ESCMID and ECMM joint clinical guidelines for the diagnosis and management of systemic phaeohyphomycosis: diseases caused by black fungi

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Abstract

The aetiological agents of many invasive fungal infections are saprobes and opportunistic pathogens. Some of these fungi are darkly pigmented due to melanin production and traditionally have been named 'dematiaceous'. The melanized fungi cause a wide array of clinical syndromes ranging from superficial to deep-seated infections. Diagnosis relies on histopathological examination of clinical specimens and on examination of cultures. Sequencing is recommended for accurate species identification, especially for unusual or newly described pathogens. In cases of mycetoma and chromoblastomycosis, pathognomonic histological findings are useful and the Fontana–Masson stain, specific for melanin, usually confirms the diagnosis. There are no standardized therapies but voriconazole, posaconazole and itraconazole demonstrate the most consistent *in vitro* activity against this group of fungi. Oral itraconazole has been considered the drug of choice, given the extensive clinical experience with this drug. However, voriconazole may presumably be superior for central nervous system infections

because of its ability to achieve good levels in the cerebrospinal fluid. Posaconazole is a well-tolerated alternative drug, backed by less clinical experience but with excellent salvage treatment results after failure of other antifungals. Amphotericin B has been useful as alternative therapy in some cases. Combination antifungal therapy is recommended for cerebral abscesses when surgery is not possible and for disseminated infections in immunocompromised patients.

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Introduction

A panel of experts of the European Fungal Infection Study Group (EFISG) of the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) undertook a data review and compiled guidelines for the diagnosis and management of infections caused by melanized (black) fungi. The deep-seated infection caused by these fungi is often referred to as phaeohyphomycosis. Many infections, however, are superficial and mild, or cause cutaneous or pulmonary colonization only. In addition, many species of black fungi have a cosmopolitan presence and are widely distributed in the environment and the possibility that a suspected clinical isolate might be a contaminant must be considered. The course of infection differs with the species, so for clinical management it is paramount to obtain an accurate species identification. Although sizeable numbers of these rare fungal pathogens have been implicated in human infections, we have reviewed only the most common ones.

Methods

The guideline development followed the AGREE II method (Appraisal of guidelines for research and evaluation II; http://www.agreetrust.org/resource-centre/agree-ii/, accessed 13 December 2013). The overall objective of the guidelines has been on the diagnosis and management of deep-seated phaeohyphomycosis, including disseminated infections. In addition, superficial and allergic manifestations caused by these

fungi are also briefly discussed. The definition of the strength of recommendation and the quality of the published evidence are defined in Table 1. The health questions covered by the guidelines are specifically described in the Tables 2–4. The population to whom the recommendations are meant to apply is any patient suffering from phaeohyphomycosis. The expert panel (35 members) was set up by ESCMID/EFISG and European Confederation of Medical Mycology (ECMM) including clinical microbiologists, infectious diseases experts, paediatricians, haematologists and intensive care unit experts taking into account the target users of these guidelines. Competing interests of guideline development group members were recorded and addressed. An expert subgroup (AC, MCE, JG, SDH, SK, OAC, JFM) reviewed the available literature. The other experts of the panel acted as external reviewers. The members actively shared their views and documents by email, teleconferences and face-to face meetings during 2012–2013.

TABLE 1. System for grading strength of recommendation and quality of evidence about diagnostic procedures and therapy of infections by black fungi

Grade of recommendation	Definition
Strength of recommendation	
Grade A	ESCMID (EFISG) and ECMM strongly support a recommendation for use
Grade B	ESCMID (EFISG) and ECMM moderately support a recommendation for use
Grade C	ESCMID (EFISG) and ECMM marginally support a recommendation for use
Grade D	ESCMID (EFISG) and ECMM support a recommendation against use

Level of evidence	Definition
Quality of evidence accepted	
Level I	Evidence from at least one properly designed randomized, controlled trial
Level II	Evidence from at least one well-designed clinical trial, without randomization; from cohort or case–control analytical studies (preferably from more than one centre); from multiple time series; or from dramatic results of uncontrolled experiments
Level III	Evidence from opinions of respected authorities, based on clinical experience, descriptive case studies, or reports of expert committees

TABLE 2. Disease spectrum of agents of phaeohyphomycosis with their *in vitro* antifungal susceptibility profile

Aetiological agents [references]	Most common described infections	Species	*In vitro* susceptibility (MIC range, mg/L)[a]								
			AMB	ITC	VRC	POS	ISA	FC	FLU	ECHINO	TERB
Alternaria [38,55,167]	Cutaneous and subcutaneous infection, sinusitis, keratitis, ABPM, disseminated disease	A. alternata	0.25–1.0	0.25–1.0	1.0–4.0	0.12–0.50	–	8.0–>64.0	8.0–32.0	0.50–1.0	>16.0
		A. infectoria	0.25–1.0	0.25–1.0	1.0–4.0	0.06–0.12	–	16.0–>64.0	16.0–32.0	1.0	>8.0
		Alternaria spp.	0.03–4.0	1.0	2.0	1.0	–	16.0–>64.0	16.0–>64.0	>16.0	16.0
Acrophialophora [183–185]	Brain abscess, ocular and lung infection	A. fusispora	0.25–4.0	0.06–0.25	0.12–2.0	0.125–2.0	–	>64.0	8.0–32.0	0.06–8.0	–
Aureobasidium [211]	Cutaneous and subcutaneous infection, ocular infection, rare deep infection, fungaemia	A. pullulans	0.01–16.0	0.01–2.0	0.01–16.0	0.01–4.0	–	–	4.0–64.0	–	–
Bipolaris [213,242]	Cutaneous and subcutaneous infection, sinusitis, ocular infection, pneumonia, cerebral infection, disseminated disease	B. hawaiiensis	0.12–0.25	0.03–0.5	0.25–2.0	0.03–0.5	–	>64.0	2.0–32.0	0.50–1.0	–
		B. australiensis	0.06–0.12	0.25–0.5	0.05–1.0	0.06	–	>64.0	8.0–16.0	1.0	–
		B. spicifera	0.03–4.0	0.03–8.0	0.25–4.0	0.03–2.0	–	>64.0	4.0–>64.0	0.25–2.0	–
Chaetomium [143,257,258]	Cutaneous and subcutaneous infection, pneumonia, brain abscess	C. globosum	0.50–8.0	0.03–0.50	0.50	–	–	32.0–>64.0	>64.0	–	–
		C. perlucidum	0.25	0.01–0.06	0.50	0.06–0.12	–	–	–	8.0–>16.0	–
Cladophialophora [87,123]	Cutaneous and subcutaneous infection, brain abscess	C. carrionii	0.5–8.0	0.01–0.12	0.01–1.0	0.01–0.06	0.01–1.0	–	4.0–64.0	0.25–4.0	0.01–1.0
		C. bantiana	0.12–2.0	0.01–0.25	0.12–4.0	0.01–0.25	0.01–1.0	–	16.0–64.0	1.0–8.0	–
Curvularia [277,284]	Cutaneous and subcutaneous infection, sinusitis, keratitis, ABPM, peritonitis, cerebral infection, disseminated disease	C. senegalensis	0.06–0.50	0.06–1.0	0.12–4.0	0.03–0.50	–	64.0–>64.0	2.0–16.0	0.50–2.0	–
		C. lunata	0.12–>16.0	0.12–>16.0	0.25–1.0	0.03–0.50	–	>64.0	2.0–64.0	0.50–>16.0	–
		Curvularia spp.	0.06–>16.0	0.03–>16.0	0.15–>16	0.03–4.0	–	64.0–>64.0	1.0–>64.0	0.50–>16.0	–
Exophiala [334–338]	Cutaneous and subcutaneous infection, pneumonia, brain abscess, disseminated disease	E. jeanselmei	0.25–2.0	0.01–0.25	0.06–2.0	0.01–0.06	0.25–2.0	64.0–>64.0	8.0–32.0	0.06–8.0	–
		E. dermatitidis	0.01–0.50	0.03–0.5	0.06–1.0	0.03–0.25	0.03–1.0	–	2.0–32.0	0.25–8.00	–
		E. spinifera	0.25–4.0	0.01–0.12	0.06–1.0	0.01–0.06	2.0	0.12–>64.0	16.0–>64.0	4.0	0.03–2.0
Exserohilum [340,375]	Cutaneous and subcutaneous infection, keratitis, meningitis and spinal infection, arthritis, disseminated disease	E. rostratum	0.03–0.12	0.03–0.12	0.03–1.0	0.03–0.12	–	–	–	0.03–>16.0	0.03–0.25
Fonsecaea [83,378]	Cutaneous and subcutaneous infections brain abscess	F. monophora	0.50–2.0	0.03–0.25	0.12–1.0	0.01–0.06	0.06–1.0	–	8.0–64.0	1.0–4.0	–
		F. pedrosoi	0.50–2.0	0.03–0.25	0.12–0.50	0.03–0.06	0.06–0.25	–	8.0–32.0	2.0–4.0	0.06–0.25
		Fonsecaea spp.	0.50–2.0	0.03–0.25	0.125–1.0	0.01–0.06	0.06–1.0	–	8.0–64.0	1.0–8.0	–
Hortae [396]	Tinea nigra, very rare deep mycosis	H. werneckii	0.12–2.0	0.03–0.50	0.06–0.25	0.01–0.12	0.06–0.5	–	8.0–64.0	1.0–8.0	–
Neoscytalidium [103,400,401,409]	Cutaneous infections and onychomycosis, very rare deep mycosis	N. dimidiatum	0.06–1.0	0.03–>16.0	0.03–4	0.06–32	–	–	0.25–32.0	0.06–>16.0	0.06–2.0
Ochroconis [434,437]	Pneumonia, brain abscess, disseminated infection	O. gallopava	0.12–1.0	0.01–0.50	0.12–2.0	0.01–0.12	–	16.0–>64.0	16.0–>64.0	1.0–8.0	0.03–1.0
		O. tshawytschae	4.0	0.50	0.12	–	–	–	>64.0	0.25	–
Phaeoacremonium [445,446]	Subcutaneous infection, arthritis, disseminated disease	P. parasiticum	2.0	0.12–8.0	0.06–0.25	0.03–0.50	–	–	8.0	>16.0	0.50–2.0
Phoma [457,459]	Cutaneous and subcutaneous infection, ocular infection, rare deep mycosis	Phoma spp.	0.5–1.0	0.25–8.0	0.25–8.0	–	–	–	–	–	–
Pyrenochaeta [462]	Cutaneous and subcutaneous infection, keratitis	P. romeroi	4.0	0.50	4.0	0.50	0.12	4.0–16.0	>64.0	8.0	–
Rhinocladiella [30,478,480,485]	Brain abscess	R. mackenziei	1.0–>16.0	0.01–0.25	0.01–2.0	0.01–0.25	–	–	16.0–64.0	1.0–8.0	–
		R. aquaspersa	1.0–2.0	0.06–0.12	2.0	0.06–0.12	–	–	32.0–64.0	8.0	–
Veronaea [494]	Cutaneous and subcutaneous infection, disseminated disease	V. botryosa	8.0–16.0	0.25–1.0	1.0–8.0	0.03–0.25	4.0–>16.0	–	>64.0	2.0–>16.0	1.0–4.0

AMB, amphotericin B; ITC, itraconazole; VRC, voriconazole; POS, posaconazole; ISA, isavuconazole; FC, flucytosine; FLU, fluconazole; ECHINO, echinocandins; TERB, terbinafine; ABPM, allergic bronchopulmonary mycosis.
[a] Depicts collective MIC ranges from all the references mentioned.

TABLE 3. Recommendations for microbiological procedures to detect infections by black fungi. Table includes grade and quality of evidences

Disease/population [references]	Intention	Diagnostic procedure	SoR	QoE	Comments
All cases with deep infections [9–13,237]	Definitive diagnosis and species identification to recommend best first-line therapy	Direct microscopy KOH, fluorescence Histopathology and Special stains H&E, Fontana–Masson stain, periodic acid Schiff (invasion) and culture	A	III	Visualization of melanized fungal structures. Fontana–Masson stain definitive detection of melanin in tissue/aspirate specimens. Conventional isolation media for species identification (BHI for some strains)
Cerebral abscess and other localized infections [9–13,237]	Definitive diagnosis and species identification	As above and specimen taken at the sources of infection	A	III	*Cladophialophora bantiana* and *Rhinocladiella mackenziei* (most common species in cerebral abscess)
Disseminated infections [9–13]	Definitive diagnosis and species identification	As above and blood cultures and other specimens when possible	A	III	None
All cases [9–13]	To know local species distribution	Periodical epidemiological surveys	A	III	None
Cases by isolates difficult to identify and sibling/cryptic species [14]	Definitive species identification	Molecular identification (DNA target sequencing)	B	III	May be essential investigation for some rare species
All cases with deep infections [15–17]	To detect high MIC values *in vitro* and recommend the best therapy	MIC determination	A	III	Use reference procedure
All cases [18,19]	To detect local resistance *in vitro*	Periodical epidemiological MIC determination surveys	A	III	Use reference procedures
All cases with deep infection [20–22]	To detect infection	β-D-glucan quantification	C	III	Panfungal detection. Insufficient data
All cases with deep infection [9]	To detect infection	*Aspergillus* galactomannan quantification	D	III	Cross-reactivity in some cases
Infections by *F. pedrosoi* and *C. carrionii* [12]	To detect infection	In-house ELISA techniques	C	III	Not validated
All cases [23,24]	Detect infection in tissues	PCR-based methods	C	III	Insufficient data
All cases [12,25]	Detect infection in blood, serum or other sterile fluids	PCR-based methods	C	III	No data

BHI, brain–heart infusion; H&E, haematoxylin and eosin; QoE, quality of evidence; SoR, strength of evidence.

Once the first consensus was reached, the preliminary recommendations were discussed, developed further and finalized as a group consensus. The methods to evaluate the quality of evidence and to reach consensus recommendations were described previously in detail when the first official ESCMID guidelines on the diagnosis and treatment of *Candida* infections were published [1–6].

The characteristic feature of phaeohyphomycosis is the presence of melanin in the fungal cell walls, which gives a dark colour to the hyphae, and is considered a major virulence factor. The criteria for selecting the evidence were searching the literature using the string 'melanized', 'dark', 'phaeoid' and 'dematiaceous' and search results were systematically reviewed. As the clinical syndromes associated with these fungi are common across the different pathogens (Table 2), the first part of this guideline presents recommendations for each clinical entity (localized cutaneous and subcutaneous infection, chromoblastomycosis, mycetoma, keratitis, pulmonary infections, cerebral infection, disseminated disease and allergic manifestations). Subsequently, specific issues for each of the fungal pathogens are presented in alphabetical order. Most recommendations in this guideline are based on dramatic results of uncontrolled experiments, opinions of respected authorities, clinical experience, descriptive case studies, or reports of expert committees. In some cases, *in vitro* data and animal studies are also included. Unfortunately, much of the older literature could not be included because of the unreliability of the non-molecular strain identification methods used. These guidelines highlight the fact that there is no standard approach for treatment of phaeohyphomycosis. Also, the reference microdilution methodologies for *in vitro* antifungal susceptibility testing have not been standardized nor are the validated MIC breakpoints that are used for interpretation of the results for antifungal drugs against the phaeoid fungi available. Unlike the other guidelines for fungal infections caused by rare yeasts and the mucorales, which recommend clear-cut therapeutic approaches [7,8], the huge diversity of dematiaceous fungi and their host range make it impossible to advise a uniform approach for phaeohyphomycosis. Length of therapy and choice of intervention (surgery, antifungals or both) for each clinical entity is primarily based on the clinical presentation, the underlying condition of the host and the initial response. The prolonged duration of therapy in the diseases caused by phaeoid fungi generally ranges from several weeks to months or longer. The clinical entities and their therapeutic recommendations are given below and summarized in Tables 1–4. Table 3 includes recommendations for diagnostic procedures and susceptibility testing of these diseases [9–25]. These guidelines will be periodically updated.

TABLE 4. Recommendations for targeted treatment of infection by black fungi. Table includes grade and quality of evidence

Disease[a]	Intention	Intervention [references]	SoR	QoE	Comments
Localized cutaneous infection or subcutaneous nodule(s)	Cure	Surgery [12,26–32]	A	II	Dramatic results of uncontrolled cases and multiple time series
Subcutaneous nodule	Cure	Cryotherapy, laser therapy, heat therapy or potassium iodide [33–37]	B	III	Reports from areas where antifungal agents are unavailable or failure/contraindication of antifungals
Multiple subcutaneous nodules	To prevent dissemination	Add itraconazole (400 mg) or voriconazole (400 mg) [12]	B	III	Expert opinion (particularly in immunocompromised patients)
	Cure	Itraconazole (400 mg) or voriconazole (400 mg) [38–44]	A	III	Descriptive case studies; treatment duration 3–12 months
	Cure	Itraconazole (200 mg) or posaconazole (800 mg), amphotericin B (1 mg/kg), liposomal amphotericin B (3 mg/kg), caspofungin (70/50 mg), terbinafine (250–500 mg) or combination therapy[b] with itraconazole PLUS terbinafine or itraconazole PLUS amphotericin B [12,41,45–58]	C	III	Few descriptive case studies and insufficient data. Some cases including surgery when possible
Mycetoma	Cure or reduce infections in advanced cases	Itraconazole (400 mg) for at least 3 months (years in some cases) PLUS surgery [59–64]	A	II	Dramatic results of uncontrolled cases and some time series
	As above	Voriconazole (400 mg), posaconazole (800 mg) or terbinafine (250 mg) PLUS surgery [66–69]	A	III	Dramatic results of uncontrolled few cases
Refractory mycetoma	As above	Ketoconazole (400 mg) [59,63,64]	D	III	Side effects
	As above	Amphotericin B (1 mg/kg) [12]	D	III	Impractical given the therapy duration
	Reduce lesions	Combination antifungal therapy (azoles PLUS terbinafine or flucytosine) [65,67]	B	III	Descriptive case studies / Surgery when possible
Chromoblastomycosis	Cure or reduced infections in advanced cases	Itraconazole (400 mg) for months to years PLUS surgery [72–74,76]	A	II	Dramatic results of uncontrolled cases and multiple time series
Refractory chromoblastomycosis	As above	Terbinafine (250 mg) or posaconazole (800 mg) PLUS surgery [72,75,77,78,88]	B	III	Descriptive case studies
	As above	Cryotherapy, laser therapy, heat therapy or potassium iodide [75,79–81]	B	III	Descriptive case studies
	Reduce lesions	Combination antifungal therapy (itraconazole plus terbinafine) [72,74,75,82–84]	B	III	Descriptive case studies / Surgery when possible
Keratitis	Cure	Natamycin alone or PLUS other topical agents [89,90,92–94]	A	II	Multiple time series
Refractory keratitis	Cure	Topical azoles alone [95–97]	B	III	Descriptive case studies
	Cure	Oral triazoles (conventional doses) PLUS surgery if needed [89,91–93]	B	III	Descriptive case studies
	Cure or control of infection	Intrastromal voriconazole injection [96,98]	C	III	Insufficient data
Pulmonary infection	Cure	Systemic liposomal amphotericin B (3 mg/kg), itraconazole (400 mg), voriconazole (400 mg) or posaconazole (800 mg) [12,102–107]	B	III	Descriptive case studies in immunocompromised or with underlying pulmonary disease (few cases for posaconazole)
Solitary pulmonary nodule in immunocompetent	Cure	Surgery [12,99,108]	B	III	Descriptive case studies
Cerebral abscess	Cure	Complete excision (when possible) [109,112,117–120]	A	II	Dramatic results of uncontrolled cases
	Cure when surgery is not possible	Voriconazole (400 mg) or posaconazole (800 mg) [121–128]	C	II	Multiple time series and animal model and in vitro data
	As above	Amphotericin B (several doses) [122–124,129]	D	III	Descriptive case studies, failures and results from animal models and in vitro data
Bone and joint infections	As above	New combination therapy (voriconazole or posaconazole plus echinocandin plus flucytosine) [12,116,130]	B	III	Expert opinion and descriptive case studies (very few)
Peritonitis	Cure	Surgery PLUS itraconazole (400 mg), voriconazole (400 mg), posaconazole (800 mg) or liposomal amphotericin B (3 mg/kg) [12,131,132]	B	III	Descriptive case studies
	Cure (associated with peritoneal dialysis)	Catheter removal PLUS systemic antifungal therapy [133–137]	A	II	Dramatic results of uncontrolled cases removing the catheter
Disseminated infection	Cure or infection control	Liposomal amphotericin B (3 mg/kg), itraconazole (400 mg), voriconazole (400 mg), or posaconazole (800 mg) [138,141–147]	C	III	Descriptive case studies
	As above	Voriconazole (400 mg) or posaconazole (800 mg) PLUS terbinafine (250 mg) PLUS colony-stimulating factors/leucocyte infusion [148–150]	B	III	Expert opinion and descriptive case studies (very few and based on experience with *Scedosporium* infections)
Allergic sinusitis	Remove the mucin and reduce symptoms	Surgery PLUS systemic steroids [151–154]	A	II	Prospective, randomized, placebo-controlled trial (24 patients only) and reviews
	Reduce requirements of steroids	Add itraconazole (several doses) [152,153,155]	C	III	Descriptive case studies
Refractory allergic sinusitis	Reduce symptoms	Add itraconazole (several doses) or voriconazole (400 mg) [156–158]	B	III	Descriptive case studies
Sinus fungus ball	Cure	Surgery [159]	A	II	Dramatic results of uncontrolled cases
Invasive sinusitis	Cure	Liposomal amphotericin B (3 mg/kg) 2 weeks followed by voriconazole (400 mg) 3 months [159]	C	III	Insufficient evidence
Allergic bronchopulmonary mycosis	Reduce symptoms	Steroids [12,151,161,162]	B	III	Descriptive case studies
	Reduce symptoms	Add itraconazole (several doses) [160,163]	D	III	Expert opinion

QoE, quality of evidence; SoR, strength of recommendation.
[a]The population to whom the recommendations are meant to apply is any patient suffering from phaeohyphomycosis.
[b]Dosage recommendation for combination antifungal therapy is the conventional dosing.

Recommendations by Clinical Entities

Localized cutaneous infection and subcutaneous nodules

One of the common manifestations of dematiaceous fungi is superficial localized cutaneous and subcutaneous disease. Most superficial infections are secondary to trauma. Lesions typically appear as isolated cystic or papular lesions on exposed areas of the body, such as limbs and hands. *Alternaria* spp. are the most common aetiological agent and others include species of *Exophiala* spp. and *Phialophora*. Clinical presentation is usually indolent, with a gradually enlarging mass. Generally immunocompromised patients are at increased risk of subsequent dissemination. On histopathological examination the phaeohyphomycotic cyst presents as a single dermal lesion with minimal changes in the epidermis and granulomatous inflammation with abundant giant cells. Fungal elements such as yeast-like structures and septate hyphae can be found in the specimen. For subcutaneous nodules in particular, surgery alone has been effective (recommendation AII) [12,26–32]. Cryotherapy, laser, heat and photodynamic therapy have also been used successfully in many cases (recommendation BIII) [33–37]. Oral antifungals, mainly azoles, have been widely used as co-adjunctive therapies particularly in immunocompromised patients and to prevent dissemination (recommendation BIII) [12]. Multiple subcutaneous nodules have to be treated with systemic antifungal agents. Itraconazole or voriconazole at 400 mg are recommended (recommendation AIII) [38–44]. Other antifungal agents have been used in some cases (recommendation CIII, Table 4) [12,41,45–58].

Eumycotic mycetoma

Mycetomas are localized infections that involve cutaneous and subcutaneous tissue, fascia and bone. Lesions consist of abscesses, granulomata and draining sinuses from which granules may be recovered. They may be caused by different fungi, which produce granules of different colours, such as *Acremonium* spp. (white), *Aspergillus nidulans* (white), *Exophiala jeanselmei* (black), *Leptosphaeria senegalensis* (black), *Madurella grisea* (black), *Madurella mycetomatis* (black), *Neotestudina rosatii* (white) and *Pyrenochaeta romeroi* (black). Mycetoma is difficult to cure and therapy includes amputation of the affected limb or large surgical excision of the affected tissue to reduce the disease burden. However, excision alone is rarely sufficient for a complete cure. This condition always requires surgery and prolonged systemic antifungal therapy (recommendation AII) [59–64]. Historically, the majority of cases reported used ketoconazole or itraconazole. Itraconazole appears to have consistent clinical activity (recommendation AII), and ketoconazole should be avoided because of side effects (recommendation DIII). Also, the newer triazoles (voriconazole and posaconazole; recommendation AIII) and combination therapy with terbinafine or flucytosine have been used successfully (recommendation BIII) [65–69].

Chromoblastomycosis

This is a chronic subcutaneous infection by dematiaceous fungi characterized by the presence of muriform cells or sclerotic bodies (medlar bodies) in tissue sections or wet preparations of pus or scrapings. Muriform cells are thick-walled, spherical, dark brown cells, which swell and often develop intersecting septa in various planes. The most commonly involved fungi are *Cladophialophora carrionii*, *Fonsecaea compacta*, *Fonsecaea pedrosoi* and *Phialophora verrucosa*. These causative agents of chromoblastomycosis are rarely recovered from nature but are selectively enriched by the human host [70]. The infection is difficult to cure, and relapses are common, possibly due to resistance development during therapy [71–76]. Overall, several studies suggest that standard of therapy should include itraconazole plus surgery (recommendation AII) [72–74,76]. In a few cases of chromoblastomycosis terbinafine monotherapy and surgery have been applied successfully (recommendation BIII) [72,75,77,78]. In addition, laser, heat and potassium iodide therapies have also been used in the past with successful outcome (recommendation BIII) [75,79–81]. Recommendations for refractory cases are combination antifungal therapy including cryotherapy or surgery when possible (recommendation BIII) [72,74,75,82–84]. Based on experimental and *in vitro* studies the new triazole drug posaconazole is promising and could be useful when other therapy has failed (recommendation BIII) [85–88].

Keratitis

Keratitis due to dematiaceous fungi is mainly reported from India where trauma accounts for up to 20% of cases [89–91]. The majority of patients can be treated with topical agents, the most commonly used are 5% natamycin and topical amphotericin B (0.15–0.3%) with or without topical azoles (1%) for at least 4 weeks to several months (recommendation AII) [89,90,92–94]. Topical azoles alone especially itraconazole and voriconazole (1%) can also be used (recommendation BIII) [95–97]. Severe and refractory cases require administration of oral azoles and usually surgery including penetrating and lamellar keratoplasty (recommendation BIII) [89,91–93]. An intracorneal injection of voriconazole (1%) as salvage therapy has been efficient in patients not responding to topical and systemic therapy in some cases (recommendation CIII) [96,98].

Pulmonary infections

These are potentially life threatening and are mainly seen in immunocompromised patients or those with underlying lung disease although cases in immunocompetent patients have been reported [99–101]. A wide variety of species can be involved and clinical manifestations include pneumonia, pulmonary nodules and endobronchial lesions. Therapy consists of intravenous liposomal amphotericin B or mould-active azoles except ketoconazole for a prolonged period (recommendation BIII). However, mortality rates are high in immunocompromised patients if underlying host defence defects are not resolved [12,102–107]. Solitary pulmonary nodule in immunocompetent patients can be treated with surgery (recommendation BIII) [12,99,108].

Cerebral infection

Cerebral abscess due to dematiaceous fungi is rare but frequently fatal and a surprisingly high proportion of these infections occurs in apparently immunocompetent individuals [109–116]. These infections are spread haematogenously, probably from an initial, presumably subclinical pulmonary focus, although spread from the sinus or following surgery may also occur. The neurotropic fungi are often geographically restricted, such as *Rhinocladiella mackenziei* occurring in the Middle East and *Cladophialophora bantiana* mainly in India. Although most infections with *Exophiala dermatitidis* are reported from East Asia the fungus is encountered worldwide. Overall, the therapeutic studies suggest that complete excision of brain abscesses has better outcome than only aspiration or partial excision (recommendation AII) [109,112,117–120]. Even with antifungal therapy outcome is poor; however, single cases suggest that voriconazole and posaconazole may provide clinical improvement and voriconazole penetrates into brain tissue most effectively (recommendation CII) [121–128]. Amphotericin B therapy generally has a poor outcome (recommendation DIII) [122–124,129]. Combination therapy including a triazole plus an echinocandin plus flucytosine, which also has *in vitro* activity against many of the black moulds and achieves good brain penetration, could be the first-line therapy when surgery is not possible (recommendation BIII) [12,116,130].

Other localized deep infections

These comprise mainly bone and joint infections and peritonitis. Recommendations can be found in Table 4 [12,131–137].

Disseminated infection

This is uncommon and reported mainly in the immunocompromised population [138]. Occasionally *Exophiala asiatica* causes dissemination in patients without known immunodeficiency or risk factors and it was recently reported from China [139,140]. There are at present no antifungal regimens associated with improved survival in disseminated infection, including multiple combination therapies (recommendation CIII) [138,141–147]. Combination antifungal therapy with adjunctive treatments has been effective in some cases of infections with hyaline fungi and multi-resistant *Scedosporium* spp. (recommendation BIII) [148–150].

Allergic fungal sinusitis

This entity is a hypersensitivity reaction, especially in immunocompetent, often atopic patients, and is caused by many species of dematiaceous fungi. The main black fungi involved are *Bipolaris*, *Curvularia*, *Exserohilum* and *Alternaria* species. Diagnosis depends on a histopathological demonstration of allergic mucin with visible fungal elements. Therapy consists of systemic steroids combined with surgical removal of the mucin (recommendation AII) [151–154]. The role of antifungal therapy, mostly azoles, is still under debate but may have a steroid-sparing effect (recommendation CIII) [152,153,155]. Recent reports indicate that oral triazole therapy can reduce symptoms of refractory sinusitis (recommendation BIII) [156–158]. In many instances the dematiaceous fungi can be the aetiological agents of sinus fungus balls. Surgical resection of fungus balls is generally sufficient (recommendation AII) unless local tissue invasion of the surrounding mucosa is demonstrated. Additional systemic antifungal drugs are indicated when this occurs (recommendation CIII) [159].

Allergic bronchopulmonary mycosis

This mycosis caused by fungi other than *Aspergillus* is a rare disease with <200 reported cases worldwide [160]. The two most commonly implicated dematiaceous fungi are *Bipolaris* and *Curvularia*. Analogous to allergic bronchopulmonary mycosis due to *Aspergillus*, the treatment of allergic bronchopulmonary mycosis consists of systemic steroids (recommendation BIII) [12,151,161,162]. Treatment with azoles is not yet clearly established and therefore, not recommended (recommendation DIII) [160,163].

Black Fungal Species with Clinical Relevance

During the last few decades the list of dematiaceous fungi implicated in human infections has continued to evolve and will further expand in line with the increase in the numbers of susceptible patients and the employment of better diagnostic tools. The important black fungi, their clinical manifestations, risk factors for infection, diagnosis and treatment are discussed along with their current taxonomical nomenclature.

Alternaria

The genus *Alternaria* is a plant pathogen and is commonly isolated from soil, air and plants [164–166]. The majority of cutaneous and subcutaneous infections are by *Alternaria alternata* followed by *Alternaria infectoria*, *Alternaria tenuissima*, *Alternaria alternatum* and *Alternaria tenuis* [55,167].

Clinical manifestations. Clinical manifestations of *Alternaria* infections are usually cutaneous or subcutaneous lesions mainly in immunosuppressed individuals [41,52,55,167]. To a lesser extent immunocompetent subjects can be affected following traumatic inoculation with plant debris and/or soil [168–171]. In cutaneous alternariosis, skin and soft tissue of the dorsal part of the hands and feet, fingers, elbows, knees and pretibial areas are the most commonly affected [55]. Most cases of subcutaneous alternariosis present with erythema, desquamation of skin, crusted ulcers, erythematous macules, yellow papules or violaceous nodules. Rarely sinusitis, keratitis and allergic bronchopulmonary mycosis have been reported, and disseminated infections occur with painless papulo-nodular lesions or cutaneous nodules. Cerebral infections due to *Alternaria* species are very rare [55,160,172]. The major predisposing factor is organ transplantation, reported in 40% of cases [39,42,55,167,173]. Bone marrow recipients are particularly at risk of sinusitis, whereas lung transplant recipients have a risk of cerebral infection [55,174]. In cutaneous/subcutaneous diseases Cushing syndrome is a major risk factor [175,176]. Other risk factors are long-term corticosteroid therapy, surgery, diabetes, human immunodeficiency virus infection, tuberculosis, neutropenia and haematological malignancies [29,31,43,47,177,178].

Diagnosis. Specific diagnosis is based on the microscopic detection of yellowish-brown hyphae with or without budding cells in tissue biopsies, aspirated pus, surgical drainage or skin scrapings. Culture and microscopic examination are mandatory for the correct identification of *Alternaria* spp. Amplification of DNA targets can be required for identification of uncommon *Alternaria* spp. [164,179].

Antifungal susceptibility and treatment. Cutaneous alternariosis usually requires the combination of wide excisional surgery, prolonged antifungal therapy, and reduction of immunosuppression [39,180]. In the case of well-delimited lesions, excision alone can lead to a total resolution of the disease, but antifungal therapy is required to avoid relapse. Itraconazole, voriconazole, posaconazole and amphotericin B constitute the cornerstones of the antifungal management of cutaneous and subcutaneous alternariosis based on clinical data available [38,55,56,167,181]. Also, a solitary case report on the successful use of intravenous caspofungin for the treatment of cutaneous alternariosis has been described [39]. As clinical trials are lacking, the optimal treatment strategy for patients with deep-seated *Alternaria* infections remains unclear [44,176]. Combination antifungal therapy can be recommended in disseminated cases [159,177,182]. *In vitro* susceptibility data suggest that the susceptibility of *Alternaria* species to antifungal agents appears to be species dependent (Table 2) [38]. Most of the species are susceptible to amphotericin B, itraconazole, voriconazole and posaconazole, and with high MIC values of echinocandins, fluconazole and flucytosine. Terbinafine also has been used successfully in the treatment of cutaneous alternariosis [31,46,173]. The role of echinocandins as part of combination therapy for alternariosis remains to be clarified.

Acrophialophora

The genus *Acrophialophora* comprises three species but only *Acrophialophora fusispora* is of clinical interest. *Acrophialophora fusispora* is a thermotolerant fungus with a wide distribution in tropical and temperate regions [164].

Clinical manifestations. Only five cases of phaeohyphomycosis have been reported so far, which include two cases of brain abscess attributed to *Acrophialophora fusispora* and three other cases involving the lung in two and cornea in one case [183–185].

Diagnosis. This fungus is similar to *Paecilomyces* spp. and sometimes misidentified as *Scedosporium prolificans* [186] but can be differentiated by the presence of pigmented, warted conidiophores, basally inflated verticillate phialides and pigmented fusiform conidia ornamented in spiral bands.

Antifungal susceptibility and treatment. Due to the small number of cases reported, the optimal treatment and management of these infections are unknown. The isolates tested have shown variable susceptibility to itraconazole, voriconazole, posaconazole, amphotericin B and resistance to echinocandins. Response *in vivo* has been unpredictable [183–185].

Aureobasidium

Aureobasidium is a genus of black yeasts that ubiquitously colonize smooth surfaces of plant leaves, glass and rocks, and may contaminate metal, glassware and tubing systems in the hospital [187]. These fungi are commonly found as contaminants in the clinical laboratory. Clinically significant species are *Aureobasidium pullulans*, *Aureobasidium proteae* and *Aureobasidium mansoni*, all of which are associated with cerebral phaeohyphomycosis [164,188].

Clinical manifestations. *Aureobasidium pullulans* has an affinity for synthetic materials and surgically implanted silastic devices, as the fungus has been isolated from indwelling peritoneal dialysis catheters and central venous lines [189–193]. In severely compromised patients deep infections are encountered, and the fungus has been isolated from blood, bronchoalveolar lavage, lymph nodes, splenic abscess or cerebrospinal fluid [187,194–203]. Infections are caused mostly by traumatic inoculation of the skin or eye, and intrathecal administration of cytotoxic drugs [204–210].

Diagnosis. Black yeasts are observed by microscopy. Classification of this fungus can be done easily by conventional methods and also by DNA sequencing.

Susceptibility testing and treatment. No standard treatment exists for *Aureobasidium* infections but amphotericin B is recommended because it has been successfully used to treat systemic infection, meningitis and peritonitis [190–192]. However, two cases of fungaemia reported to have amphotericin B treatment failure are on record [187,197]. Other alternative treatment options which are reported to be effective in localized infections could be fluconazole and flucytosine [192,199]. *In vitro* studies revealed that this organism showed variable degrees of susceptibility to commonly used antifungals (Table 2) [211]. Apart from amphotericin B in invasive cases, voriconazole could be added concomitantly because it completely cured a chronic meningitis case caused by *Aureobasidium proteae* [188].

Bipolaris

Bipolaris spp. are ubiquitous in nature and found in soil and decaying matter [212]. The commonest species in human infections are *Bipolaris australiensis*, *Bipolaris hawaiiensis* and *Bipolaris spicifera* [12,213]; however, these three species have recently been transferred to *Curvularia* [214]. *Bipolaris* spp. previously classified as *Drechslera* or *Helminthosporium* are emerging as important aetiological agents of phaeohyphomycosis in humans [164].

Clinical manifestations. *Bipolaris* spp. are associated with serious infections in immunocompetent and immunocompromised hosts, such as pansinusitis [215], endophthalmitis and orbital cellulitis [216,217], necrotizing pneumonia and allergic bronchopulmonary mycosis [160,162,218], peritonitis [219], ascending aorta endarteritis [220] and encephalitis [221,222]. Dissemination to the central nervous system via the nasal sinuses has been described [114,223–225]. Dissemination to other deep sites may occur in debilitated or compromised patients such as those having undergone either organ transplantation or other surgical procedures [226–230]. Superficial disease involving cutaneous, subcutaneous and corneal regions afflicts mainly immunocompetent patients [115,231–233].

Diagnosis. Diagnostic procedures of cutaneous and invasive infections are summarized in Table 3 and are similar for most black fungi. Molecular identification based on PCR and sequencing of the internal transcribed spacer (ITS) and D1/D2 regions of rDNA is recommended for accurate identification [234]. Direct detection of *Bipolaris* DNA by PCR has been reported [235,236]. As with all fungi in this class, the Fontana–Masson stain is helpful for diagnosis [237].

Antifungal susceptibility and therapy. Treatment involves a combination of surgical debridement and antifungal treatment, typically with amphotericin B or an azole [238–241]. With the exception of fluconazole and flucytosine, amphotericin B, itraconazole, posaconazole and voriconazole showed good activity against species of *Bipolaris* [213,242]. Surgical interventions such as removal of foreign objects, catheter tips or sinus debridement are usually necessary as adjunctive therapy, especially in localized infections and those associated with foreign implants [243,244].

Chaetomium

The genus *Chaetomium* is a large genus of saprobic ascomycetes including >180 species. *Chaetomium* species are generally found in warm, dry, cellulose-rich media, such as animal dung, straw, seeds, plant debris, bird feathers and many other substrates [245,246]. They are rarely implicated in human disease; the clinically significant species include *Chaetomium globosum*, followed by *Chaetomium strumarium*, *Chaetomium atrobrunneum*, *Chaetomium funicola* and *Chaetomium perlucidum* [247–255].

Clinical manifestations. The spectrum of mycoses caused by *Chaetomium* species includes onychomycosis, chromoblastomycosis and sinusitis in immunocompetent individuals [249,253], and empyema, pneumonia, and fatal disseminated cerebral disease in immunocompromised hosts and intravenous drug users [247,248,250–252,254,255]. The majority of reports have involved patients with haematological malignancies and/or immunosuppression secondary to bone marrow or solid organ transplantation [102,248,252,254,255].

Diagnosis. Diagnostic procedures are similar to those previously described. The main characteristic of *Chaetomium* species is the presence of hairs or setae covering the ascomata. They are differentiated by the size and shape of ascomata, the type

of setae they possess, and the size and shape of their brownish ascospores [143,164,256].

Susceptibility testing and treatment. Most patients with reported invasive disease received either conventional or lipid-based amphotericin B empirically during their treatment course [247–255]. *Chaetomium perlucidum* isolates have low MICs of amphotericin B, itraconazole, voriconazole and posaconazole, but high MICs of caspofungin. Amphotericin B had varied susceptibility profiles while itraconazole and voriconazole exhibited good activity against *Chaetomium globosum* [143,257,258].

Cladophialophora

The genus includes neurotropic fungi such as *Cladophialophora bantiana* and *Cladophialophora modesta* causing mainly brain infections [259]. While *Cladophialophora bantiana* is reported worldwide, a general preference for warm climates with high humidity is apparent [260]. *Cladophialophora carrionii* is prevalent in dry countries and desert zones, and other rarely reported species *Cladophialophora devriesii* and *Cladophialophora arxii* cause disseminated disease, while *Cladophialophora boppii*, *Cladophialophora emmonsii* and *Cladophialophora saturnica* cause mild cutaneous infections [164,245,261–263].

Clinical manifestations. Human infections, due to *Cladophialophora* range from mild cutaneous lesions to fatal cerebral infection. In a review in 2004, *Cladophialophora bantiana* was the most common species responsible for cerebral disease and accounted for 48 of 101 cases of cerebral phaeohyphomycosis [127]. Single lesions were present in the majority of cases of brain abscess. Also, no evidence of dissemination outside the central nervous system has been observed. Patients with central nervous system phaeohyphomycosis are often immunocompetent and have no known underlying diseases [123,124,264,265]. These species also cause superficial and subcutaneous diseases. Most of the aetiological agents produce only localized disease restricted to skin and subcutaneous tissue. Chromoblastomycosis due to *Cladophialophora* is mainly caused by *Cladophialophora carrionii* [12,266]. Risk factors or underlying diseases associated with infection due to *Cladophialophora* are organ transplantation, diabetes, systemic lupus erythematosus, pulmonary tuberculosis, primary immunodeficiency of unknown origin, recurrent cytomegalovirus viraemia, pneumonitis, neutropenia and nephrectomy [105,126,128,267,268].

Diagnosis. *Cladophialophora* is a genus related to black yeast-like fungi but in routine cultures it grows strictly monomorphically as a mould with long, delicate, branching chains of hydrophobic conidia and lacking yeast cells [164]. In cerebral phaeohyphomycosis and other infections a KOH preparation of pus from the lesion may show lightly pigmented yeast-like forms or more often short chains of spores and hyphae. Histopathology is essential for confirmation of subcutaneous infections. Culture is recommended and for species identification, sequencing of ITS regions of rDNA is most appropriate [245]. Although there are no specific clinical or radiological features for the diagnosis of cerebral phaeohyphomycosis, a computed tomography scan of the cranium often reveals unilateral well-circumscribed single or multiple mass lesions localized within the cerebral cortex [117,260,269]. Purulent meningitis, with or without brain abscess, may also be seen [265].

Susceptibility testing and treatment. When possible, complete surgical removal of the encapsulated abscess combined with antifungal therapy is recommended, but so far success in treating cerebral phaeohyphomycosis due to *Cladophialophora* is limited regardless of the immune status of the patient (>70% mortality) [12,127]. Adding antifungal monotherapy or combination therapy might improve survival [270,271]. When there are multiple cerebral abscesses and surgery is not practicable, combination therapy with amphotericin B, flucytosine, caspofungin and terbinafine, or an extended spectrum triazole, has been proposed as a regimen [12,128]. Itraconazole and posaconazole had the best activity *in vitro*, while voriconazole has better central nervous system penetration and better bioavailability [272–275]. Echinocandins and amphotericin B have shown also activity *in vitro* [87,123]. The newer drug isavuconazole reveals low MICs for *Cladophialophora carrionii*. In murine models of *Cladophialophora bantiana* infections, the combination of the three drugs flucytosine, micafungin and posaconazole was the only therapy that prolonged survival time [276].

Curvularia

The genus *Curvularia* comprises nearly 100 species. Most are saprobes in soil, on dead plant material or plant pathogens mainly infecting grasses [212]. The clinically relevant species are *Curvularia aeria*, *Curvularia geniculata*/*Curvularia senegalensis* and *Curvularia lunata*; less frequently implicated species are *Curvularia brachyspora*, *Curvularia clavata*, *Curvularia inaequalis*, *Curvularia pallescens* and *Curvularia verruculosa* [164,212,277].

Clinical manifestations. More commonly, species of *Curvularia* cause allergic sinusitis [278,279], but they can disseminate to the brain even in immunocompetent patients [113]. Other manifestations include subcutaneous infections following traumatic implantation [280,281], onychomycosis [282], keratitis

[283,284], endophthalmitis [285,286], mycetoma [287], invasive sinusitis [288,289], peritonitis [290,291], invasive cerebral infections [292,293], endocarditis [294] and disseminated infections [295–297].

Diagnosis. Colonies of *Curvularia* are blackish, expanding and hairy; the conidiophores are erect and the conidia are ellipsoidal, brown, usually curved and generally with three or four septa. Recent studies have demonstrated that molecular confirmation of species is usually required by sequencing the ITS regions of rDNA and the glyceraldehyde-3-phosphate dehydrogenase gene [164,212,277,298].

Antifungal susceptibility and treatment. The *in vitro* antifungal susceptibility of different clinical isolates of *Curvularia* has been determined in several studies (Table 2) [113,277,284,299]. In general, amphotericin B showed potent *in vitro* activity and triazoles and echinocandins had less *in vitro* activity. Clinical experience with the treatment of *Curvularia* infections is scarce and mainly based on a few case reports where amphotericin B and azoles have been the most frequently used drugs in monotherapy or combination therapy with variable results (Table 4) [110,279,280,286,293,295,297,300,301].

Exophiala

The genus *Exophiala* comprises the most clinically relevant black yeasts, often isolated from environmental substrates, including soil, wood and other plant material [164,298]. The species commonly involved in human infections are *Exophiala dermatitidis*, *Exophiala xenobiotica* and *Exophiala oligosperma*, followed by *Exophiala lecaniicorni*, *Exophiala phaeomuriformis*, *Exophiala jeanselmei*, *Exophiala bergeri*, *Exophiala mesophila*, *Exophiala spinifera*, *Exophiala xenobiotica* and *Exophiala oligosperma* [302–304]. Although distributed worldwide, *Exophiala dermatitidis*, a neurotropic agent, is reported mainly from Asia, whereas *Exophiala spinifera* is reported from various parts of the world as the causative agent of phaeohyphomycosis and chromoblastomycosis [259,264,304,305].

Clinical manifestations. Most of the infections caused by *Exophiala* are cutaneous and subcutaneous [306–308] whereas fatal systemic infections can occur, including rare cerebral infections [139,140,164,298,309]. *Exophiala* species produce pustules or verrucous plaques in the skin or subcutaneous tissue. These lesions can enlarge and impair mobility but rarely disseminate to the internal organs [35,305,310,311]. Chromoblastomycosis or eumycotic mycetoma is rarely caused by this genus [60,74]. Besides subcutaneous infections, this species can cause pulmonary colonization of the lungs in patients with cystic fibrosis [312] and brain abscess and disseminated,

eventually fatal, disease in patients without recognized underlying diseases [304,313,314]. Disseminated disease generally affects elderly and immunosuppressed patients such as individuals with AIDS or those on prolonged use of immunosuppressive drugs, chemotherapy treatment or systemic corticosteroids [267,315–317]. Additionally, intestinal colonization by the fungus has been reported [318,319].

Diagnosis. The histological characteristics of *Exophiala* for a cutaneous deep fungal infection include epidermal hyperkeratosis, hyperplasia, acanthosis, pseudoepitheliomatous and intraepidermal pustule formation. Pigmented fungal elements can be detected most frequently in areas of inflammation, within or adjoining to multinucleate giant cells. Diagnostic techniques are shown in Table 3. Molecular methods of detection and classification have also been reported [303,320].

Susceptibility testing and treatment. Apart from surgical resection, which in some cases is curative, treatment requires antifungal agents such as itraconazole or terbinafine alone or in combination [267,321,322]. As an alternative to the prolonged, expensive pharmacological treatments, some authors propose Mohs micrographic surgery as an effective therapeutic option with the important benefit of minimal tissue loss [26]. Other antifungal agents have also been used, and brain and disseminated infections are infections that are difficult to treat [141,323–333]. *In vitro* susceptibility studies demonstrated variable activity of posaconazole, itraconazole, voriconazole and amphotericin B [334–338]. In animal models of disseminated infection by *Exophiala dermatitidis* posaconazole was more effective than amphotericin B and itraconazole [339].

Exserohilum

The anamorphic genus *Exserohilum* comprises around 35 species, which are common saprobic fungi on plant debris [164]. Three species *Exserohilum rostratum*, *Exserohilum longirostratum* and *Exserohilum mcginnisii* have been reported in the past as opportunistic pathogens for humans. However, several molecular studies have demonstrated that they belong to a single species, *Exserohilum rostratum* being the accepted one [340].

Clinical manifestations. *Exserohilum* is a rare clinically significant pathogen causing invasive infections mainly in immunocompromised patients [222,341–356], keratitis [357–361] or localized infections in immunocompetent individuals usually after accidental inoculation [362–364]. The risk factors for *Exserohilum* infections include aplastic anaemia [345,365] and haematopoietic stem cell transplantation [341,356].

Recently, *Exserohilum rostratum* has been implicated in a fungal meningitis outbreak that was traced back to contami-

nated steroid injections [366–369]. As of 23 October 2013 there were 718 cases of fungal meningitis, stroke due to presumed fungal meningitis, **and/or** spinal or paraspinal infections; 33 cases of peripheral joint infections and 64 deaths (http://www.cdc.gov/hai/outbreaks/meningitis-map-large.html, accessed 9 December 2013).

Diagnosis. *Exserohilum* species are mainly identified by the conidial morphology when growing in its natural substratum [164]. *In vitro* identification is more difficult, the conidia tending to be smaller and the isolates often losing the ability to sporulate. At the generic level, the most useful microscopic characteristics are the conidial shape with the presence of a protruding scar or hilum. Sequencing of the ITS region of rDNA for molecular identification has been used. In the context of the above mentioned outbreak, species-specific real-time PCR assays were developed for rapid molecular diagnosis [370,371].

Antifungal susceptibility and treatment. There are limited data on the treatment of infections due to *Exserohilum*. Experience from the recent meningitis outbreak [368] and case reviews of sinusitis and cutaneous infections by these fungi reveal successful outcomes with amphotericin B [341,346,372] and more recently with itraconazole and voriconazole [347,353]. Based on historical data, amphotericin B might be the first choice in severe infections [340,373,374] but an expert group coordinated by the US Centers for Disease Control advised voriconazole because of its excellent pharmacokinetics/pharmacodynamics in cerebral infections [366,375]. However, clinical failures with voriconazole have been reported [376]. *In vitro* studies showed itraconazole, posaconazole and amphotericin B to be the most potent followed by voriconazole [340,375]. Animal models of *Exserohilum* central nervous system infection have not yet been developed for therapeutic and prophylactic studies [377].

Fonsecaea

Fonsecaea is one of the classical genera of fungi causing human chromoblastomycosis. A small group of three closely related species include *Fonsecaea pedrosoi*, *Fonsecaea monophora* and *Fonsecaea nubica* [378]. *Fonsecaea* particularly occurs in tropical climate zones, especially South America and Japan [379–381]. Most cases outside endemic zones are assumed to have been imported. However, cases that were likely to be autochthonous were reported even in northern Europe [382]. Other *Fonsecaea* species are saprobes in the environment, and occasionally cause infections in animals [383].

Clinical manifestations. The classical presentation of chromoblastomycosis caused by *Fonsecaea* is similar to that described previously above [74]. The disease is probably acquired by traumatic inoculation of plant debris and possibly hydrocarbon-rich plant material, such as coconut shells, which are preferentially infested by *Fonsecaea* species [384]. *Fonsecaea* infections other than chromoblastomycosis are rare and mainly concern brain infections by *Fonsecaea monophora* [385–387]. The portal of entry of these infections is unknown but dissemination from a pulmonary focus is likely.

Diagnosis. *Fonsecaea* species are recognized by poorly differentiated conidiophores apically producing short, branched chains of conidia [74,298,370]. For species distinction, sequencing of rDNA ITS regions is necessary [378,386]. Genus-specific PCR for detection of *Fonsecaea* species has been applied [71,388]. Detection of $1,3-\beta$-D-glucan was used to diagnose and monitor therapy against cerebral phaeohyphomycosis by *Fonsecaea monophora* in a transplant recipient [125].

Susceptibility testing and treatment. Therapy for chromoblastomycosis has already been commented on (Table 4). Surgery plus antifungal therapy is the standard of therapy. In addition, combination therapy with itraconazole plus terbinafine or flucytosine has been successfully used in severe disease [72,83]. *In vitro* susceptibility data of these species revealed lowest MICs for posaconazole followed by itraconazole, voriconazole, terbinafine, amphotericin B and caspofungin [378]. A refractory case of chromoblastomycosis caused by *Fonsecaea monophora* failed treatment with itraconazole and terbinafine. Photodynamic therapy and combination therapy with voriconazole plus terbinafine led to improvement of the lesions [37].

Hortaea werneckii

The melanized, polymorphic and yeast-like fungus *Hortaea werneckii*, previously known as *Exophiala werneckii* or *Cladosporium werneckii*, is the black yeast responsible for tinea nigra. *Hortaea werneckii* is best known from tropical climates and lives in saline environments such as seawater and natural or man-made saltpans [389,390]. Most cases of infection originate from rural areas in tropical and humid regions characterized by abundant vegetation and had close contact with plants and grasses with substrata of high salinity.

Clinical manifestations. Tinea nigra is a superficial mycosis of one or both hands and sometime affects the sole. The disease has no preference for age or sex, with cases equally occurring

in adults and children, and males and females [391–393]. Most cases are unilateral but bilateral infections can be observed [394], probably resulting from autoinoculation. The first human case not involving the skin was reported from an immunocompromised patient with endophthalmitis following cataract surgery [395]. *Hortaea werneckii* has been recovered from blood and splenic abscess of two patients with acute myelomonocytic leukaemia [396].

Diagnosis. Conidia of *Hortaea werneckii* appear as pigmented yeast cells with a dark central septum, the outer wall later becoming thick-walled and heavily pigmented. Conidia finally germinate with hyphae resulting in yeast-like colonies that gradually change into filaments. Molecular identification of *Hortaea werneckii* has been reported [388,390,397].

Susceptibility testing and treatment. The treatment of tinea nigra is simple and effective. Most cases resolve with only keratin-olytic agents like urea, salicylic acid and Whitfield ointment, applied once or twice a day [391]. *In vitro* antifungal susceptibility testing showed variable MICs of itraconazole, voriconazole, posaconazole, isavuconazole and amphotericin B (Meis J.F., unpublished data). There are reports available of high MICs of this fungus to amphotericin B, fluconazole, flucytosine and caspofungin [396].

Neoscytalidium dimidiatum

Neoscytalidium dimidiatum (formerly *Scytalidium dimidiatum*) is a known plant pathogen in tropical areas that can also be found in soil and wood and can infect humans [398,399]. *Scytalidium hyalinum*, previously considered a non-pigmented species similar to *Neoscytalidium dimidiatum* is in fact only a mutant variant [400]. The fungus is endemic in tropical and subtropical areas of South America, the Caribbean, Asia and Africa but has been increasingly reported from other non-endemic regions owing to immigration and travel [401]. It was reported that in Jamaica up to 40% of the population suffer from this infection [402].

Clinical manifestations. Neoscytalidium dimidiatum causes mainly onychomycosis and tinea pedis, and in endemic areas may rival dermatophytes as the leading cause of superficial fungal infection. This fungus most often causes chronic superficial infections of the skin and nails, clinically resembling dermat-ophytosis [399,403]. Rarely mycetoma, subcutaneous lesions, cerebral infections, fungaemia and other deep-seated infections mainly affecting immunocompromised patients [399] have also been reported. Invasive infections have been seen mostly in immunosuppressed patients [399,401,404]. The

underlying conditions reported are similar to those of other opportunistic invasive mycoses.

Diagnosis. Traditionally, the fungus has been characterized by producing dark arthroconidia when grown in culture whereas in older cultures some isolates developed a picnidial form called *Nattrassia mangiferae* (formerly *Hendersonula toruloidea*) [405]. However, molecular studies have demonstrated that they are two different species, and *Nattrassia mangiferae* is now accommodated in a different genus with non-pathogenic species [406]. *Neoscytalidium dimidiatum* is distinguished from dermatophytes by its characteristic sinuous, irregular hyphal appearance and by brown pigmentation on direct microscopy of cutaneous specimens, its fast-growing colonies, and its sensitivity to cycloheximide [401]. On microscopy of cultures, characteristic pigmented hyphae and long chains of bar-rel-shaped arthroconidia are seen. In deeper tissue the fungus has been described as producing yeast-like cells with short hyphae [404].

Susceptibility testing and treatment. Antifungal therapy with amphotericin B, voriconazole, posaconazole or ketoconazole has been used with variable results [399–404,407,408]. *In vitro* studies have shown that amphotericin B was the most active drug followed by terbinafine, whereas voriconazole and posaconazole showed less activity [400,409]. The best treatment of systemic infections by this fungus is unknown; however, in a murine model, amphotericin B, voriconazole and posaconazole had efficacy in the treatment of a disseminated infection [410].

Ochroconis

Ochroconis encompasses several species including *Ochroconis constricta, Ochroconis gallopava*, recently transferred to the new genus *Verruconis*, and *Ochroconis humicola* [136,144,411]. Members of the genus have been isolated worldwide from soil, thermal springs, decaying vegetation, in chicken litter and the effluents of thermal nuclear reactors [101,412–417]. Although the organism has a worldwide distribution, many cases of human infections have been described in the southeastern USA [418,419]. Its exact mode of transmission is unclear, but it is hypothesized that *Ochroconis* might be acquired from penetrating trauma or via inhalation of conidia [70,420,421]. Although *Ochroconis* spp. have traditionally been regarded as a cause of deep infections in birds and other animals there have been multiple reports implicating these fungi, particularly *Verruconis gallopava* and *Ochroconis constricta*, as pathogens in humans [104,144,422–427].

Clinical manifestations. The majority of these reports have been in two patient populations: those that have received transplants [415,423,424,426–431], and those with haematological malignancies undergoing chemotherapy [418,419,422,432]. Infections in these two groups presented as a combination of both pulmonary and extra-pulmonary disease, particularly involving the brain, spleen, skin and other organ sites. Although a number of patients with extra-pulmonary disease have survived [101,433], it is more frequently associated with poor clinical outcomes [418,422,424,426]. Other risk factors are HIV and chronic granulomatous disease [144,420,434]. The minority of cases of *Ochroconis* infections have been in immunocompetent patients [435,436].

Diagnosis. The colonies of *Ochroconis* species are brown-olive, and have a velvety texture. Microscopically, they are characterized by brown septate hyphae, unbranched conidiophores with apical denticles arranged sympodially, and club-shaped conidia with one to three transverse septa [164,411]. The paucity of *Ochroconis* infections in humans has two potential consequences. First, clinicians may fail to consider it in their differential diagnosis. Second, the microbiology laboratory may mistakenly dismiss the organism as a contaminant, rather than acknowledging it as a true pathogen [127,413,418]. Similar to other black fungi, sequencing of ITS and D1/D2 regions of rDNA can be used for molecular identification [234].

Susceptibility testing and treatment. Due to the high mortality rate reported in patients (estimated at 50%), proper recognition and treatment of *Ochroconis* infections are paramount [426,430]. Several studies suggest that posaconazole and itraconazole may be an optimal therapy for *Ochroconis* infection, with amphotericin B and voriconazole as valid alternatives. Flucytosine and fluconazole are the least effective drugs [423,427,430,434]. *Ochroconis gallopava* has low MICs for most antifungal drugs with terbinafine, posaconazole and voriconazole showing the best *in vitro* activity [434,437].

Phaeoacremonium

The genus *Phaeoacremonium* initially accommodated species with features similar to those seen in both *Acremonium* and *Phialophora* [406]. A recent morphological and molecular characterization of the genus using *β*-tubulin sequences [438] has more clearly defined the genus and provided differential features for clinically significant species. Human pathogens include *Phaeoacremonium parasiticum* (obsolete *Phialophora parasitica*), *Phaeoacremonium alvesii*, *Phaeoacremonium amstelodamense*, *Phaeoacremonium griseorubrum*, *Phaeoacremonium krajdenii*, *Phaeoacremonium rubrigenum*, *Phaeoacremonium inflat-*

ipes, *Phaeoacremonium tardicrescens* and *Phaeoacremonium venezuelense* [30,438–440].

Clinical manifestations. Recently, *Phaeoacremonium* infections have been increasingly reported in humans including subcutaneous abscesses, cysts, or chronic or acute osteoarthritis and disseminated infection mostly in immunocompromised patients (solid organ transplantation and haematological diseases) [28–30,441–443]. Colonization of cracked skin on the extremities has also been described [438]. In the majority of cases, a preceding trauma leading to inoculation from the environment was reported [30,442,443]. In immunocompromised patients with disseminated infections, endocarditis, brain abscess and fungaemia have been reported [12,438,440].

Diagnosis. Infections by *Phaeoacremonium* are diagnosed by biopsy of the cysts. Direct examination reveals medium brown hyphae, which become pale brown to hyaline and verrucous in the aspirated pus, biopsy material or skin scrapings [30,164]. The phialides have a funnel-shaped collarette and show a wide variety of conidia with diverse forms, including ellipsoidal, obovate, cylindrical or allantoid (sausage-like) [438,439]. PCR amplifying ITS regions of rDNA followed by sequencing was shown to be able to detect and identify species of *Phaeoacremonium* [444].

Susceptibility testing and treatment. The most active drugs *in vitro* against *Phaeoacremonium parasiticum* isolates were voriconazole, posaconazole and itraconazole whereas reduced susceptibility to amphotericin B was reported [445,446]. When possible, complete surgical removal of the encapsulated abscess combined with antifungal therapy such as posaconazole and itraconazole is the recommended treatment [28–30]. However, antifungal therapy for infections caused by some of the species of *Phaeoacremonium* in immunocompromised hosts is at present unsatisfactory [438,440,441].

Phoma

Phoma species are ubiquitous saprobes on plant material found worldwide [164,447]. Of the more than 200 species of *Phoma* currently accepted, fewer than 10 species have occasionally been found in human infections [164,448].

Clinical manifestations. Phaeohyphomycosis caused by *Phoma* has been sporadically described in the literature. Most reported cases are subcutaneous [449–456] and ocular infections [457,458]. Systemic infection with *Phoma* spp. is generally seen in severely immunocompromised patients and generally has a poor outcome [459–461]. Often the aetiological agent is not identified to the species level. The risk factors

or underlying diseases associated with *Phoma* infections may include diabetes mellitus, corticosteroid therapy and cancer chemotherapy [450,456,459–461].

Diagnosis. Phoma species produce slow-growing, dark-grey-olive, or dark-brown colonies. The fungus produces ostiolated fruiting bodies known as pycnidia and numerous, small, asexual conidia. Pycnidia are black, globose, subglobose, or pyriform and either submerged or on the surface of agar. Conidia (pycnidiospores) are produced from the phialides that line the inner wall of pycnidia and are hyaline, one-celled, elliptical, rod shaped or curved [164,460]. A PCR assay for detecting *Phoma exigua* DNA in deparaffinized lung biopsy material has been developed [459].

Susceptibility testing and treatment. Excision of phaeomycotic cysts without antifungal treatment is usually curative. For the treatment of cutaneous lesions triazoles (itraconazole and voriconazole) [451,457] and amphotericin B [450] are recommended. *In vitro* susceptibility data on *Phoma* species is based on sporadic case reports with itraconazole and voriconazole MICs ranging from 0.25 to 8 mg/L and amphotericin B MICs from 0.5 to 1 mg/L [457,459].

Pyrenochaeta

Pyrenochaeta is a genus that comprises pycnidial coelomycetes that are widely distributed in the environment, being found in soil, on wood and on plant debris and also as plant pathogens [462]. The species implicated in human infections include *Pyrenochaeta keratinophila, Pyrenochaeta unguis-hominis, Pyrenochaeta romeroi* and *Pyrenochaeta mackinnonii* [463–468]. In a recent phylogenetic study based on the analysis of large subunit, ITS, small subunit, β-tubulin and chitin synthase 1 sequences, *Pyrenochaeta romeroi* and *Pyrenochaeta mackinnonii* were accommodated in the new genera *Medicopsis* and *Nigrograna* as *Medicopsis romeroi* and *Nigrograna mackinnonii*, respectively [469].

Clinical manifestations. Pyrenochaeta keratinophila and *Pyrenochaeta unguis-hominis* are rarely reported as agents of keratitis and onychomycosis, respectively [464,465]. *Pyrenochaeta romeroi* and *Pyrenochaeta mackinnonii* have a higher clinical relevance as agents of mycetoma and subcutaneous infections in tropical areas [462,466–472].

Diagnosis. Colonies grow fairly rapidly, and are flat, velvety or floccose and produce dark olive-grey aerial hyphae with an olivaceous-black reverse. Pycnidia are produced after 2–3 weeks and are submerged, ostiolate, olivaceous to black, spherical to pyriform, with thick walls, and often covered with erect, stiff, dark hyphae. Conidia are produced from ampulliform phialides lining the innermost pycnidial wall and oozing out of the ostiolum in slimy drops, and are hyaline, one-celled and ellipsoidal to bacilliform [164,473]. Sequencing of ITS and D1/D2 regions of rDNA was successfully used for molecular identification [234].

Susceptibility testing and treatment. No standard therapy is available for infection with *Pyrenochaeta* and little is known about the relation between MIC and clinical outcome in this disease. Itraconazole has so far been used in the treatment of cases with mycetoma due to *Pyrenochaeta romeroi* [182]. Ketoconazole, itraconazole and terbinafine appear active *in vitro* against *Pyrenochaeta romeroi*, although systemic ketoconazole would not be the first choice due to unfavourable side effects [473].

Rhinocladiella

The genus *Rhinocladiella* is a small, polyphyletic genus comprising a few clinically significant species, *Rhinocladiella aquaspersa, Rhinocladiella similis, Rhinocladiella basitona, Rhinocladiella mackenziei* and *Rhinocladiella obovoideum* [164,474]. *Rhinocladiella mackenziei* and *Rhinocladiella obovoideum* are the neurotropic fungi affecting only the central nervous system [122,474–476]. *Rhinocladiella mackenziei* has never been isolated from the environment so the natural niche of this organism remains unknown [477]. Most of cases are restricted to the Middle East, Persian Gulf, Somalia and Pakistan [118,120,130,478,479]. *Rhinocladiella aquaspersa* is an agent of chromoblastomycosis reported from South America, and *Rhinocladiella similis* and *Rhinocladiella basitona* are occasional opportunists [480–482].

Clinical manifestations. Most patients (60%) with *Rhinocladiella mackenziei* brain abscess presented with solitary brain abscesses and the remainder had multiple brain lesions [109]. Among all reported cases of *Rhinocladiella mackenziei* infections, 25% of patients had no reported underlying conditions [130,477,479]. Diabetes mellitus was the predominant risk factor seen in some patients followed by solid organ failure and/or transplant [120,130,477–484]. *Rhinocladiella mackenziei* infections are associated with poor outcome and nearly 100% mortality in both immunocompetent and immunocompromised individuals despite surgical intervention and antifungal therapy [12,122,130]. Nine cerebral cases due to *Rhinocladiella obovoideum*, of which five were fatal, despite administration of amphotericin B in three of them, have been reported so far [482].

Diagnosis. General diagnostic recommendations for cerebral infections are stated in previous sections. These species appear

in culture as olive dark colonies that on microscopic examination show erect, thick-walled and darkly pigmented conidiophores that give rise to conidia only at their distal portions [298,474]. Definitive identification of the species requires sequencing of ITS and or D1/D2 regions of the rDNA gene [118].

Susceptibility testing and treatment. There is no standard therapy for cerebral infections and surgical drainage as opposed to aspiration alone did not improve survival. Medical treatment mostly involved high-dose lipid amphotericin B, itraconazole and flucytosine, or a combination of these drugs [118,120,122,130,477–484]. *In vitro* antifungal susceptibility studies of the most common pathogenic species showed that this organism has high MICs to amphotericin B and echinocandins, and low MICs to itraconazole, posaconazole and voriconazole [130,478,485]. There are many reported fatal cases of cerebral abscess where patients failed to respond to antifungal therapy with amphotericin B [109,130,480]. A single case of successful treatment of *Rhinocladiella mackenziei* brain abscess was reported in which the patient showed improvement after switching from itraconazole to posaconazole [122]. The *in vitro* data are also consistent with animal studies of a murine model of *Rhinocladiella mackenziei* cerebral phaeohyphomycosis, where posaconazole was found to be superior to amphotericin B and itraconazole and reduced the brain fungal burden [121].

Veronaea

The genus *Veronaea*, defined by its type species *Veronaea botryosa*, is a small group containing several opportunistic species infecting vertebrates [164]. *Veronaea botryosa* is an environmental fungus but with a currently undiscovered ecological niche. The phylogenetically nearest neighbours of *Veronaea botryosa* are found in *Exophiala* species inhabiting water and causing opportunistic infections in waterborne animals [245].

Clinical manifestations. The clinical presentation of the infection is a cutaneous lesion or nodular subcutaneous infection, resembling that of chromoblastomycosis, with muriform cells in tissue but with a strong tendency to disseminate. The infection has been described in both immunocompetent patients [85,486–492], and those with debilitated immunity such as liver [40] and heart transplant recipients [493].

Diagnosis. Veronaea botryosa is readily recognizable by its microscopical morphology. Its large, erect conidiophores with sympodial, uni-septate conidia on flat scars give easy clues for identification in culture [164,298]. Molecular identification using sequencing of the ITS rDNA region is applicable [494].

Antifungal susceptibility and treatment. Published cases of cutaneous and subcutaneous infections show much variation in therapeutic regimens with effective treatment mostly involving itraconazole [40,489]. There were cases that failed to respond to treatment with terbinafine, itraconazole and amphotericin B, but some showed significant improvement with posaconazole [85,487,494]. Very few studies on the *in vitro* susceptibility of this pathogen have been reported; it demonstrates high MICs for most antifungal drugs (Table 2) with the exception of posaconazole and itraconazole [487,494].

Conclusion

Although previously reported as rare agents of infections the melanized fungi are now emerging as an important fungal disease in humans and animals. These infections have not been studied in clinical trials and so far the available therapeutic data are primarily based on sporadic case reports. Furthermore, the diagnosis depends on a high index of clinical suspicion along with accurate mycological findings. There are no standardized therapies for infections caused by dematiaceous fungi but voriconazole, posaconazole, itraconazole and in some cases amphotericin B demonstrate the most consistent *in vitro* activity against this group of fungi. Oral itraconazole had been considered the drug of choice for most situations, given the extensive clinical experience with this agent. However, voriconazole may have advantages for central nervous system infections because of its ability to achieve good cerebrospinal fluid levels, unlike itraconazole. Posaconazole is a broad-spectrum alternative that is well-tolerated, though backed by less clinical experience but with excellent salvage treatment results after failure of other antifungal agents. Amphotericin B has been useful in some cases. As a result of the large variability in the spectrum of dematiaceous fungi, it is important to obtain *in vitro* susceptibilities of the individual patient's fungal isolate although it has not been firmly established that results obtained from susceptibility testing translate into better clinical outcomes.

Transparency Declaration

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