Hyalohyphomycosis: Infection Due to Hyaline Moulds

11

Duane R. Hospenthal

Introduction

Hyalohyphomycosis is a designation used to describe fungal infection caused by moulds with hyaline (clear or light colored) septate hyphae as seen microscopically in clinical samples. This terminology is similar to the use of phaeohyphomycosis to designate infections caused by fungi with dark-colored hyphae (Chap. 12). Perhaps the best use of this terminology is to describe diseases where hyaline hyphal elements are seen on smear or histopathology, but a specific fungus is not recovered by culture. Hyalohyphomycosis commonly includes infections caused by species of *Fusarium*, *Pseudallescheria*, *Scedosporium*, *Paecilomyces*, *Purpureocillium*, *Acremonium*, *Gliomastix*, *Sarocladium*, *Penicillium*, *Scopulariopsis*, *Beauveria*, and *Trichoderma*. Although *Aspergillus* also produces hyaline septate hyphae, and is considered a hyalohyphomycetes, infections secondary to this genus are typically termed aspergillosis and discussed separately as in this text (Chap. 10). *Scedosporium* and *Scopulariopsis* are commonly included in the hyalohyphomycoses, but some species produce dark hyphae and may be included in the phaeohyphomycoses. While *Penicillium marneffei* also produces hyaline hyphae, its dimorphic nature and geographical localization make placing it in the endemic mycoses also correct.

This group of fungi may cause superficial or localized infection in immunocompetent hosts (usually as a result of direct inoculation of the fungus following trauma) and invasive or disseminated infections in immunocompromised hosts. In the latter setting, the clinical infection may be indistinguishable from that of invasive aspergillosis. A remarkable feature of some of these hyaline moulds is their ability to cause fungemia (and thus be diagnosed with blood culture) and to disseminate hematogenously causing numerous embolic skin lesions. These infections may be clinically suspected on the basis of a constellation of clinical and laboratory findings. Definitive diagnosis requires isolation of these fungi from culture (or molecular methods) or from tissue. Identification to species level is ideal as these fungi have variable susceptibility to antifungal agents (Table 11.1). An important component of therapy of localized infection is surgical excision or debridement and removal of infected prosthetic devices. Outcome is usually favorable in immunocompetent hosts, but remains poor in the setting of persistent profound immunosuppression. Guidelines for the diagnosis and management of these fungal infections have recently been published [1].

D. R. Hospenthal (✉)
Adjunct Professor of Medicine, University of Texas Health Science Center at San Antonio, 7703 Floyd Curl Drive, San Antonio, TX 78229, USA
e-mail: drhospenthal@gmail.com

Fusarium Species

Fusarium species have emerged as a common cause of disseminated fungal infections in neutropenic patients and those undergoing allogeneic hematopoietic stem cell transplantation (HSCT). *Fusarium* represents the second most common fungal pathogen, after *Aspergillus*, as the cause of life threatening infection in recipients of hematopoietic transplant [2]. Because of this, *Fusarium* infections are sometimes discussed separately from hyalohyphomycosis as fusariosis. *Fusarium* causes a broad spectrum of infections in humans, including superficial and local infections in immunocompetent hosts; disseminated infections are seen almost exclusively in immunosuppressed patients.

Etiologic Agents

Four species are most commonly involved in human infections: *F. solani* (most common), *F. oxysporum*, *F. verticillioides* (*moniliforme*), and *F. proliferatum* [3]. *F. solani* species complex also includes *F. falciforme* (formerly *Acremonium falciforme*) and *F. lichenicola* (formerly *Cylindrocarpon lichenicola*). *Fusarium* species are septate filamentous

D. R. Hospenthal, M. G. Rinaldi (eds.), *Diagnosis and Treatment of Fungal Infections,* Infectious Disease,
DOI 10.1007/978-3-319-13090-3_11,

Table 11.1 Overall susceptibility of hyaline fungi to available antifungals[a]

Genus/Species	AmB	Itraconazole	Voriconazole	Posaconazole	Anidulafungin	Caspofungin	Micafungin	Ref.
Fusarium spp.	++	+	++b	++	0	0	ND	[59, 60]
F. oxysporum	++	+	++++	++	ND	ND	ND	[59, 61]
F. solani	+	+	+	+	ND	ND	ND	
Scedosporium spp.	0	0	0	0	0	ND	ND	[60]
S. prolificans *S. apiospermum*	0	++	++++	+++	0	0	ND	[60, 61]
Paecilomyces spp.	++	+++	+++	+++	++	+++	ND	[59, 60]
Acremonium spp.	++	0	++	ND	0	ND	ND	[60]
Scopulariopsis spp.	0	0	0	0	+	+	+++	[55]
Trichoderma spp.	++	0	+	0	+++	+++	+++	[58]

++++, drug of choice; +++, alternative choice; ++, some strains are susceptible (<50%); +, rarely susceptible (<10%); 0, always resistant; ND, no data available

[a] Susceptibility based on MIC_{50}

[b] In USA, the only agent indicated for invasive fusariosis

fungi that produce conidiophores, phialides, macroconidia, and microconidia. *Fusarium* species are readily and rapidly recovered in almost all fungal media. On potato dextrose agar (PDA), the colonies have a velvety or cottony surface, and are white, yellow, pink, purple salmon, or gray on the surface, with a pale red, violet, brown, or sometimes blue reverse. The characteristic sickle- or banana-shaped multiseptate macroconidia with a foot cell at the base are used in identifying the genus and species of *Fusarium* (Fig. 11.1). Molecular methods may also be used for rapid identification of *Fusarium* to the species level. In tissue, the hyphae are similar to those of *Aspergillus* species, with hyaline and septate filaments that typically dichotomize in acute and right angles. In the absence of microbial growth, distinguishing fusariosis from aspergillosis and other hyalohyphomycoses is difficult, and requires the use of in situ hybridization in paraffin-embedded tissue specimens [4]. *Fusarium* species are toxigenic, and may cause mycotoxicosis in animals and humans [3].

Fig. 11.1 *Fusarium oxysporum* macroconidia. Characteristic fusiform to sickle-shaped, multiseptate mostly with an attenuated apical cell and a foot-shaped basal cell. (Courtesy of www.doctorfungus.org © 2000)

Epidemiology

Fusarium is ubiquitous in soil and water, taking part in water biofilms, and is a human and plant pathogen [5]. *Fusarium* species are causative agents of superficial and localized infections in immunocompetent hosts, most commonly onychomycosis and cutaneous and subcutaneous infections, including mycetoma and keratitis, the latter in contact lens wearers [6]. A recent large outbreak of *Fusarium* keratitis was reported in contact lens wearers in the USA and was linked to contaminated contact lens rinse solutions. Other risk factors for keratitis are trauma and use of topical corticosteroids and antibiotics [7]. *Fusarium* endophthalmitis may arise from keratitis or by direct inoculation after cataract surgery or trauma [8]. Fusariosis may also result from skin breakdown, such as burns and wounds, or the presence of foreign bodies, such as peritonitis in patients receiving continuous ambulatory peritoneal dialysis (CAPD), catheter-associated fungemia, and thrombophlebitis [9–11]. A hospital outbreak of *F. verticillioides* fungemia in immunocompetent patients has been recently reported [12]. Other infections include sinusitis, pneumonia, cutaneous and subcutaneous infections, septic arthritis, and osteomyelitis [13–17].

Immunosuppressed patients may develop locally invasive and disseminated fusariosis [18]. Risk factors include prolonged neutropenia, such as following chemotherapy for acute leukemia, and T cell immunodeficiency, which occurs most commonly after HSCT [18–20]. In HSCT, infection may develop early during neutropenia or months after neutrophil recovery following the treatment of chronic extensive graft versus host disease (GvHD). Localized infections may also develop among solid organ transplant recipients (SOT), usually as a late infection [21].

Portals of entry are the respiratory tract and skin, the latter playing a significant role in patients with tissue breakdown such as onychomycosis. Hospital water systems are

a potential reservoir for *Fusarium*; transmission may occur from inhalation of conidia aerosolized in the shower or from direct contact of contaminated water with sites of skin breakdown [22–24].

Pathogenesis and Immunology

Similar to *Aspergillus*, this organism is highly angioinvasive and leads to tissue infarction. In contrast to *Aspergillus*, however, *Fusarium* is frequently isolated from the bloodstream, likely as a result of intravascular adventitious sporulation [25]. Phagocytes appear to be the predominant line of defense against fusarial infections [18–20].

Clinical Manifestations

Infection with *Fusarium* in immunocompetent hosts may be superficial or locally invasive, involving the skin, eyes, sinuses, lungs, and joints and bones. In immunosuppressed patients, the infection may be locally invasive, usually pneumonia and/or sinusitis, or more commonly disseminated [18–20]. The clinical picture resembles that of invasive aspergillosis. Unlike aspergillosis, however, fungemia and skin lesions are common (up to 40% of patients with disseminated disease). Skin lesions may represent the primary site of infection (onychomycosis) or secondary to disseminated infection [18–20]. Recovery of *Fusarium* from preexisting skin or nail lesions has been reported as a risk factor for invasive disease in high-risk patients [26]. Metastatic skin lesions evolve from subcutaneous painful lesions to erythematous induration followed by ecthyma gangrenosum-like necrotic center, which may be surrounded by a rim of erythema [18–20].

Diagnosis

Two characteristics suggest the diagnosis of disseminated fusariosis in the severely immunocompromised host: metastatic skin lesions and positive blood cultures for mould [18–20]. Definitive diagnosis relies on cultures (tissue and/or blood) and histopathology which show a pattern common to all hyalohyphomycosis (invasion by acute-branching, septate hyaline hyphae). The use of PCR techniques and/or in situ hybridization may be required to reach the correct diagnosis in tissues [4, 27]. The 1,3-β-D-glucan test is usually positive in invasive fusarial infections, but it cannot distinguish *Fusarium* from other fungal infections (*Candida*, *Aspergillus*, and others) which are also detected by the assay [28].

Treatment

Localized infections, particularly in immunocompetent hosts, usually respond well to treatment consisting of topical therapy for fungal keratitis or excision of involved tissue (sinuses, eye, soft tissue, bone). Removal of an infected intravascular catheter may be needed in the rare cases of catheter-related fungemia.

Outcome of invasive and disseminated fusariosis in immunosuppressed patients remains quite poor, but appears to have improved with the introduction of voriconazole and posaconazole [18–20, 29, 30]. Predictors of poor outcome are persistent neutropenia and recent therapy with corticosteroids for chronic GvHD [19]. Treatment options are limited by the lack of reliable and consistent activity of antifungal agents against *Fusarium* species. Susceptibility varies among the various species, with resistance seen to all three major classes of antifungal agents [31]. Rapid species identification may be helpful, but antifungal susceptibility testing should be considered because of this variable in vitro susceptibility among *Fusarium* species (Table 11.1). The echinocandins do not appear to be active against any *Fusarium* species

Pseudallescheria and *Scedosporium* Species

Previously, only two *Scedosporium* species, *S. apiospermum* (sexual state name, *Pseudallescheria boydii*) and *S. prolificans* (formerly *S. inflatum*), were described as human fungal pathogens [32, 33]. The fungi previously denoted *P. boydii* (asexual state name, *S. apiospermum*) have now been divided into at least four species—*P. boydii* (*S. boydii*), *P. minutispora*, *S. aurantiacum*, and *S. dehoogii* [34]. Some have called these newly described (renamed) fungi the *P.* boydii complex. In this text, we refer to this group as *P. boydii*. A spectrum of disease, ranging from respiratory tract colonization to superficial and deep infections, in both immunocompetent and immunosuppressed hosts, has been reported. Rarely, disseminated infection with high mortality is seen in the setting of severe immunosuppression. *S. prolificans* belongs to the group of fungi which causes phaeohyphomycosis (dematiaceous fungi), but will be briefly discussed because of its relation to *P. boydii*.

Etiologic Agents

Scedosporium species are identified by their characteristic macroscopic (wooly to cottony, dark gray to dark brown) and microscopic (characteristic conidia, conidiophores, and hyphae) appearance. *S. prolificans* is distinguished from *P. boydii* by the production of terminal annelloconidia with

inflated bases (cylindrical in *S. apiospermum*) and growth inhibition by cycloheximide or actidione. In tissue sections, *Pseudallescheria*/*Scedosporium* appear as septate hyaline hyphae that cannot be reliably distinguished from *Aspergillus* or *Fusarium* unless conidia are present.

Epidemiology

Pseudallescheria/*Scedosporium* have been isolated from soil, potting mix, compost, animal manure, and stagnant or polluted water. Infections occur worldwide, though a large number of reports come from Northern Spain [32]. Patients at risk for invasive and/or disseminated infection include those with HIV infection, acute leukemia, and recipients of allogeneic HSCT or SOT [35, 36].

Infection is thought to be secondary to direct inoculation (such as after trauma) or inhalation of airborne conidia. In normal hosts, *P. boydii* causes infection after penetrating trauma, including keratitis, endophthalmitis, cutaneous and subcutaneous infections, bursitis, arthritis, and osteomyelitis. Following near-drowning accidents, sinusitis, pneumonia, meningoencephalitis, and brain abscesses may develop. Allergic bronchopulmonary disease due to *P. boydii* may also occur. Like *P. boydii*, *S. prolificans* causes localized infections (usually of bone or soft tissue) in immunocompetent patients following trauma, and deeply invasive infections in immunocompromised hosts, sometimes as a nosocomial outbreak [32, 35, 36].

Clinical Manifestations

Mycetoma is the most common *P. boydii* infection in normal hosts (see Chap. 22), usually occurring after penetrating injury and presenting as lower extremity swelling with draining sinuses. Other infections include non-mycetoma cutaneous and subcutaneous infections, keratitis, and endophthalmitis [36]. Invasive *P. boydii* infection is usually seen in immunocompromised patients, most commonly as pneumonia. Disseminated infection is mainly associated with *S. prolificans*, and is characterized by refractory fever, pulmonary infiltrates (diffuse or nodular), central nervous system involvement (present in one third of patients), fungemia, renal failure, erythematous, and nodular skin lesions with central necrosis.

Diagnosis

The diagnosis relies on the combination of clinical signs and symptoms and recovery of *Pseudallescheria*/*Scedosporium* from blood and/or infected tissue, with or without demonstration of colorless septate hyphae.

Treatment

Localized infections, particularly in immunocompetent hosts, usually respond well to surgical debridement. *Pseudallescheria boydii* is resistant to fluconazole and flucytosine, but susceptible to the newer azoles—voriconazole, posaconazole, and ravuconazole (Table 11.1). Voriconazole is approved for use in *P. boydii* infections [37, 38]. Caspofungin appears to be more active than itraconazole or amphotericin B. Variable strain-to-strain susceptibility to amphotericin B can be seen [39]. Surgical resection remains the only definite therapy for *S. prolificans* infections, as this organism is resistant to all available antifungal agents in vitro. In vitro synergism between terbinafine and either voriconazole or itraconazole has been reported [40].

Paecilomyces and *Purpureocillium* Species

Paecilomyces and *Purpureocillium* species are frequent airborne contaminants in clinical microbiology laboratories but have been increasingly reported as cause of human infection.

Etiologic Agents

Two species, *Purpureocillium lilacinum* (formerly *Paecilomyces lilacinus*) and *Paecilomyces varioti*, account for most human infections. *Paecilomyces marquandii* and *P. javanicus* have also been reported to cause human disease. These fungi grow rapidly on various agar media including blood, chocolate, Sabouraud dextrose (SDA), and PDA. *P. varioti* is thermophilic and grows well at temperatures as high as 50 °C. The color of the colony and certain microscopic features help differentiate these fungal species from each other. The colonies are flat and velvety. The color is initially white and becomes yellow-green, yellow-brown, pink, or violet according to species.

Epidemiology

Paecilomyces and *Purpureocillium* are found worldwide in soil, food products, and water and causes infection in both immunocompetent and immunosuppressed patients. A strong association of these fungi with prosthetic implants may be due to their inherent resistance to most sterilizing techniques. Prosthetic implant-related infections include keratitis in contact lens wearers and after corneal implants (rarely endophthalmitis), and in recipients of CAPD, cardiac valves, and ventriculoperitoneal shunts. Other infections involve the nails, skin, subcutaneous tissues, bones and joints, sinuses, and lungs, while disseminated infections only occur in immunosuppressed patients [41].

Clinical Manifestations

The most common infections due to *Paecilomyces* and *Purpureocillium* involve the eye and eye structures (keratitis and endophthalmitis), followed by the nails (onychomycosis) and skin and soft tissues. Skin infections are characterized by erythematous macules, nodules, pustules, vesicular lesions, or necrotic crusts [41]. Sporotrichosis-like skin infection has also been described. Other reported infections in the competent host include peritonitis in CAPD, prosthetic-valve endocarditis, catheter-related fungemia, and arthritis/osteomyelitis. In immunocompromised patients, pneumonia and disseminated disease are most commonly observed.

Diagnosis

These fungi grow readily on routine fungal media, including SDA. Like all hyalohyphomycetes, they produce hyaline septate hyphae in tissue and can be seen with periodic acid–Schiff (PAS) staining in histopathology. Both may exist in various forms in tissue (conidia and phialides) and can therefore be misdiagnosed as candidiasis.

Treatment

Treatment of invasive *Paecilomyces* and *Purpureocillium* infections relies on surgical debridement and removal of infected prosthetic materials. Because of different susceptibilities to antifungal agents, these fungi should be identified to the species level (Table 11.1). *P. varioti* is susceptible to amphotericin B, flucytosine, itraconazole, voriconazole, and posaconazole, whereas *P. lilacinum* is only susceptible to the latter two triazoles [42].

Acremonium (and *Gliomastix* and *Sarocladium*) Species

Acremonium species are filamentous fungi of low pathogenicity commonly isolated from the environment (soil, insects, sewage, plants, and water) [43].

Etiologic Agents

Many species of *Acremonium* have been reported to cause human infection. Several of these have been transferred to the genera *Gliomastix* and *Sarocladium*. *A. strictum* is the most common of these species to cause of human infection, but infection has been attributed to *A. alabamensis*, *A. potronii*, *A. recifei*, *G. roseogrisea*, *S. kiliense*, and *S. strictum* [1]. One of the other more common species, *A. falciforme*, has been reclassified *Fusarium falciforme*. *Acremonium* species grow on SDA, forming white, salmon, or yellowish-green colonies that are usually velvety or cottony with slightly raised centers. This genus is distinguished by formation of narrow hyphae bearing solitary, unbranched needle-shaped phialides. Like other hyaline moulds, septate colorless hyphae are found in tissue.

Epidemiology

Most infections occur in immunocompetent hosts and include mycetoma following trauma, keratitis in contact lenses wearers, and endophthalmitis [43–45]. Fungal colonization of humidifier water in a ventilator system was thought to be the source of infections in an outbreak of endophthalmitis. Invasive disease is almost exclusively seen in immunocompromised patients.

Clinical Manifestations

Mycetoma is the most common infection due to *Acremonium* and presents in a manner similar to that of mycetoma caused by *S. apiospermum*. Keratitis and endophthalmitis constitute the second most common infections. Colonization of soft contact lenses may proceed to corneal invasion. Other reported infections include onychomycosis, peritonitis, dialysis fistulae infection, pneumonia, empyema, septic arthritis, osteomyelitis, meningitis (following spinal anesthesia in an otherwise healthy individual), cerebritis in an intravenous drug abuser, and prosthetic valve endocarditis. Disseminated infection occurs exclusively in immunosuppressed hosts and has been characterized by endocarditis, meningitis, and bloodstream infection. In vivo sporulation can occur, facilitating dissemination and perhaps explaining the high rate of metastatic skin lesions and positive blood cultures with *Acremonium*.

Diagnosis

Acremonium species grow slowly on SDA. Hence, cultures must be kept at least 2 weeks. Blood cultures may isolate *Acremonium* in cases of disseminated disease. Like other hyaline moulds, septate colorless hyphae that stain with PAS are found on histopathologic examination [45]. *Acremonium* may be difficult to identify in tissue because of morphologic similarities with other moulds, such as *Fusarium*.

Treatment

Acremonium species have a variable susceptibility to antifungal agents [43] (Table 11.1). In vitro activity of amphotericin

B and itraconazole against *Acremonium* is variable, while resistance to fluconazole and 5-fluorocytosine is uniform. The newer azoles, voriconazole and posaconazole, appear promising.

Penicillium (*Talaromyces*) *marneffei*

Although most *Penicillium* species are recovered only as laboratory contaminants, *P. marneffei* has emerged as a significant pathogen, most commonly as an opportunistic infection in HIV-infected patients residing or traveling to Southeast Asia [46].

Etiologic Agents

Penicillium marneffei is a facultative intracellular pathogen that is the only known thermally dimorphic fungus of the genus *Penicillium*. With the change in rules governing fungal taxonomy, it has been proposed that *P. marneffei* be renamed *Talaromyces marneffei*. Throughout this text, we will continue to use the name *P. marneffei*. At room temperature, *P. marneffei* exhibits the characteristic morphology of the genus, in contrast, it grows as a yeast when found in infected tissue or at 37 °C.

Epidemiology

Infection due to *Penicillium marneffei* constitutes the third most common opportunistic infection in HIV-infected patients in certain parts of Southeast Asia. Infection is most commonly reported from Thailand and Vietnam, but it is also endemic to the Guangxi province of China, Hong Kong, and Taiwan [47]. The incidence of penicilliosis has increased significantly, paralleling the incidence of HIV infection. Although penicilliosis is most commonly seen in adults infected with HIV, the disease has also been detected in children and adults without immunodeficiency [48]. The mode of transmission is thought to be due to ingestion or inhalation of the fungus. Soil exposure, especially during rainy season, has been suggested to be a critical factor.

Clinical Manifestations

P. marneffei can clinically resemble tuberculosis, molluscum contagiosum, cryptococcosis, and histoplasmosis. The most common clinical manifestation in penicilliosis includes low-grade fever, anemia, weight loss, cough, lymphadenopathy, and hepatosplenomegaly [49–51]. Skin lesions are present in up 70 % of the cases and are characterized by a central necrotic umbilication resembling molluscum contagiosum. Palatal and pharyngeal lesions can also be present. Bloodstream infection is present in approximately 50 % of the cases, in 77 % of HIV-infected, and 47 % of HIV-uninfected patients in one recent report [48]. Pulmonary involvement has been described as being diffuse or focal with either a reticulonodular or alveolar pattern. The mean number of $CD4^+$ T lymphocytes at presentation is 64 cells/μl [47].

Diagnosis

Diagnosis of *P. marneffei* infections is usually made by identification of the organism from smear, culture, or histopathologic sections. Rapid diagnosis of suspected infection could be obtained by direct examination of bone marrow aspirate, lymph node, or skin biopsy. Microscopic examination of Wright-stained smears reveals yeast forms both within phagocytes and extracellularly. The intracellular forms resemble those seen with *Histoplasma capsulatum* infection. The demonstration of characteristic central septation and elongated "sausage-shaped" forms by methenamine silver stain, clearly distinguishes *P. marneffei* from *H. capsulatum* (see Fig. 4.10, Chap. 4).

Treatment

Penicillium marneffei is usually susceptible to both amphotericin B and the azole antifungals. Amphotericin B is effective in the majority of the cases, whereas the azoles are preferred for mild-to-moderate infections. In a nonrandomized trial of 74 HIV-infected patients with disseminated penicilliosis [52], high response rate (97 %) was demonstrated with a regimen of amphotericin B (0.6 mg/k/d) for 2 weeks, followed by itraconazole (400 mg/d) for 10 weeks. Relapse is common 6 months after discontinuation of therapy in as high as 50 % of patients who do not receive maintenance antifungal therapy. Long-term suppressive therapy with itraconazole has been recommended in patients with HIV infection and penicilliosis [53]. Recent noncontrolled trials, however, demonstrated safe discontinuation of secondary prophylaxis for penicilliosis in HIV-infected patients who were responding to highly active antiretroviral therapy (HAART) [49, 54].

Other Agents of *Hyalohyphomycosis*

Scopulariopsis species are common soil saprophytes and have been isolated worldwide (see Fig. 2.12, Chap. 2). Of the many *Scopulariopsis* (sexual state *Microascus*) species, *S. brevicaulis* is the most common cause of human infection [55]. Disease in immunocompetent hosts includes onychomycosis

(most common), keratitis, and rarely, post-traumatic endophthalmitis or subcutaneous infection. Rare cases of endocarditis associated with valvuloplasty or prosthetic valves have been described. Invasive and disseminated infections, particularly with *S. brevicaulis*, may occur in immunosuppressed patients, manifesting as pneumonia or disseminated infection with skin lesions and fungemia. Patients at risk include those with acute leukemia and HSCT [56]. Typically resistant to amphotericin and the azole antifungal, prognosis is often related to immune reconstitution and the ability to perform surgical debridement on localized infections. In vitro, echinocandins appear to have some activity [55].

Beauveria are ubiquitous fungi commonly found in soil. Because of their pathogenicity to many insect species, the organisms are incorporated into pesticides worldwide. Rarely, *Beauveria* may cause infections in humans, including keratitis and subcutaneous mycosis. Disseminated infections have occurred in patients with leukemia and HSCT [57]. The organism appears to be susceptible to itraconazole and amphotericin B.

Trichoderma species are also common environmental fungi. They are rarely reported as the cause of fungal infection, including disseminated or localized disease (e.g., keratitis, sinusitis, peritonitis, pulmonary infections, endocarditis, and brain abscess). Reported risk factors for these infections include hematologic malignancy, solid organ transplantation, and peritoneal dialysis. *T. longibrachiatum* is the most common species to cause human disease. Based on in vitro susceptibilities, the echinocandin antifungal drugs or amphotericin are most likely to be effective against these fungi [58].

Acknowledgments This chapter represents an updated revision of the chapter from the first edition of *Diagnosis and Treatment of Human Mycoses* authored by Rhonda Fleming and Elias Anaissie. The author would like to thank Dr. Fleming and Dr. Anaissie for their previous work in producing this chapter.

References

1. Tortorano AM, Richardson M, Roilides E, et al. ESCMID and ECMM joint guidelines on diagnosis and management of hyalohyphomycosis: *Fusarium* spp., *Scedosporium* spp. and others. Clin Microbiol Infect. 2014;20(Suppl 3):27–46.
2. Marr KA, Carter RA, Crippa F, Wald A, Corey L. Epidemiology and outcome of mould infections in hematopoietic stem cell transplant recipients. Clin Infect Dis. 2002;34:909–17.
3. Nelson PE, Dignani MC, Anaissie EJ. Taxonomy, biology, and clinical aspects of *Fusarium* species. Clin Microbiol Rev. 1994;7:479–04.
4. Hayden RT, Isotalo PA, Parrett T, et al. In situ hybridization for the differentiation of *Aspergillus*, *Fusarium*, and *Pseudallescheria* species in tissue section. Diagn Mol Pathol. 2003;12:21–6.
5. Elvers KT, Leeming K, Moore CP, Lappin-Scott HM. Bacterial-fungal biofilms in flowing water photo-processing tanks. J Appl Microbiol. 1998;84:607–18.
6. Doczi I, Gyetvai T, Kredics L, Nagy E. Involvement of *Fusarium* spp. in fungal keratitis. Clin Microbiol Infect. 2004;10:773–6.
7. Fusarium keratitis–multiple states, 2006. MMWR Morb Mortal Wkly Rep. 2006;55:400–1.
8. Gabriele P, Hutchins RK. *Fusarium* endophthalmitis in an intravenous drug abuser. Am J Ophthalmol. 1996;122:119–21.
9. Flynn JT, Meislich D, Kaiser BA, Polinsky MS, Baluarte HJ. *Fusarium* peritonitis in a child on peritoneal dialysis: case report and review of the literature. Perit Dial Int. 1996;16:52–7.
10. Velasco E, Martins CA, Nucci M. Successful treatment of catheter-related fusarial infection in immunocompromised children. Eur J Clin Microbiol Infect Dis. 1995;14:697–9.
11. Murray CK, Beckius ML, McAllister K. *Fusarium proliferatum* superficial suppurative thrombophlebitis. Mil Med. 2003;168:426–7.
12. Georgiadou SP, Velegraki A, Arabatzis M, et al. Cluster of *Fusarium verticillioides* bloodstream infections among immunocompetent patients in an internal medicine department after reconstruction works in Larissa, Central Greece. J Hosp Infect. 2014;86:267–71.
13. Kurien M, Anandi V, Raman R, Brahmadathan KN. Maxillary sinus fusariosis in immunocompetent hosts. J Laryngol Otol. 1992;106:733–6.
14. Madhavan M, Ratnakar C, Veliath AJ, Kanungo R, Smile SR, Bhat S. Primary disseminated fusarial infection. Postgrad Med J. 1992;68:143–4.
15. Nucci M, Anaissie E. Cutaneous infection by *Fusarium* species in healthy and immunocompromised hosts: implications for diagnosis and management. Clin Infect Dis. 2002;35:909–20.
16. Jakle C, Leek JC, Olson DA, Robbins DL. Septic arthritis due to *Fusarium solani*. J Rheumatol. 1983;10:151–3.
17. Sierra-Hoffman M, Paltiyevich-Gibson S, Carpenter JL, Hurley DL. *Fusarium* osteomyelitis: case report and review of the literature. Scand J Infect Dis. 2005;37:237–40.
18. Boutati EI, Anaissie EJ. *Fusarium*, a significant emerging pathogen in patients with hematologic malignancy: ten years' experience at a cancer center and implications for management. Blood. 1997;90:999–08.
19. Nucci M, Marr KA, Queiroz-Telles F, et al. *Fusarium* infection in hematopoietic stem cell transplant recipients. Clin Infect Dis. 2004;38:1237–42.
20. Nucci M, Anaissie EJ, Queiroz-Telles F, et al. Outcome predictors of 84 patients with hematologic malignancies and *Fusarium* infection. Cancer. 2003;98:315–9.
21. Sampathkumar P, Paya CV. *Fusarium* infection after solid-organ transplantation. Clin Infect Dis. 2001;32:1237–40.
22. Anaissie EJ, Kuchar RT, Rex JH, et al. Fusariosis associated with pathogenic *Fusarium* species colonization of a hospital water system: a new paradigm for the epidemiology of opportunistic mold infections. Clin Infect Dis. 2001;33:1871–8.
23. Anaissie EJ, Stratton SL, Dignani MC, et al. Cleaning patient shower facilities: a novel approach to reducing patient exposure to aerosolized *Aspergillus* species and other opportunistic molds. Clin Infect Dis. 2002;35:E86–E8.
24. Girmenia C, Arcese W, Micozzi A, Martino P, Bianco P, Morace G. Onychomycosis as a possible origin of disseminated *Fusarium solani* infection in a patient with severe aplastic anemia. Clin Infect Dis. 1992;14:1167.
25. Schell WA. New aspects of emerging fungal pathogens. A multifaceted challenge. Clin Lab Med. 1995;15:365–87.
26. Varon AG, Nouer SA, Barreiros G, et al. Superficial skin lesions positive for *Fusarium* are associated with subsequent development of invasive fusariosis. J Infect. 2014;68:85–9.
27. Hue FX, Huerre M, Rouffault MA, de Bievre C. Specific detection of *Fusarium* species in blood and tissues by a PCR technique. J Clin Microbiol. 1999;37:2434–8.
28. Ostrosky-Zeichner L, Alexander BD, Kett DH, et al. Multicenter clinical evaluation of the (1– >3) beta-D-glucan assay as an

aid to diagnosis of fungal infections in humans. Clin Infect Dis. 2005;41:654–9.
29. Horn DL, Freifeld AG, Schuster MG, Azie NE, Franks B, Kauffman CA. Treatment and outcomes of invasive fusariosis: review of 65 cases from the PATH Alliance® registry. Mycoses. 2014; doi:10.1111/myc.12212. Epub ahead of print.
30. Nucci M, Marr KA, Vehreschild MJ, et al. Improvement in the outcomes of invasive fusariosis in the last decade. Clin Microbiol Infect. 2014;20:580–5.
31. Cuenca-Estrella M, Gomez-Lopez A, Mellado E, Garcia-Effron G, Monzon A, Rodriguez-Tudela JL. In vitro activity of ravuconazole against 923 clinical isolates of nondermatophyte filamentous fungi. Antimicrob Agents Chemother. 2005;49:5136–8.
32. Idigoras P, Perez-Trallero E, Pineiro L, et al. Disseminated infection and colonization by *Scedosporium prolificans*: a review of 18 cases, 1990–1999. Clin Infect Dis. 2001;32:E158–E65.
33. Rainer J, De Hoog GS. Molecular taxonomy and ecology of *Pseudallescheria*, *Petriella* and *Scedosporium prolificans* (Microascaceae) containing opportunistic agents on humans. Mycol Res. 2006;110:151–60.
34. Lackner M, De Hoog GS, Verweij PF, et al. Species-specific antifungal susceptibility patterns of *Scedosporium* and *Pseudallescheria* species. Antimicrob Agents Chemother. 2012;56:2635–42.
35. Castiglioni B, Sutton DA, Rinaldi MG, Fung J, Kusne S. *Pseudallescheria boydii* (anamorph *Scedosporium apiospermum*). Infection in solid organ transplant recipients in a tertiary medical center and review of the literature. Medicine (Baltimore). 2002;81:333–48.
36. Montero A, Cohen JE, Fernandez MA, Mazzolini G, Gomez CR, Perugini J. Cerebral pseudallescheriasis due to *Pseudallescheria boydii* as the first manifestation of AIDS. Clin Infect Dis. 1998;26:1476–7.
37. Carrillo AJ, Guarro J. In vitro activities of four novel triazoles against *Scedosporium* spp. Antimicrob Agents Chemother. 2001;45:2151–3.
38. Radford SA, Johnson EM, Warnock DW. In vitro studies of activity of voriconazole (UK-109,496), a new triazole antifungal agent, against emerging and less-common mold pathogens. Antimicrob Agents Chemother. 1997;41:841–3.
39. Walsh TJ, Peter J, McGough DA, Fothergill AW, Rinaldi MG, Pizzo PA. Activities of amphotericin B and antifungal azoles alone and in combination against *Pseudallescheria boydii*. Antimicrob Agents Chemother. 1995;39:1361–4.
40. Gosbell IB, Toumasatos V, Yong J, Kuo RS, Ellis DH, Perrie RC. Cure of orthopaedic infection with *Scedosporium prolificans*, using voriconazole plus terbinafine, without the need for radical surgery. Mycoses. 2003;46:233–6.
41. Fleming RV, Walsh TJ, Anaissie EJ. Emerging and less common fungal pathogens. Infect Dis Clin North Am. 2002;16:915–33.
42. Espinel-Ingroff A. Comparison of In vitro activities of the new triazole SCH56592 and the echinocandins MK-0991 (L-743,872) and LY303366 against opportunistic filamentous and dimorphic fungi and yeasts. J Clin Microbiol. 1998;36:2950–6.
43. Guarro J, Gams W, Pujol I, Gene J. *Acremonium* species: new emerging fungal opportunists – in vitro antifungal susceptibilities and review. Clin Infect Dis. 1997;25:1222–9.
44. Fincher RM, Fisher JF, Lovell RD, Newman CL, Espinel-Ingroff A, Shadomy HJ. Infection due to the fungus *Acremonium* (*Cephalosporium*). Medicine (Baltimore). 1991;70:398–09.
45. Liu K, Howell DN, Perfect JR, Schell WA. Morphologic criteria for the preliminary identification of *Fusarium*, *Paecilomyces*, and *Acremonium* species by histopathology. Am J Clin Pathol. 1998;109:45–54.
46. Supparatpinyo K, Khamwan C, Baosoung V, Nelson KE, Sirisanthana T. Disseminated *Penicillium marneffei* infection in southeast Asia. Lancet. 1994;344:110–3.
47. Sirisanthana T, Supparatpinyo K. Epidemiology and management of penicilliosis in human immunodeficiency virus-infected patients. Int J Infect Dis. 1998;3:48–53.
48. Kawila R, Chalwarith R, Supparatpinyo K. Clinical and laboratory characteristics of penicilliosis marneffei among patients with and without HIV in Northern Thailand: a retrospective study. BMC Infect Dis. 2013;13:464.
49. Sun HY, Chen MY, Hsiao CF, Hsieh SM, Hung CC, Chang SC. Endemic fungal infections caused by *Cryptococcus neoformans* and *Penicillium marneffei* in patients infected with human immunodeficiency virus and treated with highly active anti-retroviral therapy. Clin Microbiol Infect. 2006;12:381–8.
50. Supparatpinyo K, Chiewchanvit S, Hirunsri P, Uthammachai C, Nelson KE, Sirisanthana T. *Penicillium marneffei* infection in patients infected with human immunodeficiency virus. Clin Infect Dis. 1992;14:871–4.
51. Duong TA. Infection due to *Penicillium marneffei*, an emerging pathogen: review of 155 reported cases. Clin Infect Dis. 1996;23:125–30.
52. Sirisanthana T, Supparatpinyo K, Perriens J, Nelson KE. Amphotericin B and itraconazole for treatment of disseminated *Penicillium marneffei* infection in human immunodeficiency virus-infected patients. Clin Infect Dis. 1998;26:1107–10.
53. Supparatpinyo K, Perriens J, Nelson KE, Sirisanthana T. A controlled trial of itraconazole to prevent relapse of *Penicillium marneffei* infection in patients infected with the human immunodeficiency virus. N Engl J Med. 1998;339:1739–43.
54. Hung CC, Chen MY, Hsieh SM, Sheng WH, Hsiao CF, Chang SC. Discontinuation of secondary prophylaxis for penicilliosis marneffei in AIDS patients responding to highly active antiretroviral therapy. AIDS. 2002;16:672–3.
55. Sandoval-Denis M, Sutton DA, Fothergill AW, et al. *Scopulariopsis*, a poorly known opportunistic fungus: spectrum of species in clinical samples and *in vitro* responses to antifungal drugs. J Clin Microbiol. 2013;51:3937–43.
56. Cuenca-Estrella M, Gomez-Lopez A, Mellado E, Buitrago MJ, Monzon A, Rodriguez-Tudela JL. *Scopulariopsis brevicaulis*, a fungal pathogen resistant to broad-spectrum antifungal agents. Antimicrob Agents Chemother. 2003;47:2339–41.
57. Tucker DL, Beresford CH, Sigler L, Rogers K. Disseminated *Beauveria bassiana* infection in a patient with acute lymphoblastic leukemia. J Clin Microbiol. 2004;42:5412–4.
58. Sandoval-Denis, Sutton DA, Cano-Lira JF, et al. Phylogeny of the clinically relevant species of the emerging fungus *Trichoderma* and their antifungal susceptibilities. J Clin Microbiol. 2014;52:2112–25.
59. Diekema DJ, Messer SA, Hollis RJ, Jones RN, Pfaller MA. Activities of caspofungin, itraconazole, posaconazole, ravuconazole, voriconazole, and amphotericin B against 448 recent clinical isolates of filamentous fungi. J Clin Microbiol. 2003;41:3623–6.
60. Pfaller MA, Diekema DJ. Rare and emerging opportunistic fungal pathogens: concern for resistance beyond *Candida albicans* and *Aspergillus fumigatus*. J Clin Microbiol. 2004;42:4419–31.
61. Sabatelli F, Patel R, Mann PA, et al. In vitro activities of posaconazole, fluconazole, itraconazole, voriconazole, and amphotericin B against a large collection of clinically important molds and yeasts. Antimicrob Agents Chemother. 2006;50:2009–15.

Suggested Reading

Dignani MC, Anaissie E. Human fusariosis. Clin Microbiol Infect 2004;10 (Suppl 1):67–75.
Fincher RM, Fisher JF, Lovell RD, Newman CL, Espinel-Ingroff A, Shadomy HJ. Infection due to the fungus *Acremonium* (*Cephalosporium*). Medicine (Baltimore) 1991;70:398–409.

Fleming RV, Walsh TJ, Anaissie EJ. Emerging and less common fungal pathogens. Infect Dis Clin North Am 2002;16:915–933.

Husain S, Alexander BD, Munoz P, et al. Opportunistic mycelial fungal infections in organ transplant recipients: emerging importance of non-*Aspergillus* mycelial fungi. Clin Infect Dis 2003;37:221–229.

Panackal AA, Marr KA. *Scedosporium*/*Pseudallescheria* infections. Semin Respir Crit Care Med 2004;25:171–181.

Schinabeck MK, Ghannoum MA. Human hyalohyphomycoses: a review of human infections due to *Acremonium* spp., *Paecilomyces* spp., *Penicillium* spp., and *Scopulariopsis* spp. J Chemother 2003;15 (Suppl 2):5–15.

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