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Black Molds and Melanized Yeasts Pathogenic to Humans

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A review is given of melanized fungi involved in human infection, including species forming budding cells and strictly filamentous representatives. Classically, they are known as "phaeoid" or "dematiaceous" fungi, and, today, agents are recognized to belong to seven orders of fungi, of which the Chaetothyriales and Pleosporales are the most important. Infections range from cutaneous or pulmonary colonization to systemic or disseminated invasion. Subcutaneous involvement, either primary or after dissemination, may lead to host tissue proliferation of dermis or epidermis. Particularly in the Chaetothyriales, subcutaneous and systemic infections may occur in otherwise apparently healthy individuals. Infections are mostly chronic and require extended antifungal therapy and/or surgery.

Because melanin is a factor-enhancing virulence, black fungi are overrepresented as etiologic agents of opportunistic infection. Traditionally, they have been collectively indicated under umbrella terms, such as "dematiaceous" or "phaeoid" fungi, referring to the presence of brown hyphae or yeast cells. Today, the leading principle of fungal classification is molecular phylogeny. The melanized fungi appear to belong to distantly related orders of Ascomycota, and the descriptive terminology above has therefore become obsolete. Clinically, they are involved in infections ranging from mild, hardly noticeable cutaneous infections (Saunte et al. 2011) to fatal brain diseases in otherwise healthy individuals (Al-Tawfiq and Boukhamseen 2011). Tissue forms range from melanized hyphae, yeast cells, or muriform cell clumps. The term "phaeohyphomycosis" (or phaeomycosis, a better term not excluding yeast cells) is therefore useful by negation, that is, a mycosis not caused by a hyaline fungus, but otherwise its information content is minimal. The fungi listed in this article are in alphabetical order according to genus with their phylogenetic affiliation in parentheses.

The characteristic common to all species treated in this article is the presence of melanin in cell walls, which is responsible for the dark color of hyphae, yeast cells, muriform cell clumps, and conidia, and is believed to be a major virulence factor–enhancing opportunism. The function of melanin in their natural habitat mostly is protection against solar irradiation

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because of growth on exposed surfaces, such as natural rock, or against factors prevalent under conditions of stress. Another main type of natural ecology is in decomposing plant material; if the orders concerned preponderantly contain plant pathogens, then the human opportunists are found among the few saprobes on plant debris in that group. Clinical pathology mostly emerges from traumatic introduction in or below the skin resulting in a suppurative foreign body response. Inhalation mycoses are exceptional and mostly confined to pulmonary colonization in patients with cystic fibrosis. Deep-seated infections can be, depending on the species, disseminated or cerebral; their portal of entry is poorly understood. A special category is chromoblastomycosis, a disease exclusively caused by members of the *Herpotrichiellaceae* (black yeasts and relatives in the order Chaetothyriales), and is clinically exceptional by a host response with hyperproliferation rather than necrosis; the tissue form consists of muriform (sclerotic) cells. Although diseases by melanized fungi are rare, they are significant because of their occurrence in otherwise healthy individuals, and no notable increase in their frequency is noticed with the emergence of immunocompromised hospital populations. Decreased immunity, as well as diabetes, nevertheless, are risk factors for infection. Recently, some of the highly recalcitrant, disseminated infections appeared to be associated with mutations in the host's dectin signaling pathway (Wang et al. 2014).

CLINICAL SPECTRUM OF DISEASES CAUSED BY BLACK FUNGI

Colonization. Asymptomatic growth of melanized fungi is known on human skin as well as in the lungs, particularly when patients suffer from cystic fibrosis. The systemic colonizers have an invasive potential when the host immune barriers are broken, whereas colonizers of skin and nails cause cutaneous infections at most.

Superficial. Growth on human skin has classically been reported from *Hortaea werneckii*, which mainly colonizes the epidermis but also from members of *Cyphellophora* and *Phialophora*, which are known to be involved in mild skin infections and onychomycoses (Fig. 2).

Cutaneous. Cutaneous infections are uncommon. Mostly cystic or papular lesions on exposed body areas are of concern in patients under prolonged corticosteroid therapy. *Alternaria* (Fig. 1B, left) and *Exophiala* species are the most common etiological agents.

Subcutaneous. Subcutaneous infections can be necrotic phaeomycoses with hyphae or yeast-like cells in tissue, or are eumycetomata, lesions being granulomatous abscesses with draining sinuses from which granules of dense fungal material may be recovered. Osteomyelitis may occur. Etiologic agents mainly are found in *Madurella, Phaeoacremonium*, in coelomycetous representatives of *Pleosporales*, and occasionally in *Exophiala*.

Chromoblastomycosis. This is a chronic subcutaneous infection caused by members of *Herpotrichiellaceae* (black yeasts and relatives) and characterized by the presence of muriform cells (sclerotic bodies) in tissue sections or wet preparations of pus or scrapings. *Cladophialophora carrionii*, *Fonsecaea monophora*, *Fonsecaea pedrosoi*, *Rhinocladiella aquaspersa*, and occasionally *Phialophora verrucosa* are the fungal species involved. *C. carrionii* is endemic to arid climate zones, whereas *Fonsecaea* species are preponderantly found under tropical conditions.

Systemic. Cerebral abscesses are rare but fatal if untreated and are mainly reported from immunocompetent individuals (Carter and Boudreaux 2004; Delfino et al. 2006; Chang et al. 2009; Al-Tawfiq and Boukhamseen 2011). The most common neurotropic fungi, *Rhinocladiella mackenziei*, *Cladophialophora bantiana*, *Exophiala dermatitidis*, and *F. monophora*, are members of *Herpotrichiellaceae*, but also *Exserohilum*, *Bipolaris* (*Pleosporaceae*), and *Verruconis* (*Sympoventuriaceae*) can be involved. Some species are endemic to the Middle East or East Asia or show an increased prevalence in India (Delfino et al. 2006; Garg et al. 2007; Li and de Hoog 2009; Al-Tawfiq and Boukhamseen 2011; Jabeen et al. 2011; Pedersen et al. 2011). Central nervous system (CNS) infections by *Herpotrichiellaceae* are hypothesized to be acquired via inhalation and then quickly disseminated to the

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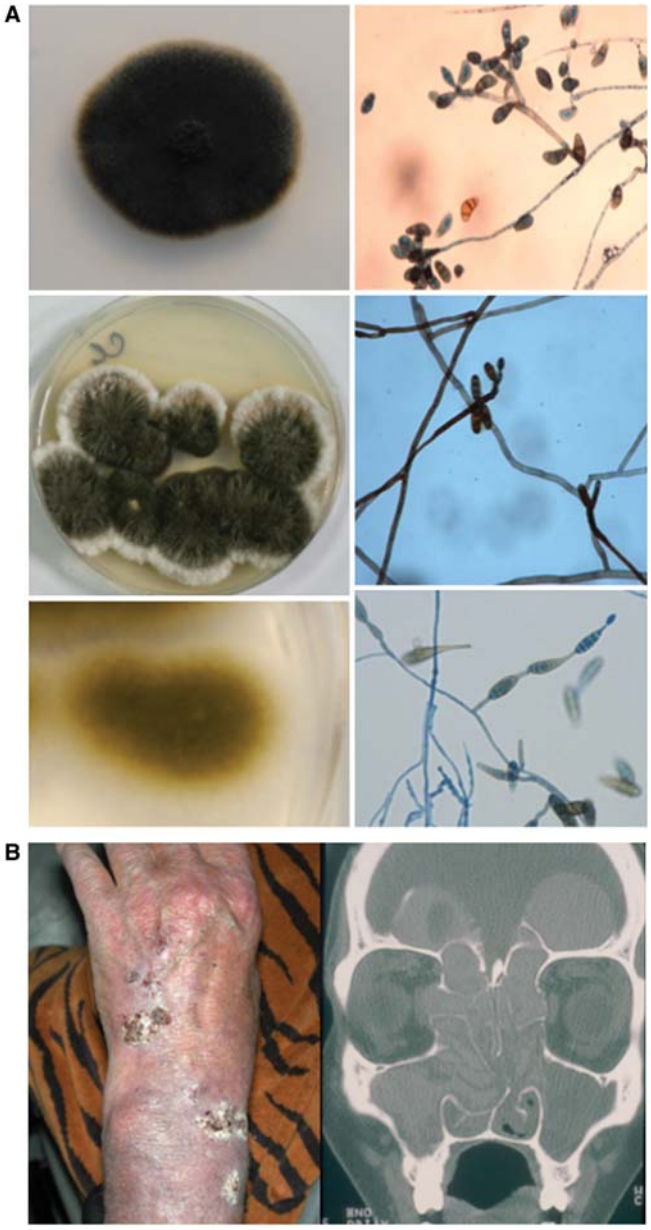

Figure 1. Pleosporalean agents. (*A*) *Top* row, *Curvularia lunata*; *middle* row, *Bipolaris hawaiiensis*; *bottom* row, *Alternaria alternata*. (*B*) *Left*, *Alternaria* cutaneous infection; *right*, *Bipolaris* chronic sinusitis.

CNS via the hematogenous route; but because of a long asymptomatic period of incubation, the actual route of infection may be difficult to establish. Another better-known development of CNS infection, mostly seen in *Pleosporaceae*, is secondary to chronic fungal sinusitis (Fig. 1B, right).

Disseminated. This type of infection is almost exclusively caused by members of *Herpotrichiellaceae*. The infections are very chronic, with a long incubation period, and highly refractory to therapy. Hematogenous spread of the fungus to one or more distant sites may

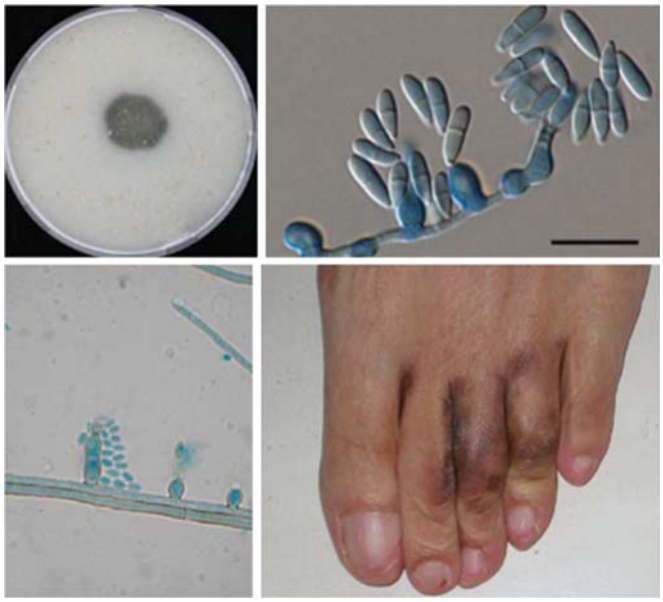

Figure 2. Chaetothyrialean agents of superficial mycoses. *Upper* row: *Cyphellophora pluriseptata*; *lower* row: *left*, *Phialophora europaea*; *right*, superficial infection. Scale bar, 10 μm.

result in visceral infections of the heart and heart valves, brain, joints, bone, kidney, liver, lymphatics, pancreas, and other organs. Secondary cutaneous lesions emerging on all parts of the body are characterized by tissue proliferation of the host, resembling chromoblastomycosis. In most patients, no predisposing factors are recognized, although some rare mutations in the dectin signaling cascade have been noted (Wang et al. 2014). The main black fungi involved are *Exophiala* and *Veronaea* (Bonifaz et al. 2013).

A summary of prevalent clinical syndromes is given in Table 1. Descriptions of relevant genera listed alphabetically below are attributed according to their phylogenetic position in the fungal kingdom.

Acrophialophora (Sordariales: Coniochaetaceae)

The small genus *Acrophialophora* comprises of some soil-borne fungi occasionally involved in human infection (de Hoog et al. 2000). Reports of brain abscess and cases involving lung and cornea have been reported (Al-Mohsen et al. 2000; Guarro et al. 2007; Li et al. 2013). The relevant species *Acrophialophora fusispora* forms white to buff colonies with darker concentric circles on Sabouraud's glucose agar. Conidiogenous cells are flask-shaped phialides with long and narrow necks, occurring alongside of thin-walled, hyaline to pale-brown hyphae, or on unbranched, brown, thick-walled, and echinulate conidiophores (Al-Mohsen et al. 2000). Conidia are limoniform, pale brown, echinulate with ornamentation in spiral bands, and adhere in long chains (de Hoog et al. 2000). Because of the scarcity of data, treatment of the infections attributed to this fungus is not well established.

Alternaria (Pleosporales: Pleosporaceae)

Alternaria is a large genus of mainly plant pathogens and some saprobes on plant debris, and found in air or in soil (de Hoog et al. 2000; Tournas 2005; De Lucca 2007). Clinical manifestations of the saprobic *Alternaria* species usually are cutaneous or subcutaneous lesions after trauma (Halaby et al. 2001; Lo Cascio et al. 2004) in patients under prolonged corticosteroid treatment. Other clinical entities, such as

Table 1. Overview of spectrum of prevalent diseases caused by black fungi

Order	Etiologic genus	Prevalent clinical manifestation[a]
Capnodiales	*Hortaea*	Cutaneous colonization
Chaetothyriales	*Cladophialophora*	Brain abscess, (sub)cutaneous infection, chromoblastomycosis
	Cyphellophora	Cutaneous colonization, onychomycosis
	Exophiala	Brain abscess, chromoblastomycosis, (sub)cutaneous infection, pneumonia, eumycetoma
	Fonsecaea	Chromoblastomycosis, brain abscess
	Knufia	Skin colonization
	Phialophora	Subcutaneous infection, disseminated, chromoblastomycosis, cutaneous colonization
	Rhinocladiella	Brain abscess, chromoblastomycosis
	Veronaea	(Sub)cutaneous infection, disseminated
Diaporthales	*Phaeoacremonium*	Subcutaneous infection, eumycetoma, **fungemia**, **osteomyelitis**, **arthritis**, **endocarditis**
Dothideales	*Aureobasidium*	**(Sub)cutaneous infection**, **fungemia**, **meningitis**, **peritonitis**
	Neoscytalidium	Onychomycosis, cutaneous infection, **fungemia**
Pleosporales	*Alternaria*	**(Sub)cutaneous infection**, **sinusitis**, **keratitis**, **onychomycosis**, **ABPM**, **disseminated**
	Biatriospora	**Eumycetoma**
	Bipolaris	**(Sub)cutaneous infection**, **sinusitis**, **keratitis**, **ABPM**, **pneumonia**, **disseminated**
	Curvularia	**(Sub)cutaneous infection**, **sinusitis**, **keratitis**, **ABPM**, **eumycetoma**, **peritonitis**, **onychomycosis**, **brain abscess**, **disseminated**
	Exserohilum	**Brain abscess**, **chromoblastomycosis**, **(sub)cutaneous infection**, **pneumonia**, **eumycetoma**
	Falciformispora	Eumycetoma
	Medicopsis	Eumycetoma
	Phoma	(Sub)cutaneous infection, keratitis
	Pseudochaetosphaeronema	Eumycetoma
	Pyrenochaeta	Keratitis, onychomycosis, (sub)cutaneous infection, eumycetoma
	Trematosphaeria	Subcutaneous infections
Sordiales	*Acrophialophora*	Brain abscess, keratitis
	Chaetomium	Brain abscess, (sub)cutaneous infection, pneumonia, eumycetoma
	Madurella	Eumycetoma
Venturiales	*Ochronis*	**Cutaneous infection**
	Verruconis	**Pneumonia**, **brain abscess**, **disseminated**

[a]Infections possible in otherwise healthy-appearing patients. Infections exclusively occurring in immunocompromised patients are shown in bold.

cerebral infections, sinusitis, keratitis, and allergic bronchopulmonary mycosis, are very rare (Hipolito et al. 2009; Chowdhary et al. 2012, 2014a). The most common etiologic agents are *Alternaria alternata* and *Alternaria infectoria* and, occasionally, *Alternaria chlamydospora*. *A. infectoria* may be difficult to recognize because of its often poor sporulation on routine media and loss of melanin in vitro and in tissue. The taxonomy and identification of other reported species, such as *Alternaria dianthicola*, *Alternaria longipes*, and *Alternaria tenissima*, has been insufficiently clarified. Morphologically, colonies generally are expanding, hairy, with gray to olivaceous black colors. Conidiophores are mostly erect, brown, and multicelled, producing conidia in sympodial order, leaving flat, dark-brown scars. The conidia are usually brown, smooth walled, or verruculose with a round base and beaked tip, with muriform septation, and are produced in

chains. Morphological characteristics distinguishing *A. alternata* from *A. infectoria* are the conidia, which often become nearly tubular and occur in strongly branched chains in the latter species. Conidia resemble multicelled chlamydospores in *A. chlamydospora.* Sequencing of the rDNA internal transcribed spacer (ITS) region is sufficient for routine identification of *A. alternata* and *A. infectoria* (Hipolito et al. 2009; Cunha et al. 2012).

Aureobasidium (Dothideales: Dothiodeaceae)

Aureobasidium pullulans is a black yeast-like fungus that is ubiquitous on poor-nutrient surfaces, such as on plant leaves, glass, and damp bathroom walls, and is commonly found as a contaminant in clinical laboratories. Recently, intraspecific molecular diversity has been found, which has led to the description of varieties and sibling species (Zalar et al. 1999). Opportunistic infections are mostly caused by *A. pullulans* but also other taxa have been reported, such as *Aureobasidium proteae* (de Hoog et al. 2000; Kutleša et al. 2012). Most infections occur by traumatic inoculation, such as keratitis and cutaneous lesions; disseminated mycoses are very rare and occur only in severely immunocompromised patients (Kaczmarski et al. 1986; Salkin et al. 1986; Arranz et al. 2006; Panda et al. 2006; Mise et al. 2008; Pikazis et al. 2009; Chawla et al. 2010; Joshi et al. 2010; Mershon-Shier et al. 2011). *A. pullulans* has an affinity for synthetic materials and surgically implanted devices, as evidenced by the relatively frequent isolation of the organism from peritoneal dialysis catheters and central venous lines (Clark et al. 1995; Caporale et al. 1996; Hawkes et al. 2005; Mise et al. 2008). The in vitro activity of antifungals against *A. pullulans* revealed resistance to fluconazole and high minimum inhibitory concentrations of voriconazole, isavuconazole, caspofungin, and micafungin. However, the isolates exhibit susceptibility to amphotericin B, posaconazole, and itraconazole (Najafzadeh et al. 2014). Colonies grow rapidly and are smooth, cream to pink, covered with slimy exudates, and become variably brown or black in a later stage. On microscopic examination, large, hyaline hyphae are seen, which variably convert into thick-walled, dark-blackish-brown chlamydospore-like cells. Conidia are produced synchronously in groups alongside undifferentiated hyphae. Species distinction is by ITS sequencing.

Biatriospora (Pleosporales: Trematosphaeriaceae)

This single species *B. mackinonii* was formerly classified in *Pyrenochaeta* or *Nigrograna*. The species is an occasional agent of human mycetoma. The natural habitat of this fungus is unknown. Colonies are gray, velvety, becoming dark gray to black with age. Pycnidia are solitary, globose to pyriform, with papillate ostioles. Conidiogenous cells are hyaline, phialidic, and discrete. Conidia are subhyaline, brown in mass, one celled, and ellipsoidal (Ahmed et al. 2014).

Bipolaris (Pleosporales: Pleosporaceae)

Most species belonging to the genus *Bipolaris* are host-specific pathogens on grasses, whereas some saprobic species in soil with dead and decaying plant material can be found as human opportunists (Revankar et al. 2010). The prevalent clinically significant saprobes are *Bipolaris australiensis*, *Bipolaris hawaiiensis*, and *Bipolaris spicifera* (Sivanesan 1987; da Cunha et al. 2012a). They are particularly associated with chronic pansinusitis (Toul et al. 2006). Other cases include endophthalmitis and orbital cellulitis (Newell et al. 2006; Sheyman et al. 2013), necrotizing pneumonia and allergic bronchopulmonary mycosis (Saenz et al. 2001; Chowdhary et al. 2011, 2014b), peritonitis (Bava et al. 2003), endarteritis (Ogden et al. 1992), and encephalitis (Morton et al. 1986; Pauzner et al. 1997). Colonies are black, hairy, and expanding. Conidiophores are brown, erect, multicelled, producing ellipsoidal, straight, or curved conidia with dark-brown, flat conidial scars. Molecular identification can be done using ITS sequencing. A specific polymerase chain reaction (PCR) has been developed for the direct detection of *Bipolaris* species (Shin et al. 2003; El-Morsy et al. 2010).

Chaetomium (Sordariales: Chaetomiaceae)

This genus comprises more than 180 species from straw, plant debris, and animal dung (Guarro 1998; de Hoog and Vitale 2007). The significance of the genus has been underestimated because clinical strains are mostly sterile in culture, and could not be recognized by morphology (de Hoog et al. 2013). Clinically significant species include *Chaetomium globosum*, followed by *Chaetomium strumarium*, *Chaetomium atrobrunneum*, *Chaetomium funicola*, and *Chaetomium perlucidum* (Abbott et al. 1995; Guarro et al. 1995; Yeghen et al. 1996; Guppy et al. 1998; Lesire et al. 1999; Thomas et al. 1999). *Chaetomium* species have mainly been reported from onychomycosis and sinusitis (Aru et al. 1997; Stiller et al. 1992). Brain infection is sometimes seen in individuals during illicit intravenous drug use (Abbott et al. 1995). A chromoblastomycosis-like infection by *C. funicola* was reported by Piepenbring et al. (2007); this is an exceptional case of this disease caused by a fungus in the *Herpotrichiellaceae*. The distinctive feature of *Chaetomium* species is the presence of pronounced hairs, or setae, on the spherical to pyriform fruit bodies. The hairs may be dichotomously branched or unbranched and are often undulate or spirally coiled. Asci are usually eight-spored and deliquescent so that brown, one-celled ascospores are easily liberated in large masses. Opportunistic species are thermotolerant; *C. globosum* grows at 35°C but not at 40°C, whereas the neurotropic species *C. atrobrunneum* and *C. perlucidum* grow at 40°C (von Arx et al. 1986; Barron et al. 2003).

Cladophialophora (Chaetothyriales: Herpotrichiellaceae)

Cladophialophora is morphologically characterized by one-celled, ellipsoidal to fusiform, and dry conidia, arising in long, branched, or unbranched chains. *Cladophialophora* species are involved in a wide diversity of infections, ranging from mild cutaneous to fatal encephalitis (Borelli 1980; Ho et al. 1999; de Hoog et al. 2000). An important species is the neurotropic fungus, *C. bantiana*, of which more than 100 case reports in mostly healthy individuals have been published. *Cladophialophora modesta* was responsible for a case after head trauma (McGinnis et al. 1999). *C. carrionii* is the prevalent agent of chromoblastomycosis in dry climates and desert zones (Mendoza et al. 1993; Jayakeerthi et al. 2004; Ameen 2009). *Cladophialophora devriesii* and *Cladophialophora arxii* are rare agents of disseminated diseases, whereas *Cladophialophora boppii*, *Cladophialophora emmonsii*, and *Cladophialophora saturnica* are causes of mild cutaneous infections (Fig. 3) (Badali et al. 2008).

Curvularia (Pleosporales: Pleosporaceae)

This genus consists of ~100 species, most of which are either saprobes in soil or on plant debris, or are plant pathogens mainly infecting grasses (Sivanesan 1987). Human infections have been reported in *Curvularia aeria*, *Curvularia geniculata*, and *Curvularia lunata*; isolated cases occurred in *Curvularia brachyspora*, *Curvularia clavata*, *Curvularia inaequalis*, *Curvularia pallescens*, and *Curvularia verruculosa*. *Curvularia* species may cause allergic sinusitis, which can disseminate to the brain of immunocompetent patients (Ebright et al. 1999). Other manifestations include subcutaneous infections following traumatic implantation, such as keratitis. Colonies of *Curvularia* are black in color, expanding, and hairy (Tanabe et al. 2010; Moody et al. 2012). Conidiophores are brown and erect, producing ellipsoidal, brown, usually curved conidia with three or four transverse septa. Species can be differentiated on the basis of ITS and glyceraldehyde-3-phosphate dehydrogenase gene sequences (de Hoog and Vitale 2007).

Cyphellophora (Chaetothyriales: Herpotrichiellaceae–Cyphellophoraceae)

The natural habitat of members of the small genus *Cyphellophora* has not been established with certainty. They are mainly known from human skin and nails, where they can be symptomatic or subclinical, but detailed case reports are as yet lacking (Feng et al. 2014). The species

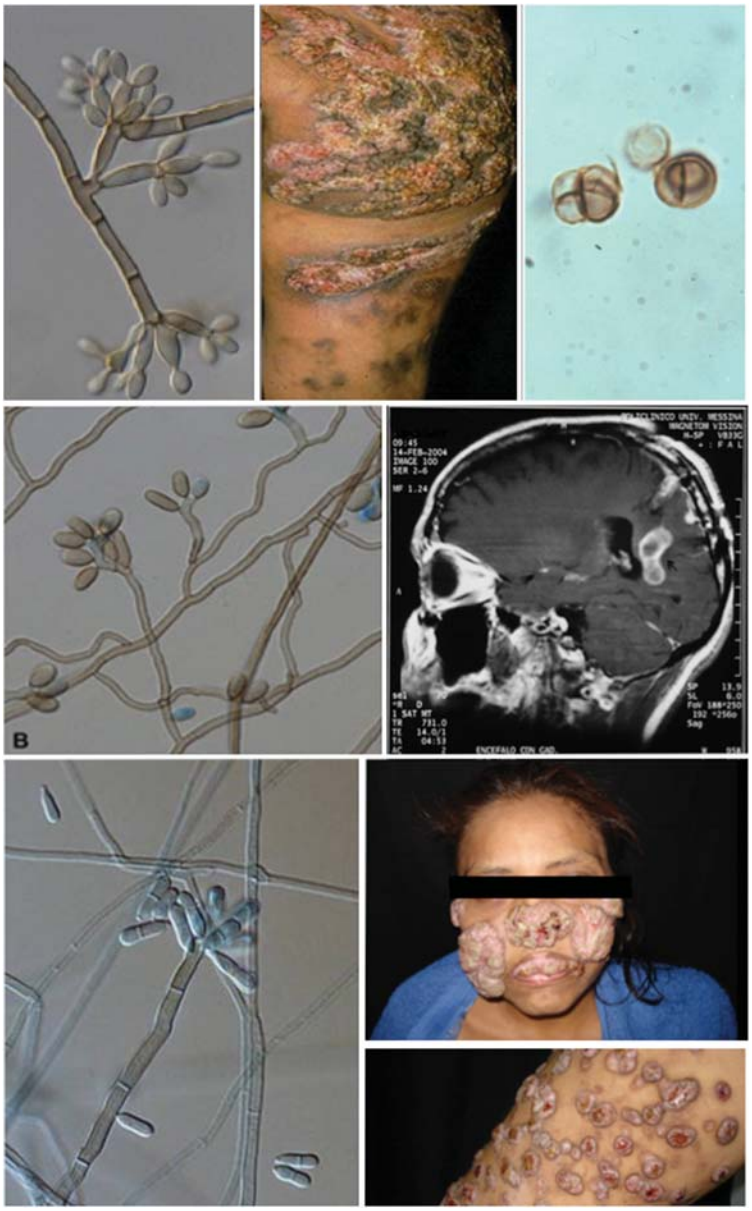

Figure 3. Chaetothyrialean agents of deep infections. *Upper* row: *Fonsecaea pedrosoi* causing chromoblastomycosis with muriform cells; *middle* row: *Ramichloridium mackenziei*, agent of cerebral phaemycosis (case shown caused by *Cladaphialophora bantiana*); *bottom* row: disseminated infection caused by *Veronaea botryosa*.

grow very slowly with olivaceous black colonies and produce thin-walled, sickle-shaped conidia with one or several transverse septa. Conidia are produced in packages from phialide openings on spherical conidiogenous cells or directly from hyphae.

Exophiala (Chaetothyriales: Herpotrichiellaceae)

Exophiala is the major genus of black yeasts, characterized by annelidic conidiogenesis and the presence of torulose hyphae, that is, hyphae

composed of chains of more or less spherical cells. They are typically associated with nutrient-poor or toxic environments, such as creosoted wood (Döğen et al. 2013), toxic mines (Seyedmousavi et al. 2011), or steam baths (Sudhadham et al. 2008). The common clinically relevant species include *E. dermatitidis*, *Exophiala xenobiotica*, *Exophiala spinifera*, and *Exophiala oligosperma*. Less common are *Exophiala lecanii-corni*, *Exophiala asiatica*, *Exophiala phaeomuriformis*, *Exophiala jeanselmei*, *Exophiala bergeri*, and *Exophiala mesophila* (de Hoog et al. 2003; Zeng et al. 2007; Badali et al. 2010). *E. dermatitidis* causes disseminated infection eventually with neurotropism, whereas *E. spinifera* is osteotropic (Horre and de Hoog 1999; Kantarcioglu and de Hoog 2004; Harris et al. 2009; Badali et al. 2010). *Exophiala* colonies are restricted, olivaceous black, and often initially slimy at the center and then becoming velvety toward the margin. Conidiogenous cells are intercalary or lateral, cylindrical, flask shaped or acicular, with relatively narrow, short, or very short annellated zones. Conidia are generally present in clumps. Molecular identification for most species is by ITS sequencing because they generally show very limited morphological differentiation (Zeng et al. 2007; Najafzadeh et al. 2013).

Exserohilum (Pleosporales: Pleosporaceae)

The genus *Exserohilum* comprises ~35 saprobic species mainly feeding on plant debris. In the clinical literature, three clinically significant species have been reported (*Exserohilum rostratum*, *Exserohilum longirostratum*, and *Exserohilum mcginnisii*), but molecular studies demonstrated that they belong to a single species, *E. rostratum* (da Cunha et al. 2012b). *Exserohilum* species are mainly involved in traumatic infections, such as keratitis (Burges et al. 1987; Pauzner et al. 1997; Mathews and Maharajan 1999; Joseph et al. 2012). Otherwise species may cause invasive infections in immunocompromised patients (Aquino et al. 1995), with risk factors including aplastic anemia (Lasala et al. 2005; Adler et al. 2006) and hematopoietic stem cell transplant (HSCT) (Togitani et al. 2007; Ritter et al. 2013). Recently, *E. rostratum* was implicated in a large meningitis outbreak that was traced back to contaminated steroid injections (Lyons et al. 2012; Gade et al. 2013; Lockhart et al. 2013; Smith et al. 2013). The species can be identified morphologically using nutritionally deficient media in which its morphology is most pronounced. Colonies are usually gray or black, hairy, and spreading. Conidiophores are brown to olivaceous brown in color, simple, thick, and smooth walled. Conidia are fusiform, cylindrical, or obclavate. Sequencing the rDNA ITS region is sufficient for routine identification, and a real-time assay for rapid identification of *E. rostratum* has been developed (Guerra et al. 2013; Zhao et al. 2013).

Falciformispora (Pleosporales: Trematosphaeriaceae)

Two species producing ascigerous fruit bodies formerly classified in *Leptosphaeria* belong to this genus, namely, *Falciformispora senegalensis* and *Falciformispora tompkinsii*, both agents of human mycetoma (Ahmed et al. 2014). Colonies are radially folded, grayish green, with brown exudate on the colony surface; the reverse is dark brown, with dark-brown pigment diffusing into the agar, and conidia absent. Ascomata appear on the agar surface after months of incubation, black, solitary, (sub)spherical, and thick walled. Asci are clavate, rounded at the apex, bitunicate, and contain eight ascospores. Ascospores are ellipsoidal, four-septate, with constrictions at the septa; the second cell from the top is the largest, leading to widening of the thin sheath that surrounds the ascospore.

Fonsecaea (Chaetothyriales: Herpotrichiellaceae)

The clinically relevant members of this genus comprise three closely related species, *F. pedrosoi*, *F. monophora*, and *Fonsecaea nubica*, all causing human chromoblastomycosis. Saprobic *Fonsecaea* species are found in the environment as degraders of plant debris (Najafzadeh et al. 2010b). The disease may be acquired by accidental inoculation of plant debris carrying

Fonsecaea cells. In vitro, colonies are dark olivaceous, velvety to cottony, and with restricted expansion growth. Budding cells are absent, but additional phialides occur on nutritionally deficient media. Conidiophores are poorly differentiated, pale to dark olivaceous, and have apically clustered, cylindrical denticles bearing conidia. Conidia are 0–1 septate, arising singly or in short, branched chains. Species distinction requires sequencing of the ITS region, or alternatively a specific PCR for identification of *Fonsecaea* species is available (Gunde-Cimerman et al. 2000; Najafzadeh et al. 2010a).

Hortaea (Capnodiales: Capnodiaceae)

H. werneckii is the causative agent of tinea nigra, a visible colonization of the palm on one or both hands, sometimes also affecting the sole. *H. werneckii* is a halophilic fungus occurring at coastal areas in (sub)tropical climates, where it lives in natural or man-made saltpans (Zalar et al. 1999; Uezato et al. 2006); one strain was recovered from house dust. Colonies in vitro have restricted growth and are tar black, smooth, slimy, and glistening. Hyphae are wide, densely septate at maturation, becoming dark brown and thick walled locally. Conidia are produced from wide annellated zones and are hyaline, later turning pale olivaceous, ellipsoidal, often developing a thick median septum; and they reproduce by budding. Conidia often get converted into clumps of chlamydospore-like cells. Molecular identification of *H. werneckii* is possible with rDNA ITS sequencing (Abliz et al. 2004).

Knufia (Chaetothyriales: Herpotrichiellaceae)

One species of this genus, *Knufia epidermidis*, formerly known as *Coniosporium epidermidis*, has been reported from human skin (Li et al. 2008). Symptoms are very mild, possibly just colonization occurs in many cases. Colonies grow slowly, velvety, and black to blackish brown. Hyphae are regularly and densely septate, profusely branched at nearly right angles, and are olivaceous black or dark brown. Cells gradually swell and develop thick walls at maturity. Conidia formed by liberation of arthric cells swell to become ellipsoidal or nearly spherical. The species can be recognized by ITS sequencing.

Madurella (Sordariales: Chaetomiaceae)

Madurella is the classical agent of human mycetoma, which is a subcutaneous infection characterized by necrosis and draining sinuses. The fungus presents in the form of compact grains. In vitro, sporulation is absent or very scant. At present, three molecular siblings are recognized, all being endemic in arid climate zones, particularly in northeastern Africa (de Hoog et al. 2012). *Madurella mycetomatis* is the prevalent species. Phylogenetically, the species cluster as a part of the ascomycete genus *Chaetomium* (de Hoog et al. 2013). *Madurella grisea* is unrelated and is now classified in *Trematosphaeria* (*Pleosporales*) (Ahmed et al. 2014).

Medicopsis (Pleosporales: Trematosphaeriaceae)

A genus with a single species, formerly known as *Pyrenochaeta romeroi*, is a rare agent of human mycetoma (Ahmed et al. 2014). The natural habitat of this fungus is unknown. Colonies are grayish green and velvety, producing rather broad hyphae. Pycnidia are black, solitary with short dark brown to black setae, and are produced after prolonged incubation. Conidiophores are phialidic, smooth walled, hyaline, ampulliform, and produce unicellular, hyaline, and cylindrical to ellipsoidal conidia.

Neoscytalidium (Dothideales: Dothioraceae)

Neoscytalidium dimidiatum causes superficial, cutaneous, and ungual infections in humans in tropical climate zones (Gentles and Evans 1970), and is now known to be a common pathogen causing onychomycosis and tinea pedis (Gugnani et al. 1989; Lacaz et al. 1999; Padin et al. 2005; Ungpakorn 2005). The species is found in the soil and vegetation, and causes diseases of deciduous trees. *N. dimidiatum* is distinguished from dermatophytes by its characteristic sinuous, irregular hyphal appearance

on direct microscopy of cutaneous specimens, its fast-growing, black, and hairy colonies, and its sensitivity to cycloheximide (Tan et al. 2008). Chains of arthroconidia with brown walls are produced in abundance in the aerial mycelium; many have two cells separated by a thick septum. Smooth- and thick-walled pycnidia may be formed after 2 wk, showing typical 1–2 septate conidia, which develop a darkened central cell on liberation. ITS sequencing is sufficient for identification (Tan et al. 2008; Madrid et al. 2009).

Ochroconis (Venturiales: Sympoventuriaceae)

The species from this genus have been isolated worldwide from soil, water, and nutritionally poor environments. About 20 species are known in the genus, many of which are rare and presently are not available for sequencing (Boggild et al. 2006; Samerpitak et al. 2014). Human infections are mainly caused by *Ochroconis musae* and usually remain superficial, because species of the genus do not grow above 35°C (Samerpitak et al., in press). Colonies are brown olive with a velvety texture, and the reverse is often rust brown. Microscopically, species are characterized by brown hyphae with small, unbranched conidiophores bearing apical collarette-like denticles arranged sympodially, and ellipsoidal conidia with one to three transverse septa (de Hoog et al. 2000). For molecular identification, sequencing of ITS and D1/D2 regions of LSU rDNA can be used.

Phaeoacremonium (Diaporthales: Togniniaceae)

The genus *Phaeoacremonium* (Crous et al. 1996) contains species that occur in plant debris and generally are known to cause plant diseases; some cause subcutaneous infections in humans when introduced traumatically. Opportunistic diseases are particularly seen with *Phaeoacremonium parasiticum*, whereas *Phaeoacremonium alvesii*, *Phaeoacremonium amstelodamense*, *Phaeoacremonium griseorubrum*, *Phaeoacremonium krajdenii*, *Phaeoacremonium rubrigenum*, *Phaeoacremonium inflatipes*, *Phaeoacremonium tardicrescens*, and *Phaeoacremonium venezuelense* (Padhye et al. 1998; Guarro et al. 2003; Mostert et al. 2005, 2006) are mainly observed as causes of mycetoma. Occasional cases of onychomycosis and arthritis have also been reported (Torstrick et al. 1979; Reyes and Buchman 1986; Fincher et al. 1988; Guarro et al. 2003; Farina et al. 2007). Morphologically, the *Phaeoacremonium* colonies are grayish olivaceous to grayish brown in color, expanding, wooly to cottony, and often produce bright pigments into the agar. Conidiophores are generally erect, stiff, cylindrical, and irregularly branched. The phialides are cylindrical, tapering at the apex, showing a wide diversity of conidial shapes including ellipsoidal, obovoidal, cylindrical, or allantoid. Sequencing of ITS regions of rDNA was able to detect and identify species of *Phaeoacremonium* (Aroca and Raposo 2007), although sequencing of the β-tubulin gene is generally used in taxonomy (Mostert et al. 2005; Crous et al. 2006).

Phialophora (Chaetothyriales: Herpotrichiellaceae)

Members of the genus may cause subcutaneous or occasionally disseminated (Hofmann et al. 2005), chromoblastomycosis-like infections with hyperproliferation of host tissue. Infections by *P. verrucosa* can be destructive and refractory to therapy (Saunte et al. 2011). Other species, such as *Phialophora europaea* are colonizers of human skin and nail without causing major symptoms (Gao et al. 2013). The natural habitat of most species is unknown, although some are regularly found in bathing facilities and similar humid, nutritionally poor environments. In vitro, the species have velvety, olivaceous colonies and produce conidia from simple, flask-shaped, to cylindrical phialides. Conidia are produced in slimy balls through more or less pronounced collarettes. Species identification is possible by ITS sequencing.

Phoma (Pleosporales: Pleosporaceae)

Phoma species are ubiquitous saprobes on plant material (de Hoog et al. 2000) and have been occasionally associated with human infections

including subcutaneous infection, keratitis, or onychomycosis that are traumatically acquired (Arrese et al. 1997; Zaitz et al. 1997; Rishi and Font 2003; Errera et al. 2008; Tullio et al. 2010). *Phoma* species produce colonies with spherical, solitary dark pycnidia, usually each with a single or sometimes with several ostioles. Phialides are arranged as the innermost wall of the fruit body and produce abundant unicellular, ellipsoidal, or cylindrical conidia, which are hyaline to pale colored and ooze out in large slimy masses. For identification of species, ITS sequencing is sufficient.

Pseudochaetosphaeronema (Pleosporales: Lentitheciaceae)

The single species, *Pseudochaetosphaeronema larense* (formerly *Chaetosphaeronema larense*), is known in this genus. The fungus was described from a case of human mycetoma. Colonies grow slowly, velvety, and gray. Pycnidia are produced after several months of incubation and they are black, solitary, and obpyriform with long necks. Conidia are hyaline, unicellular, and subspherical to ellipsoidal. Conidiophores are ampulliform, hyaline, and phialidic. For identification of species, ITS sequencing is sufficient.

Pyrenochaeta (Pleosporales: Cucurbitaceae)

Pyrenochaeta is a genus of Coelomycetes with conidial fruit bodies covered by setae. Recently, the genus has been found to be phylogenetically diverse and most species have been reclassified into other genera. Only *Pyrenochaeta keratinophila* and *Pyrenochaet unguis-hominis*, agents of superficial infections, have been retained in the genus. The species are characterized by the presence of rapidly growing flat, velvety, or floccose colonies producing dark olive-gray aerial hyphae with olivaceous black reverse. Pycnidia are usually solitary, spherical to subspherical, ostiolate, setose, and brown in color, and are produced after 2 to 3 wk. Abundant dark brown setae are present all around the ostiole usually tapering at the tip. Conidia are produced from ampulliform phialides lining the innermost pycnidial wall and are hyaline, one celled, and ellipsoidal to bacilliform. *P. romeroi* and *Pyrenochaet mackinnonii* were accommodated in the new genera *Medicopsis* and *Nigrograna*, respectively, based on the analysis of ITS, D1/D2, β-tubulin, and chitin synthase 1 gene sequences (de Gruyter et al. 2009).

Rhinocladiella (Chaetothyriales: Herpotrichiellaceae)

The genus presently contains four clinically relevant species, namely, *R. aquaspersa*, *R. mackenziei*, *Rhinocladiella basitona*, and *Rhinocladiella similis*. Two of these, *R. basitona* and *R. similis*, are rare agents of skin infections. *R. aquaspersa* is one of the agents of chromoblastomycosis. *R. mackenziei* is one of the most notorious causative agents of cerebral phaeohyphomycosis, often occurring in otherwise healthy individuals (del Palacio-Hernanz et al. 1989; Kanj et al. 2001; de Gruyter et al. 2009; González et al. 2013); it is strictly endemic to the Middle East, and its natural habitat is presently unknown. *Rhinocladiella* species have dark olivaceous-brown colonies producing conidiophores, which are pale to dark brown, somewhat or clearly differentiated from the mycelium, suberect, and mostly unbranched. Conidia arise sympodially on denticles and are hyaline to brown, one celled, and smooth walled. *R. mackenziei* is characterized by its stout conidiophores and brown, thick-walled conidia. Definitive identification of the species requires sequencing of ITS and/or D1/D2 regions of the LSU rDNA gene (Jabeen et al. 2011).

Trematosphaeria (Pleosporales: Trematosphaeriaceae)

This coelomycete, previously classified as *Madurella grisea*, occasionally has been reported to cause human subcutaneous infections (Ahmed et al. 2014), but is mostly found in water. Colonies are dark gray at the center, becoming faint toward the margin; the reverse is dark brown to black. Colonies on oatmeal agar are flat and olivaceous brown to black. Environmental isolates of *Trematosphaeria grisea* grow

rapidly with expanding, gray conidial fruit bodies (pycnidia) and are produced only after prolonged incubation. Pycnidia are globose with a wide opening from which slimy conidial masses emerge. Conidia are hyaline to pale brown, unicellular, and clavate to ellipsoidal. Conidiophores are hyaline and rostrate with a very short and hardly detectable collarette.

Veronaea (Chaetothyriales: Herpotrichiellaceae)

The genus *Veronaea* contains one clinical species, namely, *Veronaea botryosa*, which is readily recognizable by its morphology (de Hoog et al. 2000). *V. botryosa* probably is an environmental fungus but its ecological niche is still unknown. Most human infections are disseminated, leading to secondary, dry eruptions with significant hypergrowth in the infected skin (Bonifaz et al. 2013). Cutaneous lesions are nodular and subcutaneous, resembling those of chromoblastomycosis, with muriform cells in tissue; a strong tendency to disseminate is the clinical hallmark of this fungus (Ayadi et al. 1995; Chen et al. 2006; Sang et al. 2011; Bonifaz et al. 2013). The colonies are usually fast growing, velvety to lanose, and grayish brown in color. The large, erect conidiophores with sympodial, one-septate conidia on flat scars make this fungus unmistakable. Sequencing of the ITS region is applicable for the precise identification of this fungus (Badali et al. 2013).

Verruconis (Venturiales, Sympoventuriaceae)

This is a small group of fungi found in heated environments, such as chicken coop litter and the effluents of thermal nuclear reactors. In warm-blooded animals, including wild ones, brain infection is primarily noted; human patients are almost invariably immunocompromised. The exact route of infection is unclear, but inhalation of conidia has been hypothesized (Bravo and Ngamy 2004). The fungus produces rust brown colonies and has short conidiophores, which have only 1–3 open-ended conidial scars. The conidia are hyaline, clavate, and two celled. *Verruconis* is remote from other fungi and can easily be recognized by ITS sequencing (Jenney et al. 1998; Malani et al. 2001; Fukushima et al. 2005; Hollingsworth et al. 2007).

ROUTINE DIAGNOSIS OF BLACK FUNGI

Distinctive histopathologic features are observed depending on the clinical form of the disease. However, different etiological agents may produce identical pathologic features. Clinical diagnosis of chromoblastomycosis is confirmed by the presence of single or clustered thick-walled brown cells intracellularly within macrophages and lying freely in the dermis as the characteristic sclerotic cells (muriform cells, Medlar bodies) (de Hoog et al. 2000). Tissue shows hyperkeratosis with pseudoepitheliomatous hyperplasia with a lichenoid granulomatous inflammatory pattern. In (sub)cutaneous phaeohyphomycosis, necrosis rather than hyperproliferation is present, with brown hyphal elements or yeast-like cells in 20% KOH-digested tissue (Kwon-Chung and Bennett 1992). The brown pigment in the walls of fungal elements may be visible in haemotoxylin and eosin-stained tissue sections. Skin infections by *A. infectoria* often yield hyaline yeast-like elements rather than dark hyphae. In cerebral phaeohyphomycosis, a KOH preparation of pus from the lesion may also show lightly pigmented hyphae. Fontana-Masson staining helps to identify the melanized nature of the fungus.

Isolation of the fungus is recommended to confirm the diagnosis. Initial growth of black fungi is on Sabouraud's glucose agar. Often other media are recommended to enhance morphology and sporulation: potato dextrose agar for slow-growing *Chaetothyriales*, and nutritionally poor media for many *Pleosporales*, which show rapid expanding growth. In coelomycetes, fruit bodies are often produced after prolonged incubation, whereas in others sporulation may remain absent. Rapid identification by sequencing is therefore recommended; ITS mostly provides sufficient resolution down to the species level.

No specific clinical or radiological features are available for the diagnosis of cerebral phaeohyphomycosis. A computerized tomography

scan of the cranium often reveals a unilateral, well-circumscribed mass lesion in the frontal lobe (Jayakeerthi et al. 2004; Garg et al. 2007). Abscesses may be single or multiple and localized within the cerebral cortex (Garg et al. 2007). Purulent meningitis, with or without brain abscess, may also be seen (Walz et al. 1997). For definite diagnosis and distinction from other brain disorders, biopsy specimens are needed.

ANTIFUNGAL SUSCEPTIBILITY TESTING AND THERAPY

The majority of clinical experiences with black molds represent isolated cases or small series of infections with different fungi. Therefore, evidence-based algorithms for specific treatments are not robust, but there are several important surgical and medical principles to consider.

Surgery can be an essential feature in management of certain phaeomycosis. For a subcutaneous cyst, complete removal of the encapsulated structure can be curative. However, care must be taken to not leak contents in the wound, and a single aspiration of a cyst or systemic antifungal agents alone for treatment are not optimal. Furthermore, ulcerative lesions of the skin and soft tissue without a cyst can be effectively managed with debridement, such as the use of Mohs-type micrographic surgery, which can achieve low recurrence rate and maximal preservation of host tissue. In brain abscesses, surgical debulking of abscess with adjunctive medical therapy is recommended for cure because complete debridement/removal of abscess is generally not possible. Although occasionally medical therapy alone is successful, it is likely that a combined medical–surgical therapeutic approach is preferred, and medical treatment only should be reserved for patients with multiple abscesses and for patients for whom surgery is contraindicated. Eumycetomas in the extremities can be extremely difficult to manage. Because of their indolent nature, scarring, fistula formation, and bone involvement, the ability to obtain disease-free tissue margins may be difficult via surgery, and medical therapy for these infections may be the best option.

Medical therapy with antifungal agents is based on in vitro and in vivo evidence for antifungal drug activity (McGinnis et al. 1997; Espinel-Ingroff 1998a,b; McGinnis and Pasarell 1998), but is generally not genus and species specific. In fact, for these invasive fungal infections, it is reasonable to check in vitro antifungal susceptibility results of the strain to help with antifungal drug management. In vitro antifungal susceptibility data for the melanized fungi have been increasingly reported and generally reveals that most species are susceptible to triazoles. However, it is important to note that there are no clinical break points or randomized clinical trials available to evaluate efficacy of antifungal agents in this group of fungi.

With regard to the present antifungal drug classes, there are several general comments for their use in phaeohyphomycosis. First, polyene drugs show modest antifungal activity in vitro and have been used successfully in some cases of disseminated disease. However, occasional resistance is found in some species, such as strains of *Curvularia*, *Exophiala*, and *R. mackenziei*. Second, flucytosine has variable activity against dematiaceous fungi, and its use should be guided by in vitro susceptibility testing and should always be used in combination with another agent(s) secondary to rapid development of drug resistance. Third, terbinafine use should also be guided by in vitro antifungal susceptibility testing of the specific isolate (Clancy et al. 2000; Queiroz-Telles et al. 2009). Finally, the echinocandins do have in vitro antifungal activity against some dematiaceous fungi (Del Poeta et al. 1997; Espinel-Ingroff 1998b, 2003), but clinical experience with this class of antifungal agents remains minimal and their use will be most commonly considered in disseminated during combination therapy.

The azoles have been the primary agents for phaeohyphomycosis because of excellent in vitro activity, safety in long-term use, and clinical experience. Itraconazole has been the best studied with a reported success rate of 60% (Sharkey et al. 1990). The European Society of Clinical Microbiology and Infectious Diseases and European Confederation of Medical Mycology Joint Guidelines for the diagnosis and manage-

ment of systemic phaeohyphomycosis suggests oral itraconazole to be the drug of choice for most situations given the extensive clinical experience with this agent (Chowdhary et al. 2014b). However, voriconazole is preferred because of better tolerability, safety, and the availability of an intravenous formulation, and it is specifically recommended for central nervous system infections as a result of its ability to achieve good cerebrospinal fluid and brain tissue levels, unlike itraconazole (Chowdhary et al. 2014b). Both of the extended-spectrum triazoles, voriconazole and posaconazole, have also been reported to achieve excellent outcomes (McGinnis et al. 1997; Espinel-Ingroff, 1998a,b; Perfect et al. 2003; Negroni et al. 2004, 2005; Fothergill et al. 2009), but, in disseminated infection with a serious underlying disease, failures occur secondary to direct drug resistance and biofilm formation on foreign bodies and/or progression of underlying diseases or cancer (Ben-Ami et al. 2009). The length of treatment remains empirical for these infections and must be judged individually. However, these infections generally need at least several months of drug exposure. In life-threatening central nervous system infections, there has been enthusiasm for using combination antifungal therapy along with surgery because there is some supportive in vitro additive or synergistic data against dematiaceous fungi (McGinnis and Pasarell 1998; Clancy et al. 2000). Because randomized studies to prove efficacy are unlikely, it is reasonable to consult experts to help in the therapeutic strategies against these relatively rare and fatal brain abscesses and disseminated infections.

CONCLUDING REMARKS

Melanized fungi in general are underestimated as etiologic agents of varied clinical entities primarily attributed to difficulties in classical identification owing to often slow growth and poor morphology. However, this scenario has changed considerably with the introduction of molecular diagnostics. Nearly all species can confidently be recognized by the rDNA ITS barcoding marker. Also, a majority of the melanized fungi are associated with non-life-threatening infections in the clinical lab and are generally not reported. However, despite their rarity, they are highly relevant because of their potential to infect and kill apparently healthy individuals. Chronic CNS infections may remain unnoticed for a long time, or are misdiagnosed as tumors, and then take a fatal course. Disseminated and (sub)cutaneous infections, such as chromoblastomycosis, are recalcitrant to therapy and may relapse despite the fungus' in vitro susceptibility to the antifungals. Colonizers of skin and cystic fibrosis lungs are much more frequent than generally supposed. The treatment options for melanized fungi are generally limited because of the efficacy of antifungal agents and limitations of surgical interventions. Novel and rapid diagnostic methods are being developed and are likely to change the landscape of infectious molds considerably.

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