Infections due to emerging and uncommon medically important fungal pathogens

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ABSTRACT

The emergence of less common but medically important fungal pathogens contributes to the rate of morbidity and mortality, especially in the increasingly expanding population of immunocompromised patients. These pathogens include septate filamentous fungi (e.g., *Fusarium* spp., *Scedosporium* spp., *Trichoderma* spp.), nonseptate Zygomycetes, the endemic dimorphic pathogen *Penicillium marneffei*, and non-*Cryptococcus*, non-*Candida* pathogenic yeast (e.g., *Trichosporon* spp.). The medical community is thus called upon to acquire an understanding of the microbiology, epidemiology and pathogenesis of these previously uncommon pathogens in order to become familiar with the options for prevention and treatment.

Keywords Emerging pathogens, fungal infections, immunocompromised

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INTRODUCTION

Candida spp. constitute the third to fourth most common causes of nosocomial bloodstream infection. *Aspergillus* spp. is the most common cause of infectious pneumonic mortality in haematopoietic transplant recipients. *Cryptococcus neoformans* is the most common cause of fungal-related mortality in human immunodeficiency virus (HIV)-infected patients. Although these organisms are important pathogens, less common but emerging fungal pathogens also cause morbidity and mortality in an increasingly expanding immunocompromised patient population.

These emerging pathogens include septate filamentous fungi (*Fusarium* spp., *Scedosporium* spp., *Trichoderma* spp. and various dematiaceous moulds), an expanding group of nonseptate Zygomycetes, the endemic dimorphic pathogen *Penicillium marneffei* and non-*Cryptococcus*, non-*Candida* pathogenic yeasts such as *Trichosporon* species [1–3].

The increasing importance of these isolates as causes of life-threatening invasive fungal infections in the transplant recipient requires familiarity with the microbiology, epidemiology, pathogenesis and options for the prevention and treatment of these previously uncommon opportunistic pathogens. We will therefore briefly review the microbiology, pathogenesis, epidemiology, clinical manifestations, diagnosis and treatment of these organisms.

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FILAMENTOUS FUNGI

Hyaline septate moulds (agents of hyalohyphomycosis)

'Hyalohyphomycosis' is the term used to represent infections caused by colourless septate fungal hyphae in infected tissue. In tissue they appear as hyaline (lightly or nonpigmented), septate, branching filamentous organisms that can mimic aspergillosis. Definitive identification in hyalo-

hyphomycosis requires isolation of the fungal organism; they may be misidentified as *Aspergillus* spp. in routine histological sections. Hyaline septate moulds are identified in culture by their macroscopic and microscopic morphology with differences in conidiogenesis.

Fusarium spp.

Microbiology. *Fusarium* spp. are hyaline filamentous fungi that produce microconidia and macroconidia. In the early phase of growth where only microconidia are apparent, some *Fusarium* spp. may resemble *Acremonium* spp. In the later phases of growth, the more characteristic canoe-shaped or plantain-shaped macroconidia are used in identifying the genus and species of *Fusarium*. *F. solani*, *F. oxysporum* and *F. moniliforme* are the most common species.

Epidemiology. *Fusarium* spp. have become increasingly recognized as a cause of invasive fungal infections in neutropenic patients and in those undergoing transplantation [3–11]. Some centres have reported *Fusarium* to be second only to *Aspergillus* as the cause of life-threatening filamentous fungal infection in their transplant patients [3,4]. *Fusarium* species have long been associated with infections of the skin, nail and cornea but they seldom cause locally invasive disease in the immunocompetent patient [5,6].

Found in soil, water and decaying material, *Fusarium* spp. are well-known plant pathogens that may cause extensive crop destruction and contamination. Risk factors for invasive fusariosis include persistent neutropenia and graft-versus-host disease (GVHD), particularly the latter. The patient population with GVHD is particularly at risk in the setting of cord blood transplantation, matched unrelated donors and use of high-dose corticosteroids.

Pathogenesis. Inhalation of the conidia of *Fusarium* through the lung and paranasal sinuses after transplantation or intensive chemotherapy may lead to sinopulmonary infection with angioinvasion and infarction or progress to disseminated disease. Secondary disruption of skin integrity appears to be a relatively common portal of entry for disseminated infection with *Fusarium* in the immunocompromised host. This may occur after local trauma to the skin, after placement of vascular catheters, or in the setting of onychomycosis with associated cellulitis where *Fusarium* spp. are known pathogens. The most striking clinical manifestation of this propensity for local cutaneous invasion is observed in neutropenic patients with *Fusarium* paronychia of the great toe. As *Fusarium* spp. are a cause of positive blood cultures and nodular cutaneous lesions, Liu *et al.* have suggested that the pathogenesis of this dissemination may be, in part, the result of 'adventitious forms' or microconidia that occur in-vivo [12].

Clinical manifestations. Invasive fusariosis most commonly presents as fever and pulmonary infiltrates and/or sinusitis. In comparisons to invasive aspergillosis, disseminated fusariosis presents commonly with nodular cutaneous lesions [4,6–9,11]. Disseminated fusariosis is also associated with a relatively high rate (40–60%) of recovery from routine blood cultures [9,10].

Diagnosis. Histopathology of invasive fusariosis reveals branching septate hyphae that are difficult to distinguish from *Aspergillus* spp. and other hyaline moulds [13]. Thus, definitive diagnosis relies on examination of cultures. In culture, *Fusarium* spp. are characterised by canoe-shaped or banana-shaped macroconidia. Definitive diagnosis to the species level may require referral of the culture to a mycology reference laboratory. Unfortunately, the most common early presentation of infection in neutropenic hosts is fever alone without clinical signs of infection or positive culture. Recent studies using polymerase chain reaction techniques of blood and bronchoalveolar lavage samples hold promise for earlier diagnosis in patients at risk for invasive mould infections in the future.

Treatment and outcome. The outcome for disseminated fusariosis in neutropenic patients and transplant recipients remains extremely poor. Response rates vary but mortality rates as high as 100% have been reported in patients who do not recover from neutropenia [6–15]. Even with recovery from neutropenia, patients may suffer progressive fusariosis or develop a chronic infection similar to that of chronic disseminated candidiasis. No patient with GVHD responded to therapy in an earlier MD Anderson Cancer Center study [9]. Only 25% of patients from the Fred Hutchinson Cancer Center study responded

to therapy [4]. Fusarium infections in solid organ transplant recipients tend to be localised and have a better overall outcome compared to haematopoietic stem cell transplant recipients [15]. Surgical resection followed by prolonged antifungal therapy appears to be the most appropriate treatment for infection in the solid organ transplant recipient.

Fusariosis is commonly 'resistant' to amphotericin B [16,17], with breakthrough infections on empiric therapy with amphotericin B [18]. Successful response or disease 'stabilisation' has been reported with higher doses of amphotericin B in the range of 1.0–1.5 mg/kg or with lipid formulations of amphotericin B, using a dose of at least 5 mg/kg per day [19–21].

Among the antifungal triazoles, fluconazole and itraconazole are not active against *Fusarium* spp. Current in-vitro and experimental in-vivo data demonstrate that the new antifungal triazoles, such as voriconazole and posaconazole, exert antifungal activity against some *Fusarium* spp. [21–26], however they have not been shown to have fungicidal activity in-vitro. Treatment with one of the lipid formulations of amphotericin B, or voriconazole, is recommended as primary therapy while attempts are made to minimize the immune deficit with the use of granulocyte or granulocyte–macrophage colony-stimulating factor (GCSF or GMCSF) in neutropenic hosts as well as reducing immune suppressive therapy when possible.

Scedosporium spp.: *S. apiospermum* (*Pseudallescheria boydii*) and *S. prolificans*

Microbiology. The genus *Scedosporium* contains two medically significant species of emerging fungi, *S. apiospermum* and *S. prolificans* (formerly *S. inflatum*). The teleomorph (sexual state) known as *Pseudallescheria boydii* produces dark round sexual structures (cleistothecia) that contain asci and ascospores. In the absence of the sexual form in culture, the organism is identified as the anamorph (asexual form) known as *S. apiospermum*. The hyphal forms of *S. apiospermum* and of *P. boydii* in culture appear as branching septate hyphae that display terminal annelloconidia. The pyriform terminal conidia may occasionally be observed in tissue. Otherwise, the genus *Scedosporium* in tissue appears as a septate hyaline mould that resembles *Aspergillus* species.

The hyphal structures of *S. prolificans* consist of dilated or inflated phialides along the hyphal structure that give rise to one or more conidia. The inflated appearance of the phialides of *S. prolificans* gave rise to the earlier term for this organism, '*S. inflatum*'. The name of the anamorph of this organism has since been revised on molecular taxonomic grounds to sexual *S. prolificans*. The sexual stage of *S. prolificans* is a *Petriella* species.

Epidemiology. *S. apiospermum* is a saprophytic mould found in soil, polluted water, sewage, and manure. *S. apiospermum* causes three distinct patterns of infection: mycetoma, deeply invasive infection and saprophytic involvement [27–36]. *S. apiospermum* is the most common cause of mycetoma in North America. Presenting as tumour-like swelling with draining sinuses, in the immunocompetent host, *S. apiospermum* has been found to be a common isolate in mycetoma of the lower extremities and less commonly the hand. Fatal pulmonary and disseminated infection has been observed in immunocompetent victims of near-drowning accidents. Deeply invasive infection due to *S. apiospermum* is most commonly observed in immunocompromised patients, with the lungs being the most frequent site of infection. Nine patients undergoing haematopoietic stem cell transplant at the Fred Hutchinson Cancer Center were diagnosed with invasive *Scedosporium* spp. infections over a 15-year period from 1985 to 1999. *S. apiospermum* may also involve the lungs as a saprophytic process, resulting in the development of a fungus ball that is radiologically indistinguishable from aspergilloma. The organism also saprophytically involves the lower respiratory tract of patients with cystic fibrosis and broncheictasis.

S. prolificans causes localised infection, usually restricted to bone and soft tissues, in immunocompetent patients, and causes deeply invasive infection in immunocompromised patients. *S. prolificans* has been documented to cause disseminated infections in immunocompromised patients with neutropenia and after haematopoietic stem cell transplantation [30–35]. A nosocomial outbreak due to *S. prolificans* was reported recently in a haematology–oncology unit [36]. The organism was thought to be aerially transmitted. Molecular epidemiological analysis confirmed that the outbreak was caused by a single strain. In a review of the literature Revankar *et al.*

recently reported that 24 of 30 cases of infection with *S. prolificans* were reported from Spain or Australia [37].

Pathogenesis. Phagocytic host defences to conidia of *P. boydii* depend upon monocytes and macrophages, while defence against hyphae depends upon peripheral mononuclear lymphocytes. *P. boydii* is more susceptible to phagocytic host defences but is more polyene-resistant than *A. fumigatus* [38,39]. *S. apiospermum* is variably susceptible to phagocytic function. Selective inhibition of hyphal damage suggests an important difference in susceptibility to myeloperoxidase products that may be related to the variable pathogenicity of different isolates of *S. apiospermum* [39].

The portal of entry of *Scedosporium* spp. in immunocompromised patients is thought to be similar to that of *Aspergillus*, with inhalation of conidia leading to sinopulmonary infection and eventual dissemination to multiple sites including skin, brain, heart and multiple organs.

Clinical manifestations. Localised infection principally involving the musculoskeletal system is a common presentation of scedosporiosis after penetrating trauma in the immunocompetent host. Mycetoma may ensue to cause destruction of the muscle, tendons and bone. A chronic infection with draining sinus tracks is characteristic of mycetoma. The drainage of *Scedosporium* mycetoma contains 'grains' that in essence are microcolonies of organisms within a matrix of inflammatory debris. Penetrating injury to the eye may also be complicated by localised *Scedosporium* infection. Sinopulmonary disease is another form of deep localised infection that is usually present in immunosuppressed hosts.

The respiratory tract is the main portal of entry of infection by *Scedosporium* spp. in immunocompromised patients. The clinical manifestations of pulmonary scedosporiosis resemble those of aspergillosis. Fever is a common manifestation that should prompt the performance of a computed tomography scan that may demonstrate a bronchopneumonia, nodular densities, wedge-shaped infiltrates, or halo sign. In patients recovering from neutropenia, a crescent sign may be evident. *Scedosporium* spp. also may saprophytically involve pre-existing lung cavities to cause a 'fungus ball' in patients with tuberculosis or sarcoidosis.

Disseminated infection is reported for both species of *Scedosporium*. Central nervous system (CNS) infection due to *S. apiospermum* presents as focal neurological deficits, including paresis and seizures. Clinical features of disseminated infection due to *S. prolificans* have been characterised in a recent report from Spain [41]. Fever unresponsive to broad-spectrum antibiotics was the most common presentation, followed by respiratory symptoms (dyspnea and chest pain). Thirty-seven per cent of the cases developed CNS symptoms and 25% developed skin lesions characterized by nonpruriginous erythematous, nodular lesions with a necrotic centre in some cases. Radiological findings included bilateral focal and diffuse pulmonary infiltrates, single or multiple nodules and pleural effusions. Other reported cases and case series have described similar findings for *S. prolificans* [42–45]. In comparison to *Aspergillus* spp., there was a relatively high rate of fungemia, with isolation of the organism in blood cultures and dissemination to the skin lesions and central nervous system.

Diagnosis. Definitive diagnosis of scedosporiosis depends upon recovery of the organisms from clinically overt sites of infection. *Scedosporium* spp. are seldom contaminants and should be regarded as pathogenic when recovered from immunocompromised patients. *Scedosporium* spp. may be recovered from blood cultures. Although the organisms are indistinguishable histologically in most instances from *Aspergillus* species in tissue, the terminal annelloconidia of *S. apiospermum*, when present in tissue, is virtually diagnostic of the species.

Treatment and outcome. Amphotericin B exhibits variable in-vitro activity against isolates of *S. apiospermum* [38]. Itraconazole and voriconazole have been shown to be inhibitory but not fungicidal [46,47]. The echinocandins also may have inhibitory activity in-vitro against *S. apiospermum* [48,49]. Administration of high-dose amphotericin B has been the initial approach to the therapy of deeply invasive infection with *P. boydii*, however the overall response rates have been dismal in immunocompromised hosts. Treatment with voriconazole, or one of the other novel broad-spectrum triazoles still under investigation, may be more effective; a recent report described six cases of *S. apiospermum* (*P. boydii*) and two cases of

S. prolificans in paediatric patients who were treated with voriconazole [27]. The overall response of all patients with *Scedosporium* infection was 63%. In *S. apiospermum* infections, 83% had a successful outcome, however both patients with *S. prolificans* infection were refractory to voriconazole therapy. In addition to antifungal therapy, restoration of immune competence is essential for survival from these frequently fatal infections. Patients with mycetoma usually require surgery for control of infection.

Surgical resection remains the only definitive therapy for infection by *S. prolificans*. Medical therapy of nonresectable or disseminated disease in immunocompromised patients is ineffective [42]. *S. prolificans* is considered to be resistant to all current antifungal agents including the novel antifungal triazoles and the echinocandins [24,46,48]. These in-vitro observations correlate with the dismal response of *S. prolificans* infections to antifungal chemotherapy. Interferon-γ and GM-CSF have been shown to enhance neutrophil superoxide production in response to *S. prolificans* hyphae in-vitro [49].

Paecilomyces spp.

Microbiology. Paecilomyces is an asexual hyaline filamentous fungus related to *Penicillium*. *Paecilomyces* has characteristic phialides that distinguish this genus from *Penicillium* spp. There are two medically important species of the genus *Paecilomyces* responsible for human disease: *P. variotii* and *P. lilacinus*. Both species differ morphologically, clinically and also in their in-vitro susceptibility to antifungal compounds.

Epidemiology. Paecilomyces spp. are found worldwide. They are frequently encountered as airborne contaminants in clinical specimens and may be resistant to sterilising techniques. Infections due to *Paecilomyces* are uncommon but devastating events in immunocompromised patients. There have been numerous reports of invasive disease in organ and haematopoietic stem cell transplant patients [50–57], as well as other immunocompromised patients [58–60]. Several outbreaks have been attributed to *Paecilomyces* in the last two decades. The first reported surgical outbreak reported in 1980 involved 13 cases of *P. lilacinus* endophthalmitis after insertion of an intraocular lens that was manipulated with the same neutralizing solution [61]. Two subsequent outbreaks of *P. lilacinus* infections occurred in a haematology–oncology unit after administration of a contaminated skin lotion [56].

Pathogenesis. The portal of entry for this organism is the respiratory tract, indwelling catheters and the skin, resulting in pneumonitis, fungemia and disseminated infection. Similar to *Fusarium* and *Acremonium* spp., the development of adventitious forms in tissue may explain the propensity for dissemination [12].

Clinical manifestations. The majority of the human cases of infections due to *Paecilomyces* spp. have been documented in ocular mycoses (mycotic keratitis and endophthalmitis), and fungal peritonitis in patients undergoing peritoneal dialysis. Other sites of infections include musculoskeletal, cutaneous, sinopulmonary, vascular (endocarditis), as well as disseminated disease in immunocompromised patients.

Diagnosis. Definitive diagnosis in most cases rests upon recovery of the organism and demonstration of hyphal forms in tissue. Careful mycological assessment of the organism is important because a cursory review may dismiss the organism in a general clinical microbiology laboratory as a contaminating *Penicillium* species.

Treatment and outcome. Because of their different susceptibilities to antifungal agents, *Paecilomyces* should be identified to the species level. *P. variotii* is susceptible to amphotericin B, whereas *P. lilacinus* is resistant to amphotericin B and flucytosine, but demonstrates some susceptibility to voriconazole and other broad-spectrum triazoles [62–64].

High dosages of conventional deoxycholate amphotericin B (= 1 mg/kg/day) with surgical intervention for localised disease have been recommended as the initial therapy for this infection. Clinical responses with this strategy, however, have been poor in previously reported cases of disseminated disease in immunocompromised patients. The use of alternative agents such as voriconazole or the high-dose lipid formulation of amphotericin B (= 5 mg/kg/day) for primary therapy seem to be more reasonable and less toxic alternatives.

Trichoderma spp.

Microbiology. *Trichoderma* is a hyaline mould of the class Hyphomycetes. *Trichoderma* spp. are rapidly growing organisms, the colonies of which are initially smooth or translucent and later become floccose, forming concentric white and green rings. *Trichoderma* is characterised microscopically by smooth-walled, hyaline, septate and branched hyphae. Five species of the genus *Trichoderma* have been identified as human pathogens: *T. longibrachiatum*, *T. harzianum*, *T. koningii*, *T. pseudokoningi* and *T. viride*. Among these species *T. longibrachiatum* is the most commonly recovered from cases of invasive infections.

Epidemiology. Members of the genus *Trichoderma* are most commonly recovered from soil, but have also been isolated from air. Previously regarded as nonpathogenic to humans, *Trichoderma* spp. have emerged as new fungal pathogens in immunocompromised patients and peritoneal dialysis patients [64–70]. Fifteen cases of *Trichoderma* infections have been previously reported in immunocompromised patients. The first report describes a case of *T. viride* isolated from a pulmonary mycetoma in a patient with chronic lung disease [71]. Six cases of peritonitis caused by different species of *Trichoderma* were documented in patients undergoing continuous ambulatory peritoneal dialysis [70,72–76]. Only two patients (infected with *T. pseudokoningii* and *T. koningii*) survived after early catheter removal. Three cases of disseminated infection by *Trichoderma* were described in two patients receiving bone marrow transplants (*T. pseudokoningii* and *T. longibrachiatum*) and one in a renal transplant recipient (*T. harzianum*) [65].

Pathogenesis. The relative paucity of virulence of *Trichoderma* spp. in immunocompetent hosts is suggested after the report of an inadvertent infusion of *T. viride* in a contaminated intravenous solution. This patient received a single dose of amphotericin B and remained well [77]. Little is known, however, about the mechanisms of host defence against this organism. Whether *T. longibrachiatum* is more virulent compared to other members of the genus is not known.

Diagnosis. An increased awareness of this uncommon, but frequently fatal, infection should be considered in immunosuppressed patients with infections resembling those of *Trichoderma*. Definitive diagnosis is established by cultures of blood and/or other normally sterile tissue or fluids.

Clinical manifestations. Trichoderma infections appear predominantly in immunocompromised patients as nodular pulmonary infiltrates, peritonitis (complicating peritoneal dialysis), localised cutaneous lesions, and disseminated infection, including CNS infection.

Treatment and outcome. Most isolates of *Trichoderma* show resistance to fluconazole and 5-flucytosine and are found to be susceptible or intermediate to amphotericin B, itraconazole, ketoconazole and miconazole. Recent in-vitro data indicate that *T. longibrachiatum* is susceptible only to relatively high concentrations of amphotericin B [78,79].

Overall mortality associated with disseminated infections due to *Trichoderma* spp. approaches 100%. A patient with acute leukaemia and brain abscess due to *T. longibrachiatum* was successfully treated with amphotericin B and surgical drainage [80]. Invasive sinusitis in a liver transplant patient due to *T. longibrachiatum* was also successfully treated with surgery and prolonged antifungal therapy [81]. A paediatric patient with aplastic anaemia recovered from a cutaneous lesion due to *T. longibrachiatum* with prolonged antifungal therapy [78]. Favourable outcome of infections due to *Trichoderma* spp. was associated with catheter removal in cases of peritonitis, and surgical debridement of localized lesions. *T. viride* caused a persistent infection of a perihepatic haematoma in a liver transplant patient who received amphotericin B and surgical drainage [82].

Amphotericin B or lipid formulation of amphotericin B is used for treatment of patients with suspected or documented *Trichoderma* spp. Surgical resection of localised infection is recommended whenever feasible.

Acremonium spp.

Microbiology. *Acremonium* spp. (also classified by some experts as *Cephalosporium* spp.) are saprophytic hyaline moulds. Among the *Acremonium* spp., *A. stricutm* has been reported as one of the more common causes of infection by this genus.

Acremonium spp. produce hyphae with characteristic phialides, and microconidia. The microconidia in early stage of culture may resemble those of *Fusarium* spp.

Epidemiology. *Acremonium* spp. are saprophytic moulds commonly found in the environment. Colonisation of humidifier water in the ventilator system of an ambulatory surgery centre was thought to be the source of infection for four cases of endophthalmitis investigated by the Centers for Disease Control and Prevention. Many cases of human disease occur in immunocompetent hosts. Keratomycosis due to *Acremonium* regularly develops in people who wear contact lenses. Mycetoma, which is the most common nonocular infection caused by *Acremonium* in immunocompetent patients, usually develops a complication of penetrating trauma. Invasive disease, however, is almost exclusively seen in patients with neutropenia, transplantation, or other immunodeficiency [83].

Pathogenesis. The lungs and gastrointestinal tract are considered portals of entry of deep infection due to *Acremonium* spp. Species of *Acremonium* produce characteristic hyphae and phialoconidia, which may be similar to those of *Fusarium* spp. in the early stages of growth in-vitro. In a manner similar to that of *Fusarium* and *Paecilomyces* spp., *Acremonium* spp. produce small adventitious unicellular forms in-vivo that may be seen histologically in the skin and lung tissue of infected individuals. Production of small adventitious unicellular forms in-vivo may facilitate dissemination and may explain the high rate of haematogenously disseminated cutaneous lesions, as well as positive blood cultures observed with these organisms. *Acremonium* spp. can invade vascular structures resulting in thrombosis, tissue infarction and necrosis. In-vivo sporulation can occur, resulting in positive blood cultures in cases of disseminated infections [84].

Diagnosis. Like other hyaline moulds, septate nonpigmented hyphae are found on routine histopathologic examination. However, variation in the diameter of the hyphae and both acute and right-angle branching are usually present [85]. Nevertheless, the histological features of *Acremonium* infections are sufficiently variable as to preclude a direct species diagnosis.

Clinical manifestations. The spectrum of invasive disease includes sinusitis, osteomyelitis, arthritis, peritonitis, pneumonia and disseminated infection [86–92].

Treatment. Recent in-vitro studies evaluated the antifungal activity of currently available antifungals against *Acremonium* spp. The species have little susceptibility to other currently available antifungal agents [89]. Overall, the isolates were relatively resistant to safely achievable concentrations of the antifungal agents studied. In-vitro antifungal activity was demonstrated with amphotericin B but not with fluconazole and flucytosine. Given the infrequency with which this disease occurs, optimal treatment of invasive infection due to *Acremonium* has not been established. Reported cases of invasive infections, however, suggest some benefit with the use of amphotericin B and surgical excision of the infected tissue. Successful treatment of a pulmonary infection due to *A. strictum* with posaconazole has recently been reported in a leukaemic patient who had failed prior treatment with amphotericin B [92], suggesting that the second-generation triazoles may be effective agents in treatment of acremonium infections.

Scopulariopsis spp. and *Microascus* spp.

Microbiology. *Scopulariopsis* species are hyaline moulds in anamorphic (asexual) form. Among the infections due to *Scopulariopsis* spp., *S. brevicaulis* is the most frequently reported aetioliogic anamorphic species. *Microascus* spp. is the teleomorphic (sexual) form of another hyaline mould, which has been associated with deep-seated infection after transplant [93,94]. *M. cinerus* and *M. cirrosus* are teleomorphs of *Scopulariopsis* spp. that have been isolated from deep infection.

Epidemiology. *S. brevicaulis* has been isolated from immunocompetent patients with onychomycosis and localised infections associated with penetrating traumatic injury. It has also been reported to cause deeply invasive infection, including sinusitis, pulmonary and disseminated infection in immunocompromised patients [95–98].

Diagnosis. Although multiple skin lesions in a liver transplant recipient suggested hematogenous spread, this route of dissemination could not be documented by blood cultures [95]. Diagnosis

usually depends upon culture of the organism from tissue containing branching septate hyphae that are histologically compatible with *Scopulariopsis* spp.

Clinical manifestations. Scopulariopsis infections cause onychomycosis, localised infections, sinusitis, and pulmonary or disseminated infection.

Treatment. There is a paucity of data regarding in-vitro antifungal susceptibility of *Scopulariopsis* spp. and treatment of deeply invasive and disseminated infections caused by these pathogens [47,62]. For treatment of deep infection, amphotericin B, a lipid formulation of amphotericin B, itraconazole or voriconazole may be useful therapy. In the reported case of recurrent subcutaneous infections due to *S. brevicaulis* in a liver transplant recipient, long-term control was achieved with a combination of surgery and long-term therapy with terbinafine [95]. As a result of its pharmacokinetic properties, however, terbinafine has no efficacy against deep infections.

Response to amphotericin B in either the anamorph or teleomorph stage has been documented with either conventional or lipid formulation of amphotericin B. *M. cinerus* was isolated from a brain abscess in a patient with GVHD after allogeneic haematopoietic stem cell transplantation, and *M. cirrosus* in a paediatric patient with cutaneous lesion and consolidating lung infiltrate after autologous stem cell transplant. Both responded to therapy with lipid formulations of amphotericin B, with concomitant of surgical resection and itraconazole for the patient with the brain abscess [93,94].

Dematiaceous moulds

Microbiology. Dematiaceous fungi constitute a group of fungal organisms that are characterised by the presence of pale brown to dark melanin-like pigment in the cell wall. Clinical entities associated with dematiaceous fungi are chromoblastomycosis and phaeohyphomycosis. Dematiaceous fungi sometimes are also responsible for black-grained mycetoma. A detailed description of superficial localised cutaneous or subcutaneous infections due to dematiaceous fungi is beyond the scope of this review. We will focus upon the deep invasive or disseminated infections caused by dematiaceous fungi.

The term 'phaeohyphomycosis' was introduced by Ajello *et al.* [99] in 1974 and means 'condition of fungi with dark hyphae'. However, some fungi produce varying amounts of melanin pigment in their cell walls under differing conditions. Moreover, while in-vivo melanin production may be minimal and fungal elements appear 'hyaline', in culture increasing melanin production leads to darker pigmentation.

The number of dematiaceous moulds that have been documented as aetiologic agents of phaeohyphomycosis continues to increase. Several of these organisms appear to be neurotropic, where they localise in the CNS causing one or multiple brain lesions or abscesses. Dematiaceous fungi known to be neurotropic include *Cladophialophora bantiana*, *Wangiella* (*Exophiala*) *dermatitidis*, *Ramichloridium obovoideum*, *Chaetomium atrobrunneum* and *Dactylaria* (*Ochrochonis*) *gallopavum*. *Bipolaris* spp. and *Exserohilum rostratum* most commonly cause sinusitis and may also invade the CNS via extension from the paranasal sinuses. Other fungal pathogens known as aetiologic agents of sinusitis include *Alternaria* and *Curvularia* species.

Pathogenesis. Melanin plays an important role in the evasion of host defence by fungal pathogens, including dematiaceous moulds. Among the mechanisms proposed are quenching of oxidative metabolites, reduced susceptibility to antimicrobial peptides, reduced susceptibility to antifungal compounds, and decreased susceptibility to enzymatic degradation [100]. However, because much of the insight gained from melanin in fungal pathogenesis is derived from *Cryptococcus neoformans*, further investigation of the role of melanin in host defence in the dematiaceous moulds and in host defence is warranted [101]. This is particularly important because the biosynthetic pathway of melanin in *C. neoformans* differs from that of dematiaceous moulds. Melanin in *C. neoformans* is synthesized via the dihydroxyphenylalanine (DOPA) pathway, whereas melanin in dematiaceous moulds such as *W. dermatitidis* is synthesized through the dihydroxynaphthalene polyketide pathway [102].

Epidemiology. Immunocompromised and immunocompetent patients are at risk for development of CNS phaeohyphomycosis. Immunocompetent patients may have no history of exposure to a concentrated source of moulds (e.g. mulch heaps).

Although most pathogens are distributed worldwide, there are some distinctive patterns that bear note. *R. obovoideum* (*R. mackenziei*) is a well-known cause of sinusitis and CNS infection in the Middle East. This organism should be considered as an aetiologic agent in patients referred for transplantation from this region of the world and who manifest signs of sinusitis or CNS infection. *D. gallopava* (*O. gallopavum*) causes an aggressive CNS infection in immunocompromised patients. It thrives in high ambient temperatures (= 40 °C) and is a well-known cause of epidemic encephalitis in domestic poultry.

Clinical manifestations. The clinical manifestations of CNS infection by dematiaceous moulds include headache, fever, and focal neurological deficits. Immunocompetent patients may have no obvious pulmonary signs or no dissemination to other organs.

In the spectrum of sinus infection, sinusitis due to *Bipolaris* or *Exserohilum* may occur in otherwise healthy patients with nasal polyposis and allergic rhinitis [103,104]. Such patients often present with sinus pain or painless proptosis. Sudden blindness can occur as a result of compression of the optic nerve. Computed tomography or magnetic resonance imaging usually reveals maxillary and ethmoid sinus involvement.

Diagnosis. Histological examination of phaeohyphomycosis may reveal septate hyphae with irregular diameters and golden brown cell walls. Early stages of infection may lack this characteristic pigmentation. Phaeomycotic lesions vary histologically but may appear as pyogranulomas with a purulent centre with surrounding lymphocytes, monocytes, macrophages and multinucleate giant cells. By comparison, histopathologic examination of sinus tissue involved with *Bipolaris* or *Exserohilum* in otherwise healthy patients with allergic sinusitis demonstrates strands of neutrophils and eosinophils with Charcot–Leyden crystals and scattered septate hyphae. The pigmented cell wall of the hyphae in such cases may be less apparent than in brain abscesses [105].

Culture of infected tissue establishes the definitive microbiological diagnosis. *W.* (*Exophiala*) *dermatitidis* is recovered in cultures of clinical specimens as dematiaceous yeast; however, this organism is dimorphic and develops hyphae in human tissue.

Treatment and outcome. Cerebral phaeohyphomycosis has a high degree of morbidity and mortality, requiring early and aggressive therapy. The optimal medical and surgical treatment has not yet been established. Historically, early treatment with amphotericin B and complete surgical excision has been recommended until newer alternatives are found. However, the use of voriconazole in lieu of amphotericin B for CNS phaeohyphomycosis offers a less toxic alternative with oral and parenteral formulations [106].

As a class, the antifungal triazoles, itraconazole, voriconazole and posaconazole may have superior activity against many dematiaceous moulds [107–109]. For management of *Bipolaris* or *Exserohilum* in otherwise healthy patients with nasal polyposis and allergic rhinitis, good surgical curettage and initial treatment with itraconazole or voriconazole may be sufficient to eradicate the infection if there is no intracranial involvement. Long-term triazole therapy after repeat surgical therapy may prevent recurrences.

Zygomycetes

Microbiology. The class of Zygomycetes encompass two orders of medically important fungi: Entomophthorales and the Mucorales. Characterised by broad, sparsely septated, and irregularly branched hyphae in tissue, they appear in culture as a rapidly growing mould that forms a variety of structures including stolons, rhizoids, sporangia, apophyses, sporangiophores, sporangia, collumellae and sporangiospores. *Rhizopus* is the most common genus to cause infection [110,111], however a number of other Zygomycetes have been increasingly reported as causing devastating infections in immunocompromised patients [110–121], While a detailed discussion of the class Zygomycetes is beyond the scope of this paper, we will review some of the salient features of these organisms as they infect immunocompromised hosts.

Epidemiology. Zygomycosis develops most frequently in patients with diabetic ketoacidois and pharmacologically immunocompromised patients, including those with neutropenia, and following solid organ or haematopoietic transplantation [110–113]. Patients who are receiving desferoxamine, such as those with iron or aluminium overload states, are also at risk for

development of zygomycosis. Although the respiratory tract is the most common portal of entry for these pathogens, cutaneous routes of infection are particularly important in patients in the setting of surgery, trauma, burns, or neonatal intensive care. The latter situation occurs as a result of the tenuous nature of the integument of newborn infants. The development of zygomycosis in areas of skin breakdown has been associated with a variety of contaminated adhesive products, elastic bandages, and tongue depressors used in the hospital setting.

Pathogenesis. Host defences against zygomycetes are mediated by monocytes, macrophages and neutrophils. Pulmonary alveolar macrophages serve as a first line of host defence against sporangiospores while neutrophils mediate protection against hyphae. Patients suffer an increased risk for developing zygomycosis as a result of functional and/or numerical deficiencies of these cells. The paucity of reports of zygomycosis in HIV-infected patients who do not inject intravenous illicit drugs indicates that T-cell dysfunction alone is not a major determinant in the development of this disease.

Metabolic acidosis is a key factor in predisposing patients to zygomycosis. Low plasma pH diminishes the phagocytic and chemotactic ability of neutrophils and decreases the affinity for irol transferral, thus enhancing fungal growth. The role of iron availability in the host–fungus interaction is underscored by the observations of disseminated zygomycosis developing in patients receiving iron chelation therapy, where the desferroxamine molecule is subverted by the organism to serve as a siderophore.

Zygomycetes demonstrate a pattern of angioinvasive tissue invasion that is similar to that of *Aspergillus* spp. The resulting tissue infarction produces clinically apparent eschars on physical examination and necrotic tissue observed at surgery.

Clinical manifestations. Zygomycosis in diabetic patients presents classically as rhinocerebral infection. Immunocompromised patients with neutropenia or following transplantation may present with either rhinocerebral or pulmonary infection. Involvement of the ethmoidal sinuses may be associated with concomitant cavernous sinus thrombosis [122].

Diagnosis. Definitive diagnosis depends upon demonstration of the characteristic hyphal morphology in tissue. Culture of a zygomycete from such tissue further defines the species. However, cultures may prove to be negative in tissue that clearly demonstrates hyphal elements. Such culture-negative results may be due to concurrent antifungal chemotherapy or to loss of hyphal viability in tissue homogenisation prior to culture.

Treatment and outcome. High doses of amphotericin B deoxycholate have been considered standard therapy for treatment of localised or disseminated zygomycosis. Lipid formulations of amphotericin B, with or without the use of recombinant cytokines, have been shown to have activity in patients refractory to therapy with amphotericin B deoxycholate [19,123]. Currently the available triazoles, including voriconazole as well as the echinocandins, are considered inactive as single agents [124,125]. On the other hand, posaconazole has activity in-vitro, in animal models, and in some patients with refractory zygomycosis [126]. Further study of this promising triazole, as well as newer approaches of combined drug and immunotherapy, is warranted for this fungal infection with a historically poor outcome.

Finally, surgical debridement is considered an integral part of treatment for localised disease. This may be in part the result of poor antifungal activity for many isolates and of the inability of the drug to penetrate necrotic tissues, particularly in the paranasal sinuses.

Uncommon yeast pathogens

Trichosporon spp.

Microbiology. Trichosporon spp. are characterised by hyphae, pseudohyphae, blastoconidia and arthroconidia with varying morphological features depending upon the species. All of the various clinical manifestations were previously ascribed to *T. beigelii* [127–129]. Recent revisions of the taxonomic nomenclature based on differences in the morphology, biochemistry and molecular genetics of isolates of the genus *Trichosporon* have suggested that *T. beigelli* consists of 17 species with five varieties [130–135]. *T. asahii* and *T. mucoides* are most commonly isolated in deep-seated infections, *T. cutaneum* and *T. asteroides* cause superficial infection, and *T. ovoides* and

T. inkin are associated with white piedra. *T. pullulans* and *T. domesticum* have also been reported to cause systemic infection in immunocompromised hosts. Most cases of invasive trichosporonosis, heretofore attributed to *T. beigelii*, are considered to be due to *T. asahii*.

Pathogenesis. The organism expresses glucuronoxylomannan (GXM) in its cell wall. GXM in *Trichopsoron* is antigenically and biochemically similar to that of GXM in *C. neoformans* [136–138]. Similar to *C. neoformans*, isolates of *Trichosporon* from patients with fungemia have been shown to express high concentrations of the GXM antigens shown to inhibit phagocytosis by monocytes [138]. Neutrophils and monocytes mediate the phagocytic host response to *Trichosporon*. However, phagocytic host response may be attenuated by GXM-mediated immunosuppression, resulting in reduced phagocytosis and microbicidal activity [139]. In-vitro studies with monocyte and granulocyte–monocyte colony-stimulating factor as well as interferon-γ have shown enhancement of phagocytosis against *Trichosporon*, suggesting a possible role for adjuvant immunotherapy with recombinant cytokines, particularly GM-CSF.

The most common portals of entry are considered to be the gastrointestinal tract and vascular catheters [140]. Bronchopneumonia has also been seen, either because of inhalation of organisms from the surrounding environment or secondary to aspiration.

Epidemiology. Trichosporon spp. can cause life-threatening fungemia and disseminated infection similar to that caused by *Candida* spp. A common cause of white piedra and summer-type hypersensitivity in Japan, *Trichosporon* spp. also cause fatal infections in immunocompromised patients, most commonly those with leukaemia [127–129,141], as well as in solid organ and haematopoietic stem cell transplant recipients [142–145]. The risk factors for infection include neutropenia, corticosteroids and other factors of immunosuppression, as well as breaks in mucosal integrity caused by surgery, placement of vascular catheters and cytotoxic chemotherapy leading to mucositis and enteritis.

Clinical manifestations. Widespread trichosporonosis can then occur by haematogenous dissemination, leading to renal failure, pulmonary infiltrates, multiple cutaneous lesions, chorioretinitis and even septic shock. A chronic hepatic trichosporonosis similar to chronic hepatic candidiasis has also been reported with *Trichosporon* [127–129,146].

Treatment and outcome. Treatment relies on rapid diagnosis and differentiation of *Trichosporon* from the more common *Candida* spp. Although amphotericin B has been found to be inhibitory to *Trichosporon in vitro*, it has poor fungicidal activity with breakthrough infections seen in febrile neutropenic patients on high-dose empiric treatment with amphotericin B [147]. In a persistently neutropenic rabbit model of disseminated trichosporonosis, treatment with amphotericin B deoxycholate (1 mg/kg per day) and a lipid formulation of amphotericin B at 5 mg/kg per day was unable to clear tissues in comparison with saline-treated controls [140]. The mortality associated with disseminated disease has been reported as high as approximately 80% in immunocompromised patients treated with amphotericin B [127–129].

Antifungal triazoles have shown the best activity in-vitro and in animal models of disseminated infection [140,148,149]. Fluconazole alone is considered the optimal first-line therapy. A murine model of disseminated trichosporonosis revealed that the combination of fluconazole with amphotericin B may have enhanced clinical activity against some isolates [150]. Echinocandins have poor activity against *Trichosporon in vitro* and are not recommended for therapy.

Blastoschizomyces capitatus (formerly *Trichosporon capitatum*)

Microbiology. B. capitatus, previously known as *Trichosporon capitatum*, was reclassified as a separate genus due to morphological, biochemical and genetic differences. In comparison to *Trichosporon* spp., *B. capitatus* develops anelloconidia instead of arthroconidia.

Epidemiology. The risk factors for deep infection by *B. capitatus* are similar to those of *Trichosporon* spp.

Clinical manifestations. B. capitatus can disseminate haematogenously to multiple organ sites including the liver, spleen, kidneys and bone in

neutropenic patients. Blood cultures are usually positive at the time of acute infection, and fungal meningitis is more common than with disseminated candidiasis or trichosporonosis [151–159]. Cases of chronic disseminated infection have also been seen.

Treatment and outcome. Similar to that of *Trichopsoron* spp., *B. capitatus* may have decreased susceptibility to the fungicidal activity of amphotericin B and consequently poor clinical outcome after treatment with amphotericin B in the setting of neutropenia. Although fluconazole and flucytosine appear to be more active in-vitro, breakthrough infections have been reported in patients on fluconazole prophylaxis and resistant strains have been reported as nosocomial pathogens [158]. Optimal therapy remains to be defined. The combination of an azole antifungal and amphotericin B with immunotherapy for initial treatment may be the best approach for this potentially life-threatening infection.

Malassezia spp.

Microbiology. Malassezia spp. are lipophilic yeasts, which are part of the normal human cutaneous commensal flora. *Malassezia* spp. have been associated with atopic dermatitis and seborrhoeic dermatitis. *Malassezia* spp. are also considered the aetiologic agents of tinea versicolor in the immunocompetent patient. The genus *Malassezia* has recently been revised to include seven species. In a recent Canadian study the most common isolates in patients with skin disease included *M. sympodialis*, *M. globosa* and *M. furfur* [160–164].

Pathogenesis. Exposure of *Malassezia* to the lipid emulsions in total parenteral nutrition solutions enhances growth of this organism. This infection has been well characterised in neonates, where the organism causes fungemia and acute respiratory distress that corresponds to subendothelial proliferation of the organisms amidst depositions of lipid demonstrated histologically by neutral fat stains [165,166]. Organisms are not usually found in other deep tissues.

Epidemiology. In the immunocompromised patient, *Malassezia* has been noted to cause folliculitis and catheter-related fungemia in the setting of parenteral administration of lipids [167]. These infections are not thought to be associated with neutropenia. Most episodes of fungemia are thought to be due to *M. furfur*. *Malassezia* is also a well-recognized cause of canine, feline and equine dermatitis and may lead to zoonosis. *M. pachydermatis* has been reported to be spread from dogs to man via the hands of health-care workers, causing infection in preterm neonates [168].

Clinical manifestations. Infection caused by *Malassezia* spp. may present as persistent fever, fungemia, pulmonary infiltrates and thrombocytopenia. However, the organism seldom disseminates to cause disease in other sites. Overall outcome for this infection is more favourable than infections with other uncommon fungi. One should also note that isolated folliculitis in neutropenic patients may simulate the lesions of acute disseminated candidiasis. A direct smear of these lesions, however, will demonstrate organisms characteristic of *M. furfur*.

Diagnosis. Laboratory diagnosis is facilitated by the addition of a lipid source such as olive oil.

Treatment and outcome. Malassezia spp. are usually susceptible to antifungal azoles but have variable susceptibility to amphotericin B [169]. Virtually all cases of malassezia fungemia respond to removal of the central venous catheter, discontinuation of lipid parenteral nutrition, with or without administration of antifungal therapy. Management of malassezia fungemia therefore includes the discontinuation of parenteral lipids, removal of the vascular catheter, when possible, and administration of an antifungal triazole.

Hansenula anomala

Microbiology. H. anomala is a member of the group of ascomycetous yeasts. Also known as *Pichia anomala*, this organism is a rare clinical entity that has been reported with increasing frequency over the past decade. In the majority of cases the organism presents in its teleomorphic form and less commonly in the anamorphic form of *Candida pelliculosa*.

Epidemiology. Infection has been observed in children and preterm neonates [170]. Other possible risk factors include patients with acute leukaemia,

use of broad-spectrum antibacterial agents, use of central venous catheters, endotracheal intubation, and high colonization rate with *H. anomala* [171].

Clinical manifestations. The spectrum of this disease ranges from asymptomatic fungemia to severe disseminated life-threatening infection. Fungemia is by far the most common presentation of this infection.

Treatment and outcome. H. anomala is susceptible to currently available antifungal agents, however, two cases of breakthrough fungemia have been described in patients receiving fluconazole [172]. A recent outbreak of 24 cases of infection due to *H. anomala* fungemia was reported in a cancer hospital in Brazil [171]. The median age was 11 years and no deaths were attributed to the infection. Another outbreak of *H. anomala* infection in eight neonates was reported from a neonatal intensive-care unit [146]; all cases but three had fungemia and in three cases ventriculitis was demonstrated. Patients were successfully treated with a combination of amphotericin B and 5-flucytosine. Individual cases have been described of endocarditis in a previous intravenous drug user, of mediastinal lymphadenitis in a patient with chronic granulomatous disease, and of enteritis in a paediatric patient. Response rate due to *H. anomala* fungemia is high when therapy is instituted early and the intravascular catheter is removed.

Endemic dimorphic fungi: focus on *Penicillium marneffei*

Immunocompromised patients may travel to or from areas endemic for pathogenic dimorphic fungi such as *Histoplasma capsulatum*, *Coccidioides immitis*, *Blastomyces dermatitidis*, *Paracoccidioides brasiliensis* or *Penicillium marneffei*. In this section on endemic dimorphic fungi, we will focus on *P. marneffei* as an emerging pathogen.

Microbiology. Most *Penicillium* species are considered saprophytes and common laboratory contaminants. *P. marneffei* is a facultative intracellular pathogen and the only known thermally dimorphic fungus of the genus *Penicillium*. At room temperature, *P. marneffei* exhibits the characteristic morphology of the genus; in contrast, it grows as a yeast that replicates by fission with a characteristic septum when found in infected tissue or at 37 °C.

Pathogenesis. The mode of transmission is not well understood but is probably via ingestion or inhalation of the fungus. The conidia of *P. marneffei* present in the environment are apparently inhaled and undergo conversion to an elongated yeast-like form. Pulmonary alveolar macrophages appear to be the primary host defence against *Penicillium*. Alveolar macrophages and mononuclear cells may be replete with multiple yeast forms. Profound T-cell-mediated immunity impairment as a result of HIV infection accounts for the abnormal regulation of pulmonary alveolar macrophages. Three types of histopathological reactions have been described with *P. marneffei* infections: granulomatous, suppurative and necrotising. The first two reactions have been noted in persons with normal immunity, whereas the necrotising reaction was associated with penicillosis in immunocompromised patients.

Epidemiology. P. marneffei has emerged as an important fungal pathogen that causes disseminated infection in HIV-infected patients residing in or travelling to South-east Asia where the disease is endemic [173–177]. *P. marneffei* constitutes the third most common opportunistic infection in HIV-infected patients in certain parts of South-east Asia and is endemic in the Guangxi province of China, Hong Kong and Taiwan. The incidence of penicillosis has increased significantly for the past few years, paralleling the incidence of HIV infection, from 30 cases before 1990 to more than 160 by the end of 1995. Although penicillosis is most commonly seen in adults infected with HIV, the disease has also been detected in children and adults without immunodeficiency. Bamboo rats (*Rhyzomys sumatrensis*, *R. pruinosis*, *R. sinensis* and *Cannomyus badius*) were implicated in the epidemiology of penicilliosis, but their relationship to human disease is not clear.

Clinical manifestations. In a series of 80 patients reported by Supparatpinyo *et al.* [175] the most common presentation was low-grade fever, anaemia, weight loss and one or multiple skin lesions. Characteristically, most lesions had a central umbilication reminiscent of molluscum contagiosum. Palatal and pharyngeal lesions were also seen. Fungemia, cough and lymphadenopathy were present in 50% of the cases. Pulmonary lesions can appear as reticulonodular or diffuse

alveolar infiltrate, however cavitary lesions and haemoptysis were also described. The average number of $CD4^+$ T lymphocytes at presentation was 64 cells/mm^3. Gastrointestinal involvement by *P. marneffei* ranges from oesophagus to colon, and mucosal lesions appear as shallow ulcers indistinguishable from those of intestinal histoplasmosis.

Diagnosis. Diagnosis of penicilliosis is usually made by identification of the organism from smear, culture or histopathological sections. Rapid diagnosis of presumed infection could be obtained by microscopic examination of bone marrow aspirate, lymph node, or skin biopsy smear. Microscopic examination reveals yeast forms both within phagocytes and extracellularly. This organism may appear morphologically similar to *Histoplasma capsulatum* when found intracellularly [174]. In the extracellular environment in-vivo, the fungal cell elongates, becomes slightly curved, and forms an intercellular septum. The demonstration of characteristic central septation and elongated sausage-shaped forms, by methenamine silver stain, clearly distinguish *P. marneffei* from *H. capsulatum*.

Treatment and outcome. P. marneffei is usually susceptible to both amphotericin B and the antifungal azoles [178]. Treatment with amphotericin B has been successful in the majority of cases. Fluconazole and itraconazole should also be considered for mild to moderate cases of penicillosis. In a recent nonrandomized study in HIV-infected patients with disseminated *P. marneffei* infection [173], a high response (97%) rate was achieved with a regimen of amphotericin B (0.6 mg/kg/day) for 2 weeks, followed by oral itraconazole (400 mg/day) for 10 weeks. This regimen was effective and allowed a shortened hospital stay.

Relapse is common 6 months after discontinuation of therapy. A recent double-blind trial of secondary prophylaxis with itraconazole versus placebo in HIV patients with penicillosis demonstrated that none of the patients treated with itraconazole had relapsed, compared with 57% in the placebo arm [178]. Based on these data, lifelong suppressive therapy with itraconazole is recommended in HIV-patients with penicillosis. The impact of HAART on the management and outcome of penicilliosis has not been adequately assessed to permit a recommendation for discontinuation.

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