soil matter [16,25,26]. An additional risk factor for *Fusarium* keratitis is the presence of a pathological corneal condition and concomitant therapy with topical steroids and antibacterial antibiotics. Topical natamycin is the treatment of choice because of its excellent antifusarial activity, corneal penetration and safety profile, but amphotericin B ointment can also be used [27,28]. Chlorhexidine may have potential as an inexpensive topical agent for fungal keratitis and warrants further assessment as a first-line treatment in conditions where microbiological facilities and a range of antifungal agents may not be available [29]. Systemic antifungal treatment may be useful in severe mycotic keratitis and surgery may be required in refractory infections or when serious complications are likely to occur.

Endophthalmitis

Fusarial endophthalmitis can develop between 2 and 22 weeks after the onset of fusarial keratitis or following surgical and nonsurgical trauma [37].

Onychomycosis

Fusarium spp. may invade the great toenails after soil contamination, especially in individuals who walk in open sandals or barefooted. The most common clinical presentations include proximal subungual onychomycosis with or without paronychia, and white superficial onychomycosis [38,39]. Distal subungual onychomycosis can also occur following trauma or a dermatophyte infection [40]. *Fusarium* spp. were reported to be the causative agent of 9–44% of the nail invasions caused by nondermatophytic moulds [38,41–43]. A combined strategy of systemic itraconazole, systemic terbinafine, topical terbinafine after nail plate avulsion, and ciclopirox nail lacquer was able to cure only 40% of 26 patients with fusarium onychomycosis [38]. Aspergillus onychomycosis, on the other hand, responded very well to this therapy.

Although onychomycosis as a result of *Fusarium* spp. infection usually behaves as a localised infection in immune competent individuals, it could also represent the portal of entry for disseminated disease in immunocompromised patients [4,44,45].

Cutaneous infections

In immune competent individuals, localised cutaneous infections may develop in the setting of initial colonisation and the presence of excessive moisture or trauma (including burn). Skin lesions may vary including granulomas, ulcers, nodules, mycetomas, necrosis, panniculitis and intertrigo [4,46]. As reported in a recent review of cutaneous infections by *Fusarium* spp. [45], in patients presenting with localised cutaneous infections, immunocompetent patients (10 of 13) had more frequently a history of skin breakdown than those who were immunocompromised (11 of 20). While cutaneous infections in the former population were characterised by localised involvement, slow progression and good response to therapy, those in the latter population who presented as rapidly progressive usually disseminated lesions with poor response to antifungal agents. The cutaneous infections secondary to disseminated disease will be described later.

Foreign-body associated fusariosis

Keratitis in contact lens wearers

Fusarium spp. can also contaminate the contact lens paraphernalia or the lens itself, especially after improper care. In windy conditions, *Fusarium* spp. can also contaminate the lens during use. This fungus can penetrate the matrix of the soft contact lens with increasing microbial growth in lenses with high water content [30]. *Fusarium* keratitis can also develop among users of daily

disposable soft contact lenses [31]. Treatment often requires removal of the lens and topical treatment with natamycin but may require surgery in refractory patients [31–36].

Peritonitis following continuous ambulatory peritoneal dialysis

The clinical presentation is usually insidious, with fever, abdominal pain and decreasing drainage from the peritoneal catheter. Fungi can either plug or invade the catheter. Treatment often requires catheter removal and systemic antifungal therapy [47–55].

Catheter-associated fungemia

Fusarium spp. can rarely plug and invade the wall of a central venous catheter and lead to fungemia [56–58]. Treatment includes catheter removal and systemic antifungal therapy.

Other single organ infections

Less frequently, *Fusarium* spp. can also cause osteomyelitis, arthritis, otitis, sinusitis and brain abscess. *Fusarium* was the cause of 1% of 83 cases of mycotic otitis of the external ear in Gabon, Central Africa [59]. *F. solani* was found in, and was able to germinate in, the middle ear of agricultural workers [60]. Four of five cases of fusarium osteomyelitis were reported in healthy individuals following surgery or trauma [61–64]. Successful outcome resulted from a combination of surgical and medical treatment. Bone involvement by *Fusarium* spp. may also occur in the setting of disseminated disease [65]. Fusarium septic arthritis has been reported in two patients after trauma, responded to surgery and amphotericin B [66,67]. Sinusitis in a diabetic cancer patient [68] and an isolated brain abscess in a patient with chronic infectious mononucleosis syndrome [69] have also been reported.

Disseminated disease

Clinical presentation

Disseminated infections occur most commonly in patients with haematological malignancies and occasionally in patients with extensive burns [11]. The *Fusarium* spp. most frequently implicated as human pathogens include *F. solani*, *F. oxysporum*, *F. moniliforme* and less commonly, *F. anthophilum*, *F. chlamydosporum*, *F. dimerum*, *F. equiseti*, *F. lichenicola*, *F. napiforme*, *F. proliferatum*, *F. semitecum* and *F. verticilloides* (the less common species listed in alphabetical order) [11,12,70–73]. Disseminated infection usually presents as persistent fever refractory to antibacterial and antifungal agents. Other presenting features include sinusitis and/or rhinocerebral infection, cellulitis at the site of skin breakdown, endophthalmitis, painful skin lesions, pneumonia, myositis and infections of the central nervous system [11,21]. Almost any organ can be involved but the most frequently affected is the skin (70–90%), followed by lungs and sinuses (70–80%) [11]. Three types of cutaneous lesions can be observed: multiple, at times painful, subcutaneous nodules and ecthyma-like lesions, and less commonly, bullae or target lesions consisting of the ecthyma-like lesions surrounded by a thin rim of erythema [45]. Some of these lesions represent an evolution of the same lesions observed at different ages. Extensive cellulitis of the face or the extremities, with or without fascitis, has also been described [74]. Pleuritic chest pain, fever, cough and haemoptysis occur in patients with pulmonary involvement and are indistinguishable from pulmonary aspergillosis. Indeed, the clinical features of patients with disseminated fusarial infection are similar in many respects to those with disseminated aspergillosis [11]. Unlike aspergillosis, however, infection with *Fusarium* spp. is associated with a high incidence of skin and subcutaneous lesions and with positive blood cultures [11,21,45,75–77].

Among patients undergoing solid organ transplantation, fusarial infections tend to be more localised, occur later after transplantation and have a better outcome than among patients with haematological cancer or recipients of bone marrow transplantation [10].

In a recent review of cutaneous fusariosis in 259 patients including 232 who were immunocompromised, a higher rate of skin lesions was present among neutropenic (78%) than non-neutropenic patients (45%) and those with disseminated skin lesions were more likely to have fusarial fungemia [45]. Skin lesions involved practically any skin site, with predominance on the extremities, and took different forms as described above. The lesions evolved rapidly, usually over a few days (range 1–5 days) and lesions at different stages of evolution were described in many patients (usually a combination of papules, nodules and necrotic lesions), sometimes along

with myalgias (suggesting muscle involvement). The skin was the primary site of infection leading to disseminated fusariosis in 16 patients (mainly at sites of onychomycosis and less frequently at sites of trauma or insect bite). The pattern of skin lesions did not appear to be associated with any particular species of *Fusarium*.

Diagnosis

In patients with severe immunosuppression, a high index of suspicion for disseminated fusariosis should be raised when mould fungemia is reported, or when preceding or concomitant toe or finger cellulitis, or cutaneous or subcutaneous lesions are present [72,78].

Skin is a very important source for diagnosis. In one report, skin lesions were the single source of diagnosis of fusarial infection in 55% of patients. In most cases, skin lesions preceded fungemia by a median of 5 days (range 1–10 days), but they also developed after the diagnosis of fungemia (up to 13 days later) [45]. Histopathological examination of skin lesions showed hyaline acute-branching septate hyphae invading the skin and extending into the blood vessels, with thrombosis and necrosis in those patients with metastatic lesions [45].

In contrast to disseminated aspergillosis, disseminated fusariosis can be diagnosed by blood cultures in 40% of patients [11,72]. The rate of positive blood cultures increases to 60% in the presence of disseminated skin lesions, while fungemia is extremely rare in patients with localised skin infections [45].

As with aspergillosis, the radiological findings of pulmonary fusarial infection range from non-specific infiltrates (most commonly) to nodular and/or cavitary lesions, depending on the timing of the study.

The definitive diagnosis of fusariosis requires the isolation of *Fusarium* spp. from clinical specimens (blood, skin, sinuses, lungs, other). Culture identification is important because of the histopathological similarities between *Fusarium* and other members of the hyalohyphophomycosis family and the different susceptibilities of these pathogens to antifungal agents. Like *Aspergillus* spp., *Fusarium* spp. invade blood vessels causing thrombosis and tissue infarction and appear in tissues as acute branching septate hyphae [4,11]. Tissue diagnosis of fusariosis can be made by immunohistological staining, using polyclonal fluorescent antibody reagents that distinguish *Aspergillus* spp. from *Fusarium* spp. [79]. In-situ hybridisation may also help to distinguish *Fusarium* spp. from *Aspergillus* and *Pseudoallescheria* in tissue sections with a 100% positive predictive value [80].

Treatment

Prompt therapy of localised disease is critical to prevent progression to disseminated infection and includes surgical debridement, and probably systemic antifungal chemotherapy [11,76,81].

The optimal treatment for disseminated fusariosis remains unclear. Voriconazole, itraconazole and the polyenes (amphotericin B and its lipid formulations) [82–87] have been associated with some success. In the USA, voriconazole is the only agent with an indication for treating refractory fusariosis.

Fusarium spp. are some of the most drug-resistant fungi. Data on their in-vitro susceptibility to various antifungal agents indicate low susceptibility to 5-flucytosine, fluconazole and amphotericin B [88–90] and variable susceptibility to itraconazole, voriconazole and posaconazole [89,91–99]. *F. solani* seems to be somewhat more susceptible to amphotericin B but less susceptible to voriconazole than *F. oxysporum* [100].

The echinocandins caspofungin [101], anidulafungin, and micafungin [102,103] have no in-vitro activity against *Fusarium* spp.

In severely neutropenic patients, treatment with granulocyte or granulocyte–macrophage colony-stimulating factors (G- or GM-CSF) and CSF-stimulated white blood cell transfusions may also be considered [11,104–106]. Recently, a combined approach of liposomal amphotericin B, voriconazole, surgery and granulocyte transfusions was associated with a successful outcome in a child with severe aplastic anaemia and disseminated infection by *F. oxysporum* [106].

Debridement or resection of all infected tissues (sinuses, ocular tissues, soft tissue, bone, other) is recommend but frequently impossible because of severe thrombocytopenia. Catheter removal may be of benefit if the catheter is the source of the fusariosis.

Outcome

Disseminated fusariosis is a life-threatening disease whose outcome is very much influenced by the host immune status. Overall mortality of fusarial infections in immunocompromised

patients ranges from 50% to 80% [11,45,72,107]. In a retrospective study that included 84 patients with fusariosis, factors associated with poor survival by multivariate analysis included persistent neutropenia and therapy with corticosteroids. The actuarial survival of patients with both persistent neutropenia and corticosteroid therapy was 0%, compared to 67% who had neither of these two factors present, 30% for those on corticosteroids (but with adequate neutrophil counts), and 4% for those whose only negative prognostic factor was persistent neutropenia [108].

These data are in agreement with other reports that describe very high mortality in persistently neutropenic patients [11,45,72,107].

Disseminated skin lesions may be a marker of poor outcome in non-neutropenic patients. In a retrospective study of 259 patients with fusariosis [45], a higher mortality was observed among patients with skin lesions (70% vs. 56%), particularly among those who had an adequate neutrophil count throughout the course of their illness. In this group of patients, the mortality rate for patients with metastatic skin lesions was 67% vs. 21% for those with localised lesions. The mortality among neutropenic patients was high regardless of whether the lesions were localised or metastatic (64% vs. 77%), respectively.

Prevention

Because of the high morbidity and mortality of disseminated fusariosis, every effort should be made to prevent these infections, and to enhance the patient's immune status, perhaps by tapering or discontinuing immunosuppressive agents or shortening the duration of neutropenia. We also recommend that patients likely to receive severely immunosuppressive therapy undergo a thorough skin evaluation prior to commencing immunosuppression, to identify areas of tissue breakdown and evaluate these lesions with culture and biopsy and antifungal treatment if *Fusarium* spp. are identified. In addition, severely immunocompromised patients with skin or other exposed tissue breakdown should avoid exposure to environmental sources of *Fusarium* spp. such as tap water. Indeed, we have shown that hospital water may be contaminated with *Fusarium* spp. and can lead to aerosolisation (especially after showering) and to patient exposure and disease [109]. Avoiding exposure to tap water can be accomplished by the use of sterile sponge baths instead of showering (to minimise aerosolisation), and by drinking sterile water only during periods of severe immunosuppression. Cleaning water-related environmental surfaces (bathroom floors) results in a significant decrease in the airborne concentration of pathogenic moulds in the bathrooms of a bone marrow transplant unit [110]. Thus, adequate cleaning of the bathroom is recommended prior to showering (for those patients who insist on showering during the period of major immunosuppression).

Because of the risk of relapse in immunosuppressed patients with prior fusarial infections [111], secondary prophylaxis should be considered. The agent of choice would be the one associated with clinical response during the initial infection. Consideration should also be given to using prophylactic G-CSF or GM-CSF-stimulated granulocyte transfusions following initiation of severely myelosuppressive chemotherapy.

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