

**CLINICAL MICROBIOLOGY AND INFECTION**

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**ESCMID and ECMM Guidelines for the Management  
of Rare and Emerging Fungal Infections**

GUEST EDITOR

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# Clinical Microbiology and Infection

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# European Society of Clinical Microbiology and Infectious Diseases (ESCMID) Fungal Infection Study Group (EFISG) and European Confederation of Medical Mycology (ECMM) 2013 joint guidelines on diagnosis and management of rare and emerging fungal diseases

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## Abstract

This guideline is the second in the line of three for fungal diseases by ESCMID and other societies. The guideline tried to follow the AGREE criteria for the development of clinical guidelines. This guideline serves as a European and potentially world-wide recommendation for the diagnosis and management of rare and emerging fungi. They include mucormycosis, hyalohyphomycosis (*Fusarium*, *Paecilomyces*, *Scedosporium*, etc.), phaeohyphomycosis (*Alternaria*, *Bipolaris*, *Cladosporium*, *Rhinoctadiella*, etc.), and emerging yeasts (*Saccharomyces*, *Trichosporon*, *Rhodotorula*, etc.).

## Introduction

The European Society of Clinical Microbiology and Infectious Diseases (ESCMID) and European Confederation of Medical Mycology (ECMM) wanted to tackle a challenge that no major scientific society had tried: providing a guideline on the diagnosis and management of rare and emerging fungal diseases. This guideline would obviously exclude *Candida* and *Aspergillus* diseases. Practically all invasive fungal diseases (IFD), including invasive candidiasis and aspergillosis, appear to be rare and emerging infections by definition. Although many IFD are still numerically rare, physicians treating immunosuppressed patients are increasingly confronted with a wide variety of fungal pathogens. Rarity of disease is defined by their absolute frequency in a population, and definitions range around 1 in 2000. Of course these statistics are different for populations of severely ill patients, where frequencies of IFD are much higher.

In the context of the numerically increasing patient population with immunosuppression and the expanding use of antifungal agents against common pathogens such as *Candida* and *Aspergillus*, the number of patients with IFD due to emerging and often drug-resistant pathogens is rising [1].

Still, the epidemiology of many of these rare and emerging infections is not well studied, but joint multinational efforts supported by the European Fungal Infection Study Group (EFISG) of the ESCMID, the ECMM and the International Society for Human and Animal Mycology (ISHAM) are underway [2–5].

Delayed diagnosis of IFD is a well-described problem associated with increasing mortality [5–9]. For this reason, we aim to guide physicians on the clinical characteristics, diagnostic utilities and appropriate treatment choice in an area of many unmet medical needs, where almost no well-designed randomized clinical trials have been conducted. In addition, new diagnostic utilities are being implemented and together with the growth of the antifungal armamentarium, guidelines for the correct utilization in the clinical setting are urgently needed. The implementation of a pan-European guideline may help national societies to strengthen their local guidelines in patient care of invasive fungal diseases.

## Methods

**Organizational structure:** This guideline follows the structure and definitions of the ESCMID Guideline on *Candida* diseases [7,10–14]. It is in accordance with the GRADE and AGREE

systems with minor exceptions [15,16]. To adequately address the diversity of human fungal pathogens and to facilitate using the guideline we divided the recommendations into four groups: (i) Mucormycosis, Cornely *et al.*, (ii) Hyalohyphomycosis (*Fusarium*, *Paecilomyces*, *Scedosporium*) Lass-Flörl *et al.*, (iii) Phaeohyphomycosis (*Alternaria*, *Bipolaris*, *Cladosporium*, *Rhinoctadiella*) Chowdhary *et al.*, and (iv) emerging yeasts (*Saccharomyces*, *Trichosporon*, *Rhodotorula*), Arendrup *et al.*

Members of EFISG-ESCMID and/or ECMM representing 12 European countries were invited to develop the guideline as experts. Emerging fungal diseases differ in their regional distribution patterns even more than candidiasis and aspergillosis, so we strengthened the group expertise by inviting non-European mycologists as well.

**Time schedule:** In January 2012 experts were contacted by the conveners (OAC, JM), and the chairs of the four subgroups agreed to coordinate efforts. Meetings were held mostly as telephone conferences with face-to-face meetings during ECCMID in London in April 2012, ISHAM in Berlin in June 2012, and stand-alone conferences in Cologne in October 2012 and Copenhagen in November 2012, and finally recommendations were presented at ECCMID in Berlin in April 2013.

**Practical Working Procedure:** We followed a seven-step approach tabulating published literature and expert opinion on emerging fungal diseases in a transparent fashion.

For each clinical or microbiological setting or question the adequate population was defined, followed by the intention of an intervention or diagnostic procedure. Then the procedure itself was detailed, followed by the strength of recommendation (Table 1) and the level of evidence (Table 2), and the literature supporting this recommendation. Additional explanations or comments were added if they were felt to be necessary. From this set of tables the slides for ECCMID presentations were chosen, and the manuscripts were drafted.

During the development of these guidelines we used AGREE criteria for their development [15]. As these guidelines face the task of providing guidance explicitly for rare and emerging fungi, an evidence-based evaluation remains daunting. Nevertheless, the working steps were clear and developed and communicated within the group:

#### I. Scope and Purpose:

All diseases and their corresponding patient groups were predefined and appropriately covered by the guideline.

**TABLE 1. Definition of the Strength of Recommendation**

Grad	ESCMID-EFISG and ECMM
A	<b>strongly</b> support a recommendation for use
B	<b>moderately</b> support a recommendation for use
C	<b>marginally</b> support a recommendation for use
D	support a recommendation <b>against</b> use

**TABLE 2. Definition of the Quality of Evidence**

ESCMID-EFISG and ECMM	
Level	
I	Evidence from at least one properly designed randomized, controlled trial
II	Evidence from at least one well-designed clinical trial, without randomization; from cohort or case-control analytic studies (preferably from more than one centre); from multiple time series; or from dramatic results of uncontrolled experiments
III	Evidence from opinions of respected authorities, based on clinical experience, descriptive case studies, or reports of expert committees
Index	
r	Meta-analysis or systematic review of randomized controlled trials
t	Transferred evidence, i.e. results from different patient cohorts, or similar immune-status situation
h	Comparator group is a historical control
u	Uncontrolled trial
a	Abstract published at an international meeting

#### 2. Stakeholder involvement:

Due to the nature of the guideline meaning that the incidence rates are low and diversity of patient groups is wide, patients' views could not be sought. But the end-users were clearly defined by these guidelines.

These guidelines are made in collaboration between ECMM and ESCMID.

#### 3. Rigour of development: The steps of development are similar to those used for the previous guideline of our group [14]:

- Defining the rare and emerging fungi.
- Several manuscripts of individual writing groups that were established with separate chairs and corresponding mandates composed these guidelines. The entire guideline project was then reviewed by the whole guideline group.
- Predefining questions that need to be answered.
- Providing alternative answers, all weighted by the body of evidence.
- Literature research was performed in PubMed with predefined search algorithms including major scientific meetings (e.g. ICAAC and ECCMID).
- Slide kits were prepared and circulated within the whole group for commentary.
- Presentation of the guidelines during ECCMID 2013.
- Manuscript is prepared including all valid commentary during the ECCMID and again circulated within the entire group for approval.
- An updated guideline will be routinely available after 4–5 years after the previous publication. An earlier update will follow if new and striking changes are found in the body of evidence.

#### 4. Clarity of presentation:

- All recommendations are specific and unambiguous. The major messages are provided in tables designed to be easily read and understood.

- b. Clear statements of the intention of each single recommendation and clarity regarding its intervention.

#### 5. Applicability:

- a. One of the early criteria required by AGREE was the request to consider the potential cost implication by the application of the given recommendation. This is not really feasible in a European guideline because reimbursements differ between countries and some only look at acquisition cost without considering the other outcome analyses. Therefore this criterion could not be considered for each recommendation.
- b. The guidelines want to provide clear guidance to each clinician and microbiologist and recommend adaptation and individual modifications according to each hospital or country's epidemiology and abilities, without considering itself to be the whole truth of diagnosis or treatment.

#### 6. Editorial independence:

- a. These guidelines are free of any pharmaceutical company influence. No single member of pharmaceutical companies was present during the guideline discussions.
- b. A grant was provided for the development of these guidelines by ESCMID and ECMM.
- c. The guideline was peer-reviewed before its publication.

The previous definition for the strength of recommendation and quality of evidence in the ESCMID for *Candida* disease was again adopted for this guideline [14]. In brief, the four category grading system for the 'strength of a recommendation' was employed. Two extreme ends of the grading system were important: (A) ESCMID/ECMM strongly support a recommendation for use and, at the other end, (D) ESCMID/ECMM recommend against the use. This differentiation was important to clearly define treatment management for or against use of certain interventions. The two other middle graded statements (B and C) weighted in the evidence available for its recommendation and could be considered optional (Table 1). For this guideline we did adopt the strength of recommendation for the diagnostic part of the guideline.

The criteria for the quality of evidence did not differ from the previous guidelines [7,10–12,14].

## Conclusions

This guideline is the second in a row of three grouped guidelines by ESCMID and others for the diagnosis and management of fungal diseases. Other groups are now adopting the ESCMID strength of recommendation and quality

of evidence as well (ESCMID Study Group for *Clostridium difficile* [17], and ESCMID Study Group for Biofilms). This guideline serves as guidance in the clinical care of patients in Europe and potentially worldwide. Although guidelines are helpful tools for everyday decision-making, a clinical judgement call for the individual patient remains the main fundamental requirement for the physician in charge.

## Transparency Declaration

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MCE has received research grants from MSD, Astellas, Pfizer, Gilead and Ferrer, is a consultant to MSD, Astellas, Pfizer, Gilead and Ferrer, has provided expert testimony for MSD, Astellas, Pfizer, Gilead and Ferrer and received lecture honoraria from MSD, Astellas, Pfizer, Gilead and Ferrer.

JFM received grants from Astellas, Basilea and Merck. He has been a consultant to Astellas, Basilea and Merck and received speaker's fees from Merck and Gilead. He has been supported in part by a grant from Qatar National Research Fund NPRP 5-298-3-086.

AJU has received research grants from Astellas, Gilead, Merck/Schering and Pfizer, is a consultant to Astellas, Basilea, Gilead, Merck/Schering and Pfizer, received payment for development of educational presentations from Gilead, and received lecture honoraria from Astellas, Gilead, Merck/Schering and Pfizer.

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# ESCMID<sup>†</sup> and ECMM<sup>‡</sup> joint clinical guidelines for the diagnosis and management of mucormycosis 2013

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## Abstract

These European Society for Clinical Microbiology and Infectious Diseases and European Confederation of Medical Mycology Joint Clinical Guidelines focus on the diagnosis and management of mucormycosis. Only a few of the numerous recommendations can be summarized here. To diagnose mucormycosis, direct microscopy preferably using optical brighteners, histopathology and culture are strongly recommended. Pathogen identification to species level by molecular methods and susceptibility testing are strongly recommended to establish epidemiological knowledge. The recommendation for guiding treatment based on MICs is supported only marginally. Imaging is strongly recommended to determine the extent of disease. To differentiate mucormycosis from aspergillosis in haematological malignancy and stem cell transplantation recipients, identification of the reverse halo sign on computed tomography is advised with moderate strength. For adults and children we strongly recommend surgical debridement in addition to immediate first-line antifungal treatment with liposomal or lipid-complex amphotericin B with a minimum dose of 5 mg/kg/day. Amphotericin B deoxycholate is better avoided because of severe adverse effects. For salvage treatment we strongly recommend posaconazole 4 × 200 mg/day. Reversal of predisposing conditions is strongly recommended, i.e. using granulocyte colony-stimulating factor in haematological patients with ongoing neutropenia, controlling hyperglycaemia and ketoacidosis in diabetic patients, and limiting glucocorticosteroids to the minimum dose required. We recommend against using deferasirox in haematological patients outside clinical trials, and marginally support a recommendation for deferasirox in diabetic patients. Hyperbaric oxygen is supported with marginal strength only. Finally, we strongly recommend continuing treatment until complete response demonstrated on imaging and permanent reversal of predisposing factors.

**Keywords:** Diagnosis, fungal infection, guideline, mucormycosis, mycosis, prophylaxis, treatment, zygomycosis

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## Introduction

Mucormycosis is a very aggressive invasive fungal disease [1,2]. It is a fungal emergency that affects a variety of patient groups [3]. The disease, previously termed zygomycosis [4], is caused by mucoralean fungi, which have collectively also been called Mucormycetes [5,6]. However, we prefer to use the name of the order, i.e. Mucorales.

The genera causing the majority of mucormycoses are *Rhizopus*, *Mucor*, *Lichtheimia* (previously classified as *Absidia*), *Cunninghamella*, *Rhizomucor*, *Apophysomyces* and *Saksenaea* [7]. Granulocytopenia, immunosuppression, diabetes and penetrating trauma are the most prevalent predisposing diseases associated with mucormycosis [7]. Cavitory pulmonary disease due to *Rhizopus homothallicus* has been described as a distinct pattern in diabetic patients in India [8]. Besides patients with these typical risk factors, mucormycosis has been reported in otherwise healthy individuals in India and China, e.g. in the forms of renal mucormycosis and chronic (sub-)cutaneous infections due to *Mucor irregularis* (*Rhizomucor variabilis*) [8–16]. Recently, the different clinical manifestations have been reviewed [17].

Arnold Paltauf reported the first histologically proven case of *Mycosis mucorina* at the University of Graz, Austria in 1885 [18]. Though the disease has been known for a long time, the epidemiology is not well defined. In a study from France mucormycosis had increasingly been diagnosed over the past years, culminating in a general population incidence of 1.2 per million/year [19]. Two further studies from Spain and California report incidences between 0.4 and 1.7 cases per million population/year [20,21]. In patients with haematological malignancy mucormycosis was less common than invasive aspergillosis, but mucormycosis independently predicted death in these patients [22,23]. Lymphocytopenia has recently been identified as independently predicting death in this setting [24]. Mortality rates in patients with mucormycosis remain high and in recent reports they ranged from 24% to 49% [7,19,25,26].

Guidance for diagnosis and treatment of mucormycosis is needed, because in rare diseases it is difficult to execute comparative clinical trials and to accumulate substantial personal experience. This is particularly true for a disease that is likely to be underdiagnosed and in which individual prognosis is driven by early treatment [2,27]. This guidance document will provide help to improve management of invasive mucormycosis.

## Methods

An expert group (OAC, SAA, AC, ED, AHG, KL, FL, LP, GP and AS) was set up by the European Society of Clinical

Microbiology and Infectious Diseases (ESCMID) Fungal Infection Study Group (EFISG) and the European Confederation of Medical Mycology (ECMM) and searched the literature using the search string 'mucormycos\* OR zygomycos\* NOT entomophthoramycos\* NOT phycomycos\*'. Documents and views were shared by email, teleconferences and face-to-face meetings during April 2012 to April 2013. Once a structured first consensus was reached the preliminary recommendations were presented to the whole group, i.e. the other authors, discussed, developed further and finalized as a group consensus. The methods to evaluate the quality of evidence and to reach group consensus recommendations are described in the context of the ESCMID clinical guidelines on *Candida* infection [28]. For the present guideline we applied the same system to diagnostic procedures. The definition of the strength of recommendation is given in Table 1. The quality of the published evidence is defined in Table 2(a). To increase transparency regarding the evaluation of available evidence we added an index (Table 2b) to the level II recommendations, where appropriate. Of note, the evaluation of the strength of recommendation and of the quality of evidence was performed in two separate evaluations, so allowing for a recommendation strongly supporting a procedure even if there is a lower level of evidence. If ESCMID EFISG and ECMM marginally support a recommen-

**TABLE 1. Definition of the strength of recommendation**

Grade	ESCMID EFISG and ECMM
A	Strongly support a recommendation for use
B	Moderately support a recommendation for use
C	Marginally support a recommendation for use
D	Support a recommendation against use

**TABLE 2. Definition of the quality of evidence**

Level	ESCMID EFISG and ECMM
(a)	
I	Evidence from at least one properly designed randomized, controlled trial
II	Evidence from at least one well-designed clinical trial, without randomization; from cohort or case-control analytic studies (preferably from more than one centre); from multiple time series; or from dramatic results of uncontrolled experiments
III	Evidence from opinions of respected authorities, based on clinical experience, descriptive case studies, or reports of expert committees
Index	ESCMID EFISG and ECMM
(b)	
r	Meta-analysis or systematic review of randomized controlled trials
t	Transferred evidence, i.e. results from different patients' cohorts, or similar immune status situation
h	Comparator group is a historical control
u	Uncontrolled trial
a	Abstract published at an international meeting

dition for use, the respective intervention can be considered optional [28].

## Results

### Recommendations on diagnostics in mucormycosis

**Conventional microbiological methods.** Direct microscopy of clinical specimens, preferably using optical brighteners, allows a rapid presumptive diagnosis of mucormycosis. Blankophor and Calcofluor bind to chitin and cellulose and fluoresce in ultraviolet light [29]. Hyphae of Mucorales have a variable width (6–25 µm), are non-septate or pauci-septate and have an irregular, ribbon-like appearance. The angle of branching is variable and includes wide-angle (90°) bifurcations. Culture of specimens is considered an essential investigation. Although the sensitivity of culture is not optimal, it allows identification and susceptibility testing of the isolate in case of growth. Histopathological examination of tissue specimens may allow differentiation between hyphae of *Aspergillus* or morphologically related fungi, and hyphae of Mucorales, which is important for treatment decisions. Mucormycosis is characterized by prominent infarcts, angioinvasion and perineural invasion.

**Evidence**—The value of fluorescent whiteners for computed tomography (CT) -guided percutaneous lung biopsy specimens was assessed in 61 patients with CT findings highly suggestive of an invasive fungal infection [30]. Calcofluor white staining revealed fungal elements in 49 specimens (80%) and allowed the differentiation between septate ( $n = 36$ ) and non-septate ( $n = 13$ ) hyphae. The DNA of mucoralean fungi was detected by PCR in all samples with non-septate hyphae. Calcofluor white analysis was considered false negative in 5% of specimens [30]. In a patient with acute myelogenous leukaemia and periodontal mucormycosis, intraoperative calcofluor white fluorescence microscopy was used for a prompt diagnosis and to guide the extent of surgical debridement. Maxillary biopsies with intraoperative calcofluor white analysis were used to rule out persistent oral mucormycosis in this case [31].

Mucorales grow well on both non-selective and fungus-selective media and the growth tends to be rapid, i.e. covers the entire plate in a few days. The recovery of Mucorales from tissues may be problematic and negative cultures seem to be correlated with aggressive processing of the specimens before plating. Grinding of specimens should therefore be avoided [32]. The specimen is preferably incubated at 37°C [33–35].

Histopathological review of tissue samples from 20 patients with rhinocerebral disease ( $n = 11$ ), pulmonary disease ( $n = 6$ ), or a fungus ball ( $n = 3$ ) revealed that the inflammatory

responses were predominantly neutrophilic (50%), pyogranulomatous (25%) or absent (20%). Invasive disease was characterized by prominent infarcts (94%), angioinvasion (100%) and prominent perineural invasion (90%) in biopsies that contained nerve structures for evaluation. The presence of septa in the hyphae was rare and hyphal branching angles varied from 45 to 90° [36]. Pulmonary mucormycosis in cancer patients ( $n = 20$ , 19 patients with haematological malignancy) is characterized by angioinvasion (100%), haemorrhagic infarction (90%), coagulative necrosis (85%) and intra-alveolar haemorrhage (85%). Neutropenic patients had more extensive angioinvasion compared with non-neutropenic patients [37]. In recent registries of mucormycosis, histopathology led to the diagnosis in 63% [26] and 66% [7] of cases. The diagnosis of 75 cases from an Indian tertiary-care hospital was based on histopathology [38].

In a separate report three cases of mucormycosis were diagnosed by immunohistochemistry using monoclonal antibodies against somatic antigens of *Rhizopus oryzae*; two of three had been misclassified as aspergillosis based on histopathology alone [39].

**Recommendations**—Direct microscopy of clinical specimens preferably using optical brighteners and culture is strongly recommended for the diagnosis of mucormycosis. Histopathology may allow differentiation of mucormycosis from aspergillosis—and other hyalohyphomycoses and phaeohyphomycoses—and is strongly recommended. Notably, scrapings do not reliably prove tissue invasion. Any microscopic examination should evaluate morphology, width, branching angle and septation. Direct microscopy is not useful for species identification, and immunohistochemistry is only marginally supported for the diagnosis of mucormycosis due to the lack of commercially available monoclonal antibodies and clinical validation. For further recommendations refer to Table 3.

**Detection of antigen and Mucorales-specific T cells.** There are no standardized assays available for the detection of Mucorales-specific antigens. The healthcare provider should have a high level of suspicion that the patient has mucormycosis rather than aspergillosis in patients with CT lesions that are highly suggestive for invasive fungal disease, specifically if *Aspergillus* galactomannan test results on serum and bronchoalveolar lavage are negative [40]. Of note, 1,3-β-D-glucan is a common component of the cell wall of a wide variety of fungi but not of the Mucorales.

**Evidence**—At two centres with a high autopsy rate, mucormycosis diagnosis was missed using a diagnostic strategy with regular galactomannan testing of serum samples [41,42]. In a study of breakthrough invasive mould infections in patients

**TABLE 3.** Recommendations on diagnosis of mucormycosis: laboratory diagnosis using conventional, serological and molecular methods

Population	Intention	Method/Finding	SoR	QoE	References	Comment
Any	To diagnose mucormycosis	Direct microscopy preferably using optical brighteners	A	IIu	30,31	Allows rapid presumptive diagnosis; non-septate or pauci-septate, irregular, ribbon-like hyphae, angle of branching 45–90°, identification to genus and species level not possible, hyphal diameter in aspergillosis 2–3 µm, in mucormycosis 6 to >16 µm
Any	To diagnose	Culture	A	IIIr	32,35	Avoid grinding, preferred temperature 37°C
Any	To diagnose	Histopathology	A	IIu	7,26,36–38	Features as in direct microscopy, does not allow for genus or species differentiation; perineural invasion commonly seen, if nerves sampled
Any	To diagnose	Immunohistochemistry	C	IIu	39	No commercial assay available Monoclonal antibodies commercially available
Any	To diagnose	Galactomannan in blood or bronchoalveolar lavage	B	III	41 43 192	$n = 2$ $n = 1$ $n = 2/8$ missed mucormycoses: consider mucormycosis, if galactomannan test negative, but radiology positive
Any	To diagnose	1,3-β-D-glucan in blood	D	III	44,45	Not a reliable marker
Haematological malignancy	To monitor treatment	ELISPOT	C	IIu	46	No commercial assay available
Any	To diagnose	Molecular based tests on fresh clinical material	B	IIu	30,47,193,194	No commercial assay available; fresh material preferred over paraffin-embedded
Any	To diagnose	Molecular based tests on paraffin slides	B	IIu	48,49, 51	No commercial assay available

treated with caspofungin, two cases of mucormycoses occurred among eight patients in whom galactomannan tests remained negative [43].

*In vitro* analysis of culture supernatants of different species causing mucormycosis ( $n = 8$ , four different species) revealed a low antigen reactivity compared with other mould isolates, presumably because of their low cell wall 1,3-β-D-glucan concentrations [44]. Three patients with mucormycosis had negative 1,3-β-D-glucan results in a multicentre evaluation of the performance of the 1,3-β-D-glucan test for the diagnosis of invasive fungal infections [45].

Mucorales-specific T cells were detected by an enzyme-linked immunospot (ELISPOT) assay in three haematological patients developing invasive mucormycosis at diagnosis and throughout the entire course of the invasive disease but not for long after resolution of the infection. None of the 25 control patients without mucormycosis had Mucorales-specific T cells [46].

**Recommendations**—The use of galactomannan detection is moderately supported for the diagnosis of invasive mucormycosis. In patients with a possible invasive fungal infection, negative galactomannan test results in serum and BAL increase the likelihood of invasive mucormycosis. 1,3-β-D-Glucan testing is not recommended for the diagnosis of invasive mucormycosis. For further recommendations refer to Table 3.

**Molecular-based methods for direct detection. Evidence**—An in-house semi-nested PCR that targets the 18S ribosomal DNA of Mucorales was evaluated on fresh tissue specimens in

two prospective studies [30,47]. In the first study, PCR was performed on 56 respiratory biopsy specimens obtained by different procedures from immunocompromised patients suspected of having a mould infection. The PCR was positive in six samples with histopathological detection of Mucorales hyphae but culture was positive in only two of these samples. One false-positive result was obtained (2% of samples tested) [47]. The second study was conducted on CT-guided percutaneous lung biopsy specimens obtained from 46 patients with a haematological malignancy and 15 patients with solid-organ transplantation. PCR detected mucoralean fungi in all specimens with non-septate hyphae ( $n = 13$ , sensitivity 100%) whereas culture remained negative in five cases [30].

The performance of the same semi-nested PCR as described above was also evaluated on formalin-fixed paraffin-embedded tissue specimens in two different studies [48,49]. Mucorales PCR was positive in 22 of 27 tissue specimens from patients with a haematological malignancy or a haematopoietic stem cell transplant who were diagnosed with mucormycosis [48] and in 14 of 23 specimens from patients with the diagnosis of mucormycosis based on histopathology [49]. The failure to amplify specific DNA might result from fungal DNA concentrations below detection limits, a focal infection with varying amounts of fungal elements within the tissue or the destruction of DNA during formalin fixation. In four cases no human β-globin DNA could be detected by the control PCR [49]. A recent exercise evaluated a pan-fungal real-time PCR-based technique in formalin-fixed paraffin-embedded tissue specimens [50]. In a total of 89 biopsies from patients with invasive fungal diseases the average

sensitivity of the PCR assay was 89% and Mucorales were detected in 11% of biopsies, although the technique exhibited some limitations to detect *Rhizopus microsporus*, *Rhizopus oryzae* and *Saksenaia vasiformis* [50]. In an interlaboratory evaluation of the reproducibility of an internal transcribed spacer (ITS) PCR performed on formalin-fixed paraffin-embedded tissue specimens from experimentally infected mice, positive results were obtained in 93% of samples with 30 slide cuts of 10 µm. Sensitivity decreased to 27% when tissue quantity was reduced to one section. Interlaboratory reproducibility was excellent [50,51]. Mucorales DNA was detected in 40–60% of plasma samples with real-time PCR as early as one day post-inoculation in a rabbit model of experimental pulmonary mucormycosis [52].

**Recommendations**—Currently, in the absence of a standardized test, the use of molecular methods on both fresh clinical material and paraffin slides for the diagnosis of mucormycosis is moderately supported. Fresh material is preferred over paraffin-embedded tissue because formalin damages DNA. For further recommendations refer to Table 3.

**Genus and species identification.** There is no strong evidence that identification to the genus/species level may be important to guide treatment. Identification to the species level is of interest for a better epidemiological knowledge of mucormycosis and may be of value for outbreak investigation. Molecular techniques are more reliable than phenotypic identification of Mucorales in culture to the species level. Sequencing of ITS is currently the best molecular technique for species identification. Carbon assimilation profiles using the commercialized kits ID32C and API 50 CH (bioMérieux, Marcy l'Etoile, France) allowed precise and accurate identification of Mucorales to the species level [53]. Alternative techniques such as matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) mass spectrometry are promising but not yet validated for all species.

**Evidence**—Although some genera, such as *Cunninghamella*, may be associated with a higher mortality rate in patients [3,5] and have been shown to be more virulent in experimental models [54], there is currently sparse evidence that identification of the causative Mucorales to the genus and/or species level could guide the choice of the antifungal treatment [55,56].

In contrast, identification to the species level is of interest for better epidemiological knowledge of the disease. In particular, the clinical picture may be different depending on the species [3,5,57]. Moreover, species identification could be valuable for investigation of healthcare-associated mucormycosis and outbreaks [58].

Identification of Mucorales in culture by standard mycological methods such as morphology is notoriously difficult because the different species share similar morphological characteristics. This has been highlighted by recent molecular description of cryptic species that can hardly be distinguished morphologically [59–62]. Moreover, some species fail to sporulate in standard media, precluding a timely and easy morphological identification [63]. A comparison of morphological versus molecular identification of 19 isolates of Mucorales from patients with mucormycosis showed that identification by morphology was erroneous in >20% of the cases [64]. A high level of concordance (>90%) between morphology and molecular identification may be only seen in reference laboratories [65].

Several DNA targets have been evaluated for a reliable identification to the species level. The best informative target should have a large interspecific (between species) and a low intraspecific (within a given species) sequence variability. Moreover, a comprehensive and accurate database must be available. In a study of 54 isolates from 16 different species it has been shown that ITS sequencing was a reliable and accurate method for identification to the species level [66]. Similar results were obtained by other authors [67,68]. Based on published results and expert opinions, the CLSI has proposed ITS sequencing as a valuable method for identification of genus and also of species [69]. More recently, the International Society for Human and Animal Mycology (ISHAM) working group on fungal molecular identification has recommended using ITS sequencing as a first-line method for species identification of Mucorales [70]. Other DNA targets have also been evaluated including 18S, 28S, cytochrome *b* or FTR I [71–75] and could be used as alternatives but for some of these targets there is less evidence of their usefulness.

Alternative methods for rapid identification of filamentous fungi in clinical microbiology laboratories have been recently evaluated. In particular, using ID32C strips or API 50 CH carbon assimilation strips and 57 Mucorales strains, intraspecies variation was found to be low, whereas large differences were found between genera and species, allowing identification to the species level for all included strains except for *Rhizopus oryzae*. The clustering of isolates based on their carbon assimilation profiles was in accordance with DNA-based phylogeny of Mucorales [53]. MALDI-TOF mass spectrometry may be of interest although limited data are currently available for Mucorales [76–78]. In an analysis of 103 filamentous fungi by MALDI-TOF, the eight tested Mucorales were correctly identified to species level [77]. In a more recent study it was shown that 34 strains of *Lichtheimia* spp. could be reliably identified by comparison to an in-house database constructed

with 19 strains belonging to eight species [78]. Although MALDI-TOF identification of Mucorales seems promising, more data are needed to validate this technique and commercially available databases should be validated.

**Recommendations**—Identification to the genus and species level is strongly supported for a better epidemiological knowledge of the disease. Guiding treatment by identifying to the genus level is marginally supported. Carbon assimilation is moderately supported and molecular identification is strongly supported in comparison to morphology. The best technique for molecular identification is ITS sequencing. There are currently limited data for MALDI-TOF as an identification method. For further recommendations refer to Table 4.

**Susceptibility testing. Evidence**—European Committee on Antimicrobial Susceptibility Testing (EUCAST) and CLSI (CLSI M38-A2) [79,80] reference microdilution methods are used as standard assays for antifungal susceptibility testing of Mucorales. Using methods other than the reference assays such as Etest<sup>®</sup> [21,55] or XTT assay [81,82] remains investigational. Except for posaconazole, moderate (<80%) correlation of Etest<sup>®</sup> and Sensititre YeastOne<sup>®</sup> with the CLSI M38-A2 method was noted in antifungal susceptibility testing of Mucorales [21,79]. Rapid (within 6–8 h) susceptibility testing can be achieved with the XTT assay [81]. Currently, there are no validated MIC breakpoints for any of the drugs against fungal genera in this order and so determination of susceptibility categories (S, I and R) is not possible.

A correlation between the generated MIC and clinical outcome was addressed in only a few studies. In a retrospective analysis of 16 patients infected with *Apophysomyces elegans*, an amphotericin B MIC of <1 µg/mL correlated with recovery.

Of those infected with strains with an amphotericin B MIC of ≥1 µg/mL, 43% failed to respond [83]. Animal studies for determination of *in vitro*–*in vivo* correlation are also limited. In murine models of infections due to *Rhizopus microsporus* [84] and *Rhizopus oryzae* [85] posaconazole was shown to be more effective in infections due to strains with an MIC of 0.25 µg/mL compared with those with an MIC of 2 µg/mL. On the other hand, a low minimum fungicidal concentration, i.e. 0.5 µg/mL of posaconazole was associated with response in mice infected with *Rhizopus oryzae*. High posaconazole minimum fungicidal concentration values, i.e. >16 µg/mL, correlated with clinical failure in a similar murine model [82].

Antifungal susceptibility testing of the strains in the order Mucorales has been performed mostly for epidemiological purposes. The data presented in these studies provide significant clues for the expected susceptibility profiles and are useful to evaluate genus-, species- and strain-based variations in susceptibility. Fluconazole [84,86,87], voriconazole [84,86–91], echinocandins [84,87,90,91] and flucytosine [84,87,88,90,91] lack meaningful *in vitro* activity against Mucorales. In general, amphotericin B and posaconazole are the most active drugs *in vitro* [84,86–92]. The comparative activities of amphotericin B and posaconazole may vary depending on the genus and species of the infecting strain. Although amphotericin B yields lower MICs against *Mucor circinelloides* compared with posaconazole [55,92], posaconazole MICs are lower than those of amphotericin B against *Cunninghamella bertholletiae* [92,93]. On the other hand, high MICs of both amphotericin B and posaconazole have been reported for strains of *Cunninghamella echinulata* [93]. Species-specific differences in azole and terbinafine susceptibilities are noted particularly for *Rhizopus* and *Mucor* [84,85,88,90]. Finally, strain-based variations have also been described, as for

**TABLE 4. Recommendations on molecular based methods of identification**

Population	Intention	Method/Finding	SoR	QoE	Comment	References
Any	To guide treatment	Identification to genus level	C	IIu	Some species may be more virulent and/or associated with higher mortality, e.g. <i>Cunninghamella</i>	3,5,54
Any	To establish epidemiological knowledge and for outbreak investigation	Identification to species level	A	IIu		3,5,25,65
Any	To establish epidemiological knowledge	Molecular identification to species level versus morphology	A	IIu	<i>n</i> = 19; ITS sequencing, concordance 79%, morphology not reliable.	64
Any	To establish epidemiological knowledge	Molecular identification to species level by ITS sequencing	A	IIu	<i>n</i> = 190; ITS sequencing concordance 93%	65
Any	To establish epidemiological knowledge	Molecular identification to species level with other DNA targets	C	IIu	Good discrimination of genera and species, first-line technique	66–70
					28S PCR plus sequencing	71
					18S PCR plus RFLP	72
					28S MicroSeq kit	73
					Cytochrome b gene real-time PCR	74
					FTR1 gene sequencing	75
Any	To establish epidemiological knowledge	Carbon assimilation for species identification	B	II	ID32C and API 50 CH kits allowed precise and accurate identification	66
Any	To establish epidemiological knowledge	MALDI-TOF identification	C	IIu	Limited data, in house databases	77,78

ITS, internal transcribed spacer; MALDI-TOF, matrix-assisted laser desorption/ionization time-of-flight mass spectrometry; QoE, quality of evidence; RFLP, restriction fragment length polymorphism; SoR, strength of recommendation.

posaconazole susceptibility of *Rhizopus oryzae* strains [85,91]. Despite the lack of preference for its use in treatment of mucormycosis, itraconazole MICs are relatively low for a number of strains, including those of *Rhizomucor* [90,92] and *Lichtheimia* [86,88,90,92].

Efficacy of combination therapy was addressed in murine models of mucormycosis. Improved survival was observed with the combination of amphotericin B lipid complex and caspofungin compared with monotherapy and untreated controls in diabetic ketoacidotic mice infected with a more virulent brain isolate of *Rhizopus oryzae*. However, improved organ clearance was not achieved with combination therapy [94]. In a murine model of disseminated mucormycosis caused by *Rhizopus oryzae*, posaconazole combined with amphotericin B at low dose (0.3 mg/kg/day) prolonged survival, and reduced tissue burden was observed compared with monotherapy and controls. However, it was not superior to amphotericin B (0.8 mg/kg/day) alone [95].

*In vitro* combination studies have also been performed to explore the interaction of antifungal agents against members of the order Mucorales. The previously published reports include data for combinations of amphotericin B and rifampin (69% synergy, 31% indifference), amphotericin B and flucytosine (100% indifference), amphotericin B and terbinafine (80% indifference, 20% synergy), and terbinafine and voriconazole (56% indifference, 44% synergy) for miscellaneous genera of Mucorales ( $n = 35$ ) [96]. Data are also available for combinations of amphotericin B and posaconazole: miscellaneous genera ( $n = 21$ ) with indifference in all strains [91]; *Rhizopus oryzae* ( $n = 11$ ), indifference in all strains [89]. The above combination was more synergistic against hyphae than conidia of miscellaneous genera ( $n = 30$ ) [97]. Further data are available for amphotericin B and anidulafungin (miscellaneous genera,  $n = 21$ , indifference in 20 and synergy in one strain)

[91], for posaconazole and caspofungin (miscellaneous genera,  $n = 12$ ; synergy in all strains) [98], for posaconazole and anidulafungin (miscellaneous genera,  $n = 21$ , indifference in all strains) [91], and for itraconazole and terbinafine (miscellaneous genera,  $n = 17$ ; synergy in 14 strains) [99].

Overall, and of major importance, the clinical significance of these and other *in vitro* and *in vivo* combination data remains uncertain [100].

**Recommendations**—Given the relative lack of clinical break-points and still limited sufficient data to indicate a clear reading correlation between MIC or minimum fungicidal concentration values and clinical outcome, use of antifungal susceptibility testing for guiding treatment in mucormycosis is recommended only with marginal strength. Susceptibility testing for attaining epidemiological data is strongly recommended. For further recommendations refer to Table 5.

**Imaging.** There are obvious limitations for the differential diagnosis between filamentous fungal infections if no histological or cultural evidence is available. Some imaging characteristics have been evaluated regarding their potential to differentiate between fungal genera.

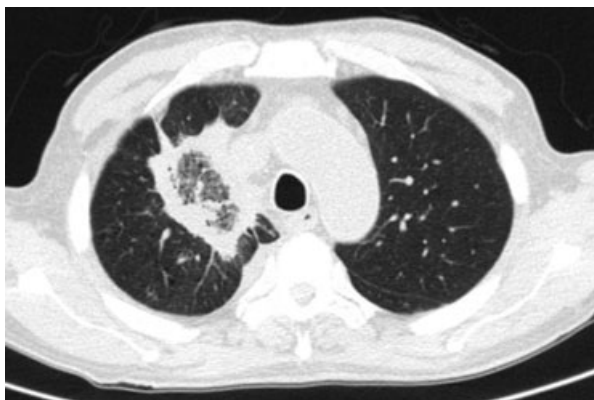
**Evidence**—The halo sign, i.e. a ring of ground glass opacity surrounding a nodular infiltrate, and the air crescent sign, are clinical criteria indicating lower respiratory tract fungal disease [101], but they were not predictive of the genus of an invasive fungal pathogen in a historical control study [102].

The reversed halo sign (also known as inverted halo sign or atoll sign) is an area of ground glass opacity surrounded by a ring of consolidation (Fig. 1). In an uncontrolled study on 189 patients treated for proven or probable invasive fungal pneumonia the reversed halo was present in 19% of patients

**TABLE 5. Recommendations on susceptibility testing in mucormycosis**

Population	Intention	Method/Finding	SoR	QoE	Comment	References
Any	To guide treatment	EUCAST/CLSI reference microdilution methods	C	IIu	Clinical relevance uncertain. No data available to correlate MIC and outcome	79,80,83
Any	To guide treatment	Correlation of MIC with <i>in vivo</i> outcome	C	IIu	For <i>Apophysomyces elegans</i> , limited retrospective data suggest correlation	83
Any	To guide treatment	Correlation of MIC/MFC with <i>in vivo</i> outcome	B	III	Animal, posaconazole better in <i>Rhizopus microsporus</i> and <i>Rhizopus oryzae</i> strains MIC 0.25 µg/mL than in those with MICs 2 µg/mL	82,84,85
Any	To establish epidemiological knowledge	Susceptibility testing	A	IIu	$n = 37$ $n = 36$ $n = 217$ $n = 45$ $n = 77$ $n = 18$ , <i>Apophysomyces elegans</i> $n = 21$ $n = 66$ Review	86 88 87 21 92 83 91 90 195
Any	To establish epidemiological knowledge	MIC determined by reference method	A	III	e.g. Etest® not validated for Mucorales	79,80

MFC, minimum fungicidal concentration; QoE, quality of evidence; SoR, strength of recommendation.



**FIG. 1.** Computed tomography in mucormycosis revealing a reversed halo sign, also known as inversed halo or atoll sign.

with mucormycosis, in <1% of patients with invasive aspergillosis, and in no patient with fusariosis. The majority of patients with a reversed halo sign had undergone haematopoietic stem cell transplantation for acute myelogenous or chronic lymphatic leukaemia [103]. As a wide range of infectious and non-infectious diseases may present with a reversed halo sign on CT, the diagnostic value of this finding depends on the pre-test probability [104].

Patients with more than ten nodular infiltrates were more likely to have mucormycosis than aspergillosis in one historical control study [102], whereas in a separate patient series this was not the case [104].

If mucormycosis is the suspected diagnosis, histological proof is urgently needed. Computed tomography-guided needle biopsy was successfully applied in 61 patients with possible invasive fungal diseases. Mucormycosis was diagnosed in 13 (21%) [30]. In a separate series of 56 patients with pulmonary nodular infiltrates on CT, biopsy identified proven

mucormycosis in six (11%) [47]. In both series a prerequisite was a minimum platelet count of 50 000/ $\mu$ L, which can be achieved by platelet transfusion [30].

Pleural effusion independently predicted mucormycosis in a historical control study ( $n = 16$ ) [102], and was found in all patients of a second, independent series ( $n = 18$ ) [104].

In a population of patients with haematological malignancies ( $n = 59$ ) about 20% of patients had disseminated disease, so that cranial, thoracic and abdominal imaging studies appear warranted [105]. In a historical control study, 31% of mucormycosis patients had sinus involvement [102].

In the 1980s, in two series ( $n = 10$ , each) of patients with poorly controlled diabetes and mucormycosis cranial CT revealed typical signs of sinusitis and orbital involvement [106,107].

Sinusitis was more commonly associated with mucormycosis than with invasive aspergillosis in patients with haematological disease [102]. Mucosal thickening without air/fluid levels was the usual finding in two series comprising ten patients each [106,107].

In case of bone destruction diagnosed on CT, magnetic resonance imaging should be used to reveal the full extent of disease [108,109]. In an institutional series of patients with mucormycosis ( $n = 27$ ) approximately half of the patients with sinus involvement showed intracranial spread of disease [110].

**Recommendations**—In patients with haematological malignancy it is recommended that the possibility of mucormycosis be considered, particularly in the case of a lung infiltrate with a reversed halo sign on CT. If mucormycosis is a potential differential diagnosis, biopsy should be pursued. Once mucormycosis has been proven in a patient with underlying

**TABLE 6.** Recommendations on diagnosis of mucormycosis: imaging to differentiate between pulmonary mucormycosis and invasive pulmonary aspergillosis

Population	Intention	Method/Finding	SoR	QoE	References
Patients with haematological malignancy	To differentiate mucormycosis from invasive pulmonary aspergillosis	CT/reversed halo	B	IIu	103,104
Patients with haematological malignancy	To differentiate mucormycosis from invasive pulmonary aspergillosis	CT/pleural effusion	C	IIh	102,104
Patients with haematological malignancy	To differentiate mucormycosis from invasive pulmonary aspergillosis	CT/>10 nodular infiltrates	C	IIh	102,104
Patients with haematological malignancy	To determine extent of disease	CT cranial, sinus, thoracic, abdominal	B	III	105
Diabetic with facial pain, sinusitis, proptosis, amaurosis	To diagnose invasive mould disease and to determine extent of disease	Cranial CT/destruction of bone <sup>a</sup>	A	IIu	106–108
As above, but with bone destruction on CT	To determine extent of disease (orbit, cerebral, cavernous sinus thrombosis)	Cranial MRI	A	IIu	109,110
Asia, specifically China and India: No underlying disease, flank pain, fever, haematuria, renal infarct on Doppler ultrasound	To diagnose renal mucormycosis	CT or MRI	A	IIu	9–11
Any	To diagnose mucormycosis	CT-guided biopsy	A	IIu	30,47

CT, computed tomography; MRI, magnetic resonance imaging; QoE, quality of evidence; SoR, strength of recommendation.

<sup>a</sup>Same approach for invasive aspergillosis.



malignancy, cranial, thoracic and abdominal imaging studies are recommended to determine the extent of disease. For further recommendations refer to Table 6.

**Recommendations on treatment of mucormycosis**

*Prophylaxis. Evidence*—In two well-designed clinical trials evaluating primary antifungal prophylaxis during high-risk periods of immunosuppressed patients, i.e. during long-lasting neutropenia in acute myelogenous leukaemia and during graft-versus-host disease with augmented immunosuppression, the incidence rates of invasive fungal diseases were successfully reduced by posaconazole 200 mg three times daily. Mucormycosis only occurred in the comparator treatment arms of the trials, i.e. fluconazole or itraconazole, but the overall rate was very low [111,112]. The prospective SEIFEM-B 2010 registry on newly diagnosed acute myelogenous leukaemia (n = 515) compared posaconazole with itraconazole prophylaxis and no mucormycosis cases were diagnosed in either group [113]. While fluconazole [114] and voriconazole [115] are not active against mucormycosis, itraconazole may yield some activity, but may be inferior to posaconazole [116].

In immunosuppressed patients with a previous diagnosis of mucormycosis (n = 3) surgery in combination with secondary antifungal prophylaxis successfully prevented recurrence [117]. Another study reported a single case in support of this approach [118].

*Recommendations*—During periods of graft-versus-host disease with augmented immunosuppression and during outbreak situations posaconazole primary prophylaxis is recommended with marginal support for the specific prevention of mucormycosis. We acknowledge that this is a rather artificial scenario, since prophylaxis of invasive aspergillosis will be given already. In patients with previous mucormycosis, surgical resection and individualized secondary antifungal prophylaxis are strongly supported. The last effective antifungal in the respective individual should be preferred. For further recommendations refer to Table 7.

*Fever-driven treatment. Evidence*—No clinical trial has been conducted evaluating the timing of fever-driven treatment

directed against mucormycosis. In general, a diagnosis-driven antifungal treatment is preferable [119].

*Recommendations*—If institutional epidemiology advocates mucormycosis to be part of the antifungal spectrum, refer to drugs and doses used for targeted treatment.

*Targeted first-line treatment. Evidence*—In the field of mucormycosis no well-designed randomized clinical efficacy trial has been published. In a retrospective study on 30 patients combined with a literature analysis of 225 patients with mucormycosis, surgical debridement of lung involvement was associated with a decrease of mortality from 62% to 11%. Procedures were lobectomy, pneumonectomy or wedge resection and patients with non-disseminated disease were more likely to be treated surgically [120]. Two recent literature reviews documented higher survival rates with a combined modality approach of surgical and medical treatment [3,121]. A large institutional series reinforced the need for a combined therapeutic approach [38] and in posaconazole salvage treatment of mucormycosis the highest cure rates were achieved when surgery was part of the strategy [122]. A multivariate analysis from an ECMM case registry [7] and a retrospective analysis of a national case series also found surgery associated with survival [25]. Surgery is of major importance in rhino-orbito-cerebral locations, as evidenced in a retrospective study, where the impact of local control on survival was striking [123].

In an uncontrolled study in patients with haematological malignancy the 12-week mortality rate increased two-fold with medical treatment deferred for 6 or more days from onset of symptoms [27].

Murine models suggest that liposomal amphotericin B is more effective than the deoxycholate formulation against mucormycosis [124], and that for liposomal amphotericin B and amphotericin B lipid complex efficacy was dose-dependent [125]. Actually the lipid complex formulation reached higher lung concentrations and better fungal tissue clearance than liposomal amphotericin B [125]. Whereas both formulations had similar efficacy in neutropenic and diabetic ketoacidotic mice, liposomal amphotericin B was more effective in reducing

**TABLE 7. Recommendations on prophylaxis of mucormycosis**

Population	Intention	Intervention	SoR	QoE	Comment	References
Neutropenic or GvHD patients in an outbreak situation	To prevent	Posaconazole 3 × 200 mg/day	C	III	n = 1/602 n = 1/600 n = 0/353	111 112 113
Neutropenic or GvHD patients in an outbreak situation	To prevent	Fluconazole, itraconazole, voriconazole, any dose	D	II	In vitro	114–116
Immunosuppressed, previous diagnosis of mucormycosis	To prevent recurrence, 'secondary prophylaxis'	Surgical resection and last drug effective in the same patient, same dose as for treatment	A	III	n = 3 n = 1	117 118

GvHD, graft versus host disease; N/A, not applicable; QoE, quality of evidence; SoR, strength of recommendation.

brain fungal burden [126]. In central nervous system disease amphotericin deoxycholate and liposomal amphotericin achieved the highest efficacy in a rabbit model; however, this model evaluated candidiasis [127].

In an uncontrolled retrospective study on patients with haematological malignancy multivariate analysis revealed treatment with liposomal amphotericin B 3 mg/kg/day to be independently associated with cure [105]. An analysis from the ECMM FungiScope™ registry ([www.fungiscope.net](http://www.fungiscope.net)) demonstrated that liposomal amphotericin B at an average dose of 5 mg/kg/day was associated with increased response and survival rates [26]. The ECMM mucormycosis registry ([www.zygomycosis.net](http://www.zygomycosis.net)) reported that a liposomal amphotericin B median dose of 5 mg/kg/day (range 3–10 mg/kg/day) leads to favourable response rates [7]. In invasive aspergillosis high-dose liposomal amphotericin B (10 mg/kg/day) caused significantly more renal toxicity than the standard dose of 3 mg/kg/day, but proved the general feasibility of high-dose regimens [128]. A subsequent non-comparative clinical trial evaluated the feasibility and efficacy of liposomal amphotericin B 10 mg/kg/day for the initial treatment of mucormycosis [129]. Renal toxicity was frequent (40%), but treatment was feasible in more than half of the patients; at week 12 the response rate was 45% [57].

First-line treatment with amphotericin B lipid complex 5 mg/kg/day has been reported in a very limited number of patients only [7,130]. In conjunction with the evidence from animal models, central nervous system involvement should be excluded if this formulation is to be used [126,127].

In immunocompetent mice amphotericin B prolonged survival, whereas for itraconazole and posaconazole there are heterogeneous effects depending on the fungal species used for infection [131–133]. The ECMM clinical registries reported successful first-line treatment with posaconazole in about 50–60% of patients [7,26]. Split doses of posaconazole yield higher exposure, so that posaconazole 200 mg four times daily is the preferred dosing regimen in mucormycosis treatment [134].

Concomitant treatment with an amphotericin B formulation and caspofungin has been described as successful in a limited number of predominantly diabetic patients with rhinocerebral mucormycosis [135].

Amphotericin B deoxycholate has been used as standard treatment when no alternative was available [3]. When the comparison to liposomal amphotericin B in fever-driven treatment provided objective proof of its substantial toxicity, the deoxycholate formulation was no longer appropriate, although it is still used where resources are a constraint [136,137]. Amphotericin B deoxycholate did not correlate with superior recovery in a multivariate analysis in a haema-

tological malignancy population [105], in a large institutional series with a variety of underlying diseases [38], and most recently in an ECMM registry [7].

**Recommendations**—In patients with mucormycosis, surgery whenever possible is strongly recommended to be combined with medical treatment. Immediate treatment initiation is strongly supported to increase survival rates. Liposomal amphotericin B is the drug of choice and the dose should be at least 5 mg/kg/day. The use of amphotericin B deoxycholate is discouraged. For further recommendations refer to Table 8.

**Salvage treatment. Evidence**—Salvage treatment may be necessary because of refractoriness of disease, or because of intolerance towards previous antifungal therapy, or because of a combination of both.

In the posaconazole compassionate use programme, investigators were allowed to switch between two oral suspension dosing regimens, i.e. 200 mg four times daily and 400 mg twice daily. Rates of complete and partial response [138] as well as survival approached 80% in patients with refractory disease and in patients intolerant to previous therapy [122]. A second analysis of a larger population from the same programme described a treatment response rate of 60% (overlap between both articles was 11 patients). An additional 20% of patients achieved stable disease [139,140]. In the ECMM registry on mucormycosis patients the survival rate of patients receiving posaconazole was 72% [7]. A retrospective analysis of 96 published case reports of posaconazole treatment found a 73% complete response rate [141].

Other reports on salvage treatment cover series of smaller patient numbers ( $n = 2$  to  $n = 323$ ). Liposomal amphotericin B 5 mg/kg/day has been used in patients intolerant to previous amphotericin B deoxycholate treatment [105]. Amphotericin B lipid complex 5 mg/kg/day was given in some patients with refractory disease [130,142], in those intolerant to previous therapy or with pre-existing renal disease [130]. In the latter group, use of amphotericin B colloidal dispersion 5 mg/kg/day was also reported [143].

The combination of lipid-based amphotericin B plus caspofungin has been described in a few patients [135]. In models of neutropenic and ketoacidotic mice the combination of liposomal amphotericin B and posaconazole did not improve survival rates or reduce fungal tissue burden [144]. However, in a recent report on 32 patients with mainly haematological diseases, combinations of lipid-based, mostly liposomal, amphotericin B 3–5 mg/kg/day and posaconazole 800 mg/day were analysed [145]. Three months after

**TABLE 8. Recommendations on targeted first-line treatment of mucormycosis in adult patients**

Population	Intention	Intervention	SoR	QoE	Comment	References
Any	To increase survival rates	Surgical debridement	A	IIu	n = 32 n = 90 n = 45 n = 9 n = 59 n = 92, paediatric	120 3 38 7 25 121
Any	To cure and to increase survival rates	Surgical debridement in addition to antifungal treatment	A	IIu	n = 470 n = 19 n = 90 n = 92, paediatric	3 122 7 121
Immunocompromised	To increase survival rates	Immediate treatment initiation	A	IIu	n = 70	27
Any	To cure and to increase survival rates	Amphotericin B, liposomal $\geq 5$ mg/kg <sup>a</sup>	A	IIu	n = 4 n = 16 n = 5 n = 21 n = 28 n = 130 n = 40	105 196 128 26 152 7 57
CNS	To cure	Amphotericin B, liposomal 10 mg/kg, initial 28 days <sup>a</sup>	A	II	Animal model	124
Any, except CNS	To cure	Amphotericin B, lipid complex 5 mg/kg <sup>a</sup>	B	IIu	Animal model n = 10 n = 7 Animal model	125 127 126 130 7 126 127
Any	To cure	Posaconazole 4 $\times$ 200 mg/day or 2 $\times$ 400 mg/day <sup>a</sup>	B	IIu	n = 8 n = 17 Animal model	26 7 131
Any	To cure	Lipid-based amphotericin plus caspofungin <sup>a</sup>	C	III	n = 7	135
Any	To cure	Amphotericin B, deoxycholate, any dose <sup>a</sup>	D	I	Renal toxicity n = 9 n = 532	137 105 3
					Renal toxicity n = 10 n = 21	136 38 7

CNS, central nervous system; QoE, quality of evidence.  
<sup>a</sup>Treatment duration is determined on a case-by-case basis and depends, for example, on extent of surgery and organs involved.

initiation of treatment 56% had responded to treatment [145].

**Recommendations**—For salvage treatment posaconazole 200 mg four times daily is strongly recommended, while lipid-based formulations of amphotericin B and combination of these two compounds are supported with moderate strength. For further recommendations refer to Table 9.

#### Specific patient settings

**Children.** Mucormycosis is a life-threatening disease in immunocompromised children and adolescents with haematological malignancies, transplantation, immunosuppressive therapy, diabetes, trauma or burns, and may also occur in premature neonates. Whereas gastrointestinal and cutaneous disease is the most common reported presentation in neonates, older children and adolescents typically present with pulmonary, rhino-orbital-cerebral, cutaneous, and disseminated disease. Overall mortality is 64% in neonates and 42–56% in children. Dissemination and age below one year are independent risk factors for death in children. Similar to adults, surgery combined with antifungal therapy is a factor associated with survival [121,146–149]. Of note, in a large epidemiological study from the USA, the incidence of mucormycosis was stable

over time and no relationship to the increasing use of voriconazole among children was found [150].

**Evidence**—While the recommendations are similar to those for adults, there are, however, subtle but important differences for paediatric patients. These differences are consistent with paediatric development regulations and guidelines from the European Medicines Agency (EMA) whose concepts have been adopted by the 2012 ESCMID guideline for prevention and management of invasive *Candida* infections in neonates and children [151]. On the basis of this conceptual framework, the group considered four components for grading of therapeutic interventions: (i) evidence for efficacy from adult phase II trials and case series; (ii) existence and quality of paediatric pharmacokinetic data and dosing recommendations; (iii) specific paediatric safety data and supportive efficacy data; and (iv) regulatory approval for use in paediatric age group(s) [151].

**Recommendations**—Due to the absence of substantially different and/or separate paediatric data, recommendations for diagnosis (patient evaluation, diagnostic methods), principles of management (antifungal therapy, control of the predisposing condition, surgery), adjunctive treatments (granulocyte transfusions, cyto-

**TABLE 9.** Recommendations on salvage treatment of mucormycosis in adult patients

Population	Intention	Intervention	SoR	QoE	Comment	References
Refractory to prior antifungal therapy	To cure	Posaconazole, oral suspension, 4 × 200 mg/day or 2 × 400 mg/day <sup>a</sup>	A	llu	n = 19 n = 81 <sup>b</sup> n = 61 n = 15 <sup>c</sup>	122 139 7 141
Intolerant to prior antifungal	To cure	Posaconazole, oral suspension, 4 × 200 mg/day or 2 × 400 mg/day <sup>a</sup>	A	llu	n = 5 n = 43 <sup>b</sup> n = 15 <sup>c</sup>	122 139 141
Intolerant to prior antifungal	To cure	Amphotericin B, liposomal, 5 mg/kg	B	llu	n = 8	105
Refractory to prior antifungal therapy	To cure	Amphotericin B, lipid complex, 5 mg/kg	B	llu	n = 16 n = 23	142 130
Intolerant to prior antifungal	To cure	Amphotericin B, lipid complex, 5 mg/kg	B	llu	n = 12	130
Intolerant due to pre-existing renal disease	To cure	Amphotericin B, lipid complex, 5 mg/kg	B	llu	n = 18	130
Intolerant due to pre-existing renal disease	To cure	Amphotericin B colloidal dispersion 5 mg/kg	B	llu	n = 21	143
Refractory disease or intolerant to prior antifungal therapy	To cure	Polyene plus caspofungin	C	lll	n = 2	135
Any	To cure	Polyene plus posaconazole	B	llu	n = 32	145

SoR, strength of recommendation; QoE, quality of evidence.

<sup>a</sup>Treatment duration is determined on a case-by-case basis and depends, for example, on extent of surgery and organs involved.

<sup>b</sup>Thirty-three patients had both refractory disease and intolerance, 11 individuals are part of the Greenberg report, too.

<sup>c</sup>The reason for salvage treatment, i.e. refractoriness versus intolerance, was not reported in this study.

kines, hyperbaric oxygen, deferasirox), and timing/duration of antifungal treatment of paediatric mucormycosis are similar to those outlined for adults and are not recapitulated here.

Prompt initiation of treatment with amphotericin B and consideration of surgery are critical for successful management [121,146,148]. Based on observational data in adults [7,26,130,142,152], paediatric pharmacokinetics [153–155], safety data [148,154,156–159] and the existence of a paediatric label, the choices for first-line treatment in neonates, children and adolescents include amphotericin B lipid complex and liposomal amphotericin B. For pharmacokinetic and pharmacodynamic reasons liposomal amphotericin B is the preferred drug for infections involving the central nervous system [127]. While amphotericin B deoxycholate may have acceptable safety and tolerability profiles in neonates [160], its use is discouraged based on superior outcomes of lipid-amphotericin B in animal models and adults [124,136]. Predominantly due to the lack of clinical efficacy data in adults in this setting, posaconazole [7,26] and the combination of lipid-amphotericin B plus caspofungin [135] are only recommended with marginal strength for first-line therapy of paediatric patients.

Indications for salvage therapy include refractory disease and life-threatening toxicities of lipid amphotericin B; considering the high mortality of mucormycosis, pre-existing kidney dysfunction is not a priori a contraindication for treatment with lipid amphotericin B. Options for salvage therapy of mucormycosis in children  $\geq 2$  years and adolescents include posaconazole. This recommendation is based on adult efficacy data [122,139] and limited paediatric pharmacokinetic [161,162] and safety data [161–164]. Although no data for mucormycosis exist, demonstrating a trough serum concentration of 0.7–1.0  $\mu\text{g/mL}$  is reasonable to assume exposure on

the basis of treatment data obtained in patients with invasive aspergillosis [165]. Further options for salvage therapy include the combination of lipid amphotericin B plus caspofungin [121,135,166–170], both compounds are approved for all age groups, and the combination of lipid amphotericin B plus posaconazole for children  $\geq 2$  years of age [95,144]. Of note, posaconazole may also be used for consolidation treatment and as secondary prophylaxis, respectively. For further recommendations on first-line treatment refer to Table 10, and for salvage treatment refer to Table 11.

*Haematological malignancy. Evidence*—With the intent to cure infection, granulocyte colony-stimulating factor has been applied to shorten neutropenia as the key predisposing factor for mucormycosis in this patient group. The results are difficult to interpret because of the small published patient numbers ( $n = 5$  to  $n = 18$ ) [3,105,171–175]. Granulocyte transfusion has been reported in an even more limited number of patients ( $n = 7$  to  $n = 8$ ) to cure mucormycosis [3,105,175]. Granulocyte transfusion has been combined with recombinant interferon- $\gamma$  1b ( $n = 4$ ) [176].

*Recommendations*—In patients with neutropenia, granulocyte colony-stimulating factor is strongly recommended. The dose should be chosen as licensed. For further recommendations refer to Table 12.

*Solid organ transplant recipients. Evidence*—In solid organ transplant recipients use of liposomal amphotericin B has been reported to be associated with increased response rates [25,177–179]. Specifically in pulmonary mucormycosis [177] and in sino-nasal-cerebral disease surgery was associated with

**TABLE 10. Recommendations for mucormycosis in paediatric patients: first-line**

Population	Intention	Intervention	SoR	QoE	Comment	References
Paediatric Paediatric beyond neonatal period	To cure To cure	Amphotericin B and surgery Amphotericin B, lipid complex 5 mg/kg/day	A A	II II	Paed. Paed. PK Paed. safety Paed. safety Adult Adult	121,146,148 153 156 157 142 155
Paediatric beyond neonatal period	To cure	Amphotericin B, liposomal $\geq 5$ mg/kg/day	A	II	Paed. PK Paed. safety Paed, n = 20 Adult Adult Adult	159 148 26 152 7
Paediatric beyond neonatal period and $\geq 2$ years old	To cure	Posaconazole 4 $\times$ 200 or 2 $\times$ 400 mg/day; <13 years old: body-weight-based $\leq 34$ kg 18-24 mg/kg/day given in 4 divided doses.	C	III	Paed. PK Paed. safety Paed, n = 5 Adult n < 17 Adult TDM	161,162,200 163 164 26 7 165
Paediatric patients beyond the neonatal period	To cure	Amphotericin B lipid-based plus caspofungin	C	III	n = 7, adult, 2nd line Paed. PK Paed. PK Paed. safety	135 168 169 170
Neonates, in particular premature neonates	To cure	Amphotericin B, lipid complex 5 mg/kg/day	A	II	Neo PK Paed safety Paed safety Adult Adult Adult	154 156 157 142 130 158
	To cure	Amphotericin B, liposomal $\geq 5$ mg/kg/day	A	II	Neo safety Paed safety Paed, n = 20 Adult Adult Adult	159 148 26 152 7
	To cure	Amphotericin B, lipid-based plus caspofungin	C	III	Neo PK Adult, second line	167 135
CNS involved	To cure To cure	Amphotericin B, deoxycholate 1–1.5 mg/kg/day Amphotericin B, liposomal 5–10 mg/kg/day	D A	III II	Animal Animal	124 127

CNS, central nervous system; Neo, neonates; Paed, paediatric; PK, pharmacokinetics; QoE, quality of evidence; SoR, strength of recommendation.

**TABLE 11. Recommendations for mucormycosis in paediatric patients: salvage treatment**

Population	Intention	Intervention	SoR	QoE	Comment	References
Paediatric beyond neonatal period and $\geq 2$ years old	To cure	Posaconazole, 4 $\times$ 200 mg/day or 2 $\times$ 400 mg/day; <13 years old: body-weight-based	A	II	Paed. PK Paed. PK Paed. safety Paed, n = 5 Adult Adult Adult Adult TDM	161 162 163 164 122 139 165
Paediatric including neonates	To cure	Amphotericin B, lipid-based, plus caspofungin	C	III	Adult, n = 7 Animal Neo PK cas, Paed PK cas Paed PKcas Safety cas	135 166 167 168 169
Paediatric beyond neonatal period and $\geq 2$ years old	To cure	Amphotericin B, lipid-based, plus posaconazole	C	III	Animal Animal	170 144 95

cas, caspofungin; Neo, neonates; Paed, paediatric; PK, pharmacokinetics; QoE, quality of evidence; SoR, strength of recommendation; TDM, therapeutic drug monitoring.

increased survival rates [179].

**Recommendations**—In solid organ transplant recipients surgery and liposomal amphotericin B—usually in combination—are strongly recommended. For further recommendations refer to Table 13.

**HIV infection and AIDS. Evidence**—Mucormycosis may be found in human immunodeficiency virus (HIV)-infected patients; indeed, 2% of all mucormycosis patients in a large literature

review were infected with HIV. However, HIV and AIDS are not considered risk factors specifically for mucormycosis [3].

**Recommendations**—Recommendations do not differ from other populations described above. In HIV patients drug–drug interactions of protease inhibitors and non-nucleoside reverse transcriptase inhibitors would need to be considered.

**Diabetes. Evidence**—Control of hyperglycaemia and ketoacidosis was suggested to be a beneficial reversal of a risk factor

for mucormycosis in a review of 145 patients (87 with diabetes) [180], and in two institutional cohorts of 35 and 33 diabetic patients [38,181].

Surgery was associated with improved cure and survival rates in a retrospective analysis of 101 patients with mucormycosis, 23 of these were diabetic patients with a 64% rate of rhinocerebral involvement [25]. Institutional cohorts of diabetic patients found surgery associated with increased survival rates [38,181]. Across these studies *Rhizopus oryzae* was the most frequently identified single pathogen [25,38,180,181].

**Recommendations**—In uncontrolled diabetes mellitus the control of hyperglycaemia and ketoacidosis is strongly supported. Surgery should be part of the therapeutic approach. For further recommendations refer to Table 14.

**Trauma patients. Evidence**—Trauma is the third major group of patients with mucormycosis [25]. Natural disaster and accidents are the usual settings [2,182]. In trauma patients mortality rates are lower than in patients with underlying haematological malignancy or diabetes [3,25]. In addition, trauma patients may be more likely to receive surgery and less likely to develop disseminated disease. Although a shorter duration of antifungal treatment may be feasible, a multimodal approach of surgical debridement (until clear margins) and

antifungal treatment should improve response rates and has therefore been advocated [2,7,67,182].

**Recommendations**—Surgical debridement and antifungal treatment are strongly recommended in trauma patients with mucormycosis (Table 15).

**Adjunctive treatments and general management.** Iron overload may be a risk factor for mucormycosis [183,184], consequently iron depletion through chelators could be a useful adjunctive treatment.

**Evidence**—In murine models the iron chelator deferasirox protected from mucormycosis [183] and enhanced the efficacy of liposomal amphotericin B [185]. Furthermore, deferasirox was found to be safe in a phase II study in patients ( $n = 8$ ) with proven mucormycosis [186]. However, when deferasirox was added to liposomal amphotericin B in a small ( $n = 20$ ) prospective, double blind, placebo-controlled trial in haematological patients, the combination treatment group had a higher mortality rate (82% versus 22%) at 90 days [187]. These results are difficult to interpret and may have been caused by imbalanced baseline characteristics between the treatment groups. In any case, it is difficult to prescribe chelators in haematological patients with mucormycosis, although it is unclear whether other patient groups, e.g. diabetic patients

**TABLE 12. Recommendations for mucormycosis in haematological malignancy**

Population	Intention	Intervention	SoR	QoE	Comment	References
Haematological malignancy with ongoing neutropenia	To cure infection	GCSF, dose not reported	A	IIu	$n = 8$ $n = 12$ $n = 18$ $n = 18$ $n = 5$	171 175 105 3 174
Haematological malignancy with ongoing neutropenia	To cure infection	Granulocyte transfusion	C	IIu	$n = 8$ $n = ?$ $n = 8$	173 105 175
Haematological malignancy with ongoing neutropenia	To cure infection	Granulocyte transfusion plus interferon- $\gamma$ 1b	C	III	$n = 7$ $n = 4$	3 176

GCSF, granulocyte colony-stimulating factor; QoE, Quality of evidence; SoR, Strength of recommendation.

**TABLE 13. Recommendations for mucormycosis in solid organ transplant recipients**

Population	Intention	Intervention	SoR	QoE	Comment	References
Solid organ transplantation	To cure	AmB lipid formulation	A	IIh	$n = 25$ $n = 14$ , pulmonary	178 177
Solid organ transplantation	To cure	Surgery	A	IIu	$n = 3$ $n = 11$ , pulmonary $n = 10$ , sinu-nasal-cerebral	25 177 179

QoE, quality of evidence; SoR, strength of recommendation.

**TABLE 14. Recommendations for mucormycosis in diabetic patients**

Population	Intention	Intervention	SoR	QoE	Comment	References
Uncontrolled diabetes	To cure	Control of hyperglycaemia and ketoacidosis	A	IIu	<i>n</i> = 87 <i>n</i> = 35 <i>n</i> = 33 Review	180 181 38 197
Uncontrolled diabetes with rhinocerebral involvement	To cure and to increase survival	Surgery	A	III	<i>n</i> = 26 <i>n</i> = 14 <i>n</i> = 23 <i>n</i> = 14	181 38 25 123
Uncontrolled diabetes	To cure	GM-CSF 250–425 µg/day	C	III	<i>n</i> = 3, adjunctive to medical and surgical treatment	198

GM-CSF, granulocyte–macrophage colony-stimulating factor; QoE, quality of evidence; SoR, strength of recommendation.

**TABLE 15. Recommendations for mucormycosis in trauma patients**

Population	Intention	Intervention	SoR	QoE	Comment	References
Trauma	To cure	Surgical debridement and antifungal treatment	A	II	<i>n</i> = 38 <i>n</i> = 5/129 <i>n</i> = 3/8 <i>n</i> = 44/929 <i>n</i> = 39/230 <i>n</i> = 13/13 <i>n</i> = 18/101	182 199 67 3 7 2 25

QoE, quality of evidence; SoR, strength of recommendation.

**TABLE 16. Recommendations for adjunctive treatments and general management in mucormycosis**

Population	Intention	Intervention	SoR	QoE	Comment	References
Haematological malignancy	To cure	Deferasirox 20 mg/kg/day, days 1–14	D <sup>a</sup>	II	<i>n</i> = 8 <i>n</i> = 20, increased mortality	186 187
Haematological malignancy Other than haematological malignancy	To cure	Exposure to 100% hyperbaric oxygen	C	IIIr	<i>n</i> = 3	3,191
Other than haematological malignancy	To cure	Deferasirox, any dose	C	III		No reference found.
Other than haematological malignancy	To cure	Exposure to 100% hyperbaric oxygen	C	IIr	<i>n</i> = 28, primarily patients with improvable risk factors, i.e. diabetes, trauma	3,191
Glucocorticosteroid recipients	To cure	Stop, if feasible, if not: reduce dose of glucocorticosteroids to minimum required	A	IIr		190
Uncontrolled diabetes	To cure	Hyperbaric oxygen	C	IIu	<i>n</i> = 5	107
Any	To cure	Lovastatin	C	III	<i>In vitro</i> animal model	188 189
Any	To cure	Continue treatment until complete response (on imaging) and permanent reversal of immunosuppression are achieved.	A	III	Optimal duration of treatment has not been studied prospectively	No reference found.

QoE, quality of evidence; SoR, strength of recommendation.  
<sup>a</sup>Votes: C 4, D 9, abstain 3.

with rhinocerebral mucormycosis, are suitable for such treatment. This is one of the rare occasions when the group had to vote on a recommendation (Table 16).

Lovastatin inhibits the *in vitro* growth of *Rhizomucor pusillus* [188]. In a *Drosophila* model lovastatin had activity against *Mucor* sp. and *Rhizopus* sp., and exhibited a synergistic effect when combined with voriconazole, which species in the order Mucorales are intrinsically resistant [189]. It is unknown whether these observations are clinically meaningful.

Glucocorticosteroid treatment is a risk factor for fungal infection and in patients with mucormycosis it should be avoided. If this is not feasible then the dose should be reduced to the minimum required [190].

Hyperbaric oxygen has been reported in small numbers of patients in uncontrolled settings [3]. In a review of 28

published cases treated with adjunctive hyperbaric oxygen mortality was only 6%. Besides small patient numbers, bias in selecting patients suitable for the procedure, publication bias and generally lower survival rates in haematological patients limit the quality of evidence [107,191].

The optimal duration of treatment has not been studied prospectively and is generally unknown. Duration of any of the treatments above is based on individual decision.

**Recommendations**—In haematological patients with mucormycosis, adjunctive treatment with deferasirox is discouraged, whereas in other patient groups it is recommended with marginal strength. It is strongly recommended to stop glucocorticosteroid treatment in patients with mucormycosis. We strongly recommend continuing antifungal treatment until

complete resolution as demonstrated on imaging and permanent reversal of risk factors is achieved. For further recommendations refer to Table 16.

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## Transparency Declarations

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MCA has received research grants from Astellas, Gilead, Merck/Schering and Pfizer, is a consultant to Merck, Gilead, Pfizer, received travel support from Astellas, Merck/Schering and Pfizer and received lecture honoraria from Astellas, Gilead, Merck/Schering and Pfizer. TB has received royalties from Elsevier and is in part supported by QNRF grant NPRP5-298-3-086. AnC has no conflicts of interest to declare. MCE has received research grants from MSD, Astellas, Pfizer, Gilead and Ferrer, is a consultant to MSD, Astellas, Pfizer, Gilead and Ferrer, has provided expert testimony for MSD, Astellas, Pfizer, Gilead and Ferrer and received lecture honoraria from MSD, Astellas, Pfizer, Gilead and Ferrer. TF is a consultant to Hutman AG. JeG has received research grants from Basilea, BioMerieux, Astellas, Pfizer, Fundacion Mutua Madrilenia, Fondo de Investigacion Sanitaria (FIS), and received lecture honoraria from Astellas, Pfizer, Gilead, MSD and Hickma Pharma. JoG has no conflicts of interest to declare. SdH has no conflicts of interest to declare. WH has received research grants from Pfizer, Astellas, Gilead and F2G, is a consultant to Pfizer, Astellas, Gilead and F2G, and received lecture honoraria from Astellas, Gilead, Merck/Schering and Pfizer. EJ is a consultant to Astellas, Gilead, Merck/Schering and Pfizer, received travel support from Astellas, Merck/Schering and Pfizer, received payment for development of educational presentations from Astellas, Merck/Schering and Pfizer, and received lecture honoraria from Astellas, Gilead, Merck/Schering and Pfizer. SK has no conflicts of interest to declare. ML has no conflicts of interest to declare. CLF has received research grants from Astellas, Gilead, Pfizer, Schering-Plough and MSD, is a consultant to Gilead, MSD, Pfizer and Schering-Plough, received payment for development of educational presentations from Pfizer, received travel support from Gilead, MSD, Pfizer, Astellas and Schering-Plough, and received lecture honoraria from Astellas, Gilead, Merck/Schering and Pfizer. OL is a consultant to Astellas and Gilead, and received lecture honoraria from Astellas, Gilead, Merck/Schering and Pfizer. JFM has received research grants from Astellas, Merck and MSD, is a consultant to Astellas, Basilea, Merck and MSD, received travel support from Astellas, and received lecture honoraria from Merck. JoM has received research grants from Gilead, Merck/Schering and Pfizer, and received lecture honoraria from Gilead, Pfizer and Liofilchem. PM is a consultant to Astellas, Gilead, Merck/Schering and Pfizer, received payment for development of educational presentations from Merck, and received lecture honoraria from Astellas, Gilead, Merck/Schering and Pfizer. MR has received payment for development of educational presentations from Pfizer, received royalties from Blackwell Publishing, received travel support from Astellas, is a consultant to Gilead and MSD, and received lecture honoraria from Astellas and



Pfizer. ER has received research grants from Enzon, Gilead, Pfizer and Schering, is a consultant to Astellas, Gilead, Merck, Pfizer and Schering, and received lecture honoraria from Astellas, Aventis, Cephalon, Gilead, Merck, Pfizer, Schering and Wyeth. AT has received research grants from Astellas and MSD, and received lecture honoraria from Astellas, Gilead and MSD. AJU has received research grants from Astellas, Gilead, Merck/Schering and Pfizer, is a consultant to Astellas, Basilea, Gilead, Merck/Schering and Pfizer, received payment for development of educational presentations from Gilead, and received lecture honoraria from Astellas, Gilead, Merck/Schering and Pfizer. AvD has no conflicts of interest to declare. PV has received research grants from Astellas, Gilead, Merck/Schering and Pfizer, is a consultant to Astellas, Gilead, Merck and Pfizer, received payment for development of educational presentations from Merck and Pfizer, and received lecture honoraria from Astellas, Gilead, Merck/Schering and Pfizer. GP has received research grants from Pfizer, Gilead, AstraZeneca, Novartis, Astellas, GSK, is a consultant to MSD, received travel support from Gilead, Astellas and Pfizer and received lecture honoraria from MSD, and Astellas.

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## ESCMID and ECMM joint guidelines on diagnosis and management of hyalohyphomycosis: *Fusarium* spp., *Scedosporium* spp. and others

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### Abstract

Mycoses summarized in the hyalohyphomycosis group are heterogeneous, defined by the presence of hyaline (non-dematiaceous) hyphae. The number of organisms implicated in hyalohyphomycosis is increasing and the most clinically important species belong to the genera *Fusarium*, *Scedosporium*, *Acremonium*, *Scopulariopsis*, *Purpureocillium* and *Paecilomyces*. Severely immunocompromised patients are particularly vulnerable to infection, and clinical manifestations range from colonization to chronic localized lesions to acute invasive and/or disseminated diseases. Diagnosis usually requires isolation and identification of the infecting pathogen. A poor prognosis is associated with fusariosis and early therapy of localized disease is important to prevent progression to a more aggressive or disseminated infection. Therapy should

include voriconazole and surgical debridement where possible or posaconazole as salvage treatment. Voriconazole represents the first-line treatment of infections due to members of the genus *Scedosporium*. For *Acremonium* spp., *Scopulariopsis* spp., *Purpureocillium* spp. and *Paecilomyces* spp. the optimal antifungal treatment has not been established. Management usually consists of surgery and antifungal treatment, depending on the clinical presentation.

**Keywords:** *Acremonium*, *Fusarium*, hyalohyphomycosis, *Paecilomyces*, *Scedosporium*, *Scopulariopsis*

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## Background

The frequency and diversity of serious fungal infections is increasing [1–3]. Severely immunocompromised patients are particularly vulnerable to infection from unusual moulds and yeasts, which are present in the environment. Clinical manifestations range from colonization to chronic localized lesions to acute invasive and/or disseminated diseases. Localized infections may occur following penetrating trauma in healthy individuals; dissemination usually occurs among immunocompromised patients and the outcome is closely related to the degree and persistence of immunosuppression [4]. Diagnosis usually requires isolation and identification of

the infecting pathogen; however, serology, imaging techniques and clinical manifestations are not specific, and pan-fungal and species-specific PCR are useful investigational tools. Many of the emerging opportunistic moulds demonstrate *in vitro* and *in vivo* resistance to various antifungals. As a result, successful treatment may require adjunctive surgical debridement and, when possible, reconstitution of the host immune system.

Mycoses in the hyalohyphomycosis group are heterogeneous, defined by the presence of hyaline hyphae in tissues [3,5]. The number of organisms causing hyalohyphomycosis is increasing and the most clinically important genera are *Fusarium* spp., *Scedosporium* spp., *Acremonium* spp., *Scopulariopsis* spp., *Purpureocillium* and *Paecilomyces* spp. [3,6–9]. Table 1 displays an overall summary of the *in vitro* antifungal susceptibility for selected fungi. Table 2 gives an overview of antifungals and dosages for adults and paediatric patients.

The executive board of the European Fungal Infection Study Group (EFISG) of the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) and the European Confederation of Medical Mycology (ECMM) decided to proceed with a pan-European guideline for the diagnosis and management of hyalohyphomycosis. Participants were chosen on the basis of their expertise in the field of medical mycology and for further proficiency, EFISG and ECMM set up group

**TABLE 1.** Overview of possible *in vitro* antifungal susceptibility patterns for selected hyalohyphomycetes

Pathogen	AMB	Flucytosine	Echinocandins	Fluconazole	Itraconazole	Voriconazole	Posaconazole
<i>Fusarium solani</i>	I-R	R	R	R	R	S-I-R	S-I-R
<i>Scedosporium apiospermum</i>	I-R	R	S	I-R	S-R	S	S
<i>Scedosporium boydii</i>	I-R	R	S	I-R	S-R	S	S
<i>Scedosporium aurantiacum</i>	R	NT	R	NT	R	S	S-R
<i>Scedosporium prolificans</i>	R	R	S-I-R	R	R	R	R
<i>Paecilomyces</i> species	S	I	R	R	S	I-S	S
<i>Purpureocillium liliacinum</i>	R	R	R	R	S	S	S
<i>Acremonium</i> species	S-R	R	R	R	S-R	S-R	S-R
<i>Scopulariopsis</i> species	I-R	R	NT	R	R	R	I-R

The classifications here (S, I, R) only indicate a gross guide, deviations may occur. Susceptibility testing gives an overview of drug activity and therefore may support choice of antifungals.

Combinations of MIC data are not shown.

Data are collected from references [47–51,125,155–157,162,181–185].

AMB, amphotericin B and its lipid formulations; S, susceptible; I, intermediate; R, resistant; NT, not tested.



**TABLE 2.** Adult and paediatric<sup>a</sup> dosages of systemic antifungal agents

Agent	Daily dosage per age group				
	>18 years	13–18 years	2–12 years	1–24 months	Neonates
Amphotericin B deoxycholate <sup>b</sup>	1–1.5 mg/kg QD	1–1.5 mg/kg QD	1–1.5 mg/kg QD	1–1.5 mg/kg QD	1–1.5 mg/kg QD
Liposomal amphotericin B <sup>b</sup>	3 (–5) mg/kg QD	3 (–5) mg/kg QD	3 (–5) mg/kg QD	3 (–5) mg/kg QD	3 (–5) mg/kg QD
Amphotericin B lipid complex	5 mg/kg QD	5 mg/kg QD	5 mg/kg QD	5 mg/kg QD	5 mg/kg QD
Amphotericin B colloidal dispersion	3–4 mg/kg QD	3–4 mg/kg QD	3–4 mg/kg QD	3–4 mg/kg QD	n/a
Itraconazole IV	200 mg BID (for 2 days), followed by 200 mg daily	n/a	n/a	n/a	n/a
Itraconazole oral suspension/capsules <sup>c</sup>	600 mg/day (for 3 days), followed 400 mg/day	2.5 mg/kg BID	2.5 mg/kg BID	n/a	n/a
Voriconazole IV <sup>c</sup>	6 mg/KG IV q 12 h on day 1 4 mg/kg BID	4 mg/kg BID	8 mg/kg BID	n/a	n/a
Voriconazole oral suspension/capsules <sup>c</sup>	200 mg BID	200 mg BID	9 mg/kg BID (max: 350 mg BID)	n/a	n/a
Posaconazole <sup>c</sup>	200 mg QID or 400 mg BID	200 mg QID or 400 mg BID*	n/a	n/a	n/a
Caspofungin	50 mg/day (day 1: 70 mg) IV	50 mg/m <sup>2</sup> (day 1: 70) IV (max: 70)	50 mg/m <sup>2</sup> (day 1: 70) IV (max: 70)	50 mg/m <sup>2</sup> (day 1: 70) IV	25 mg/m <sup>2</sup>
Anidulafungin	100 mg (day 1: 200 mg) IV				
Micafungin	100 mg/day	100 mg/m <sup>2</sup>	>40 kg: 100 mg/day <40 kg: 2–4 mg/kg/day	>40 kg: 100 mg/day <40 kg: 2–4 mg/kg/day	>40 kg: 100 mg/day <40 kg: 2–4 mg/kg/day

QD, once a day; BID, twice a day; QID, four times a day; IV, intravenous; PO, oral; n/a, no or no sufficient data.  
<sup>a</sup>European Society of Clinical Microbiology and Infectious Diseases (ESCMID) guidelines for the diagnosis and management of *Candida* diseases 2012: prevention and management of invasive infections in neonates and children caused *Candida* spp. [186].  
<sup>b</sup>Due to toxicity reasons we recommend the usage of lipid amphotericin B instead of amphotericin B deoxycholate.  
<sup>c</sup>Therapeutic drug monitoring is recommended if itraconazole, voriconazole or posaconazole is prescribed; monitoring is highly recommended in unsatisfactory response to therapy, suspicion of toxicity or drug interactions, impaired liver or renal function and also in patients on extracorporeal membrane oxygenation (ECMO) [187–189].

coordinators for each thematic allocation to provide and present the results of the discussion of subgroups to the complete guideline development group. The subgroups were set up according to the content-related topics fusariosis, scedosporiosis and others (*Paecilomyces*, *Purpureocillium*, *Acremonium* and *Scopulariopsis* infections): the fungal pathogen, clinical spectrum, diagnosis and therapy. The manuscript was drafted by the subgroup coordinators Marianna Tortorano, Clinical Microbiologist (CM) with a strong expertise in diagnosing fungal infections and fungal identification, Malcolm Richardson, CM with specialization in general medical mycology, Emmanuel Roilides, Infectious Diseases doctor (ID) with intense expertise in the management of fungal infections in immunocompromised patients, Anne von Diepingen, Molecular Microbiologist with a focus on fungal typing methods, Patrizia Munoz, ID with broad expertise in clinical mycology, Elisabeth Johnson, Joseph Meletiadis and Paul Verweij, CMs with a strong focus on diagnosing fungal infections, identification of pathogenic fungi and antifungal susceptibility testing, Thomas Freiberger, CM representing an expert in immunology and molecular-based techniques and Cornelia Lass-Flörl, CM with expertise in diagnosing fungal infections. The complete guideline development group includes 37 individuals from all relevant professionals (e.g. intensive care units, fungal taxonomy, molecular-based techniques) and different geographical regions to ensure broad coverage of the different domains dealt with by the work presented herein. The detailed expert input is given in the author contribution section.

## Guideline Approach

The overall aim of this guidance is to address the difficulties in managing and diagnosing invasive fungal infections due to hyalohyphomycetes.

The objectives of the guidelines are to:

- Recommend approaches and practical tools for education and training of healthcare professionals in managing invasive fungal infections due to hyalohyphomycetes.
- Present practical considerations that should be taken into account when dealing with fungal infections.

The guideline covers epidemiology, clinical spectrum, diagnosis and therapy, mainly for species associated with the genera *Fusarium* and *Scedosporium*. The guidelines presented herein are limited to invasive infections caused by these fungi. For diagnosis and treatment recommendations, tables list the scientific evidence. Recommendations for various patients at risk are weighted differently based on available literature.

## Methods for Literature Search

Main keywords/MeSH terms were retrieved from reviews on hyalohyphomycoses and were defined by separate search strings according to the different topics (e.g. *Fusarium* AND/OR fusariosis). Systematic literature searches in the Medline

database, using PubMed, and the Cochrane Database, were performed. Our research was limited to the period 1984–2012, abstracts and unpublished studies as well as studies written in a language other than English were excluded. No studies were excluded *a priori* for weakness of design or data quality. For further proficiency, a group coordinator of each subgroup (*Fusarium* and fusariosis, *Scedosporium* and scedosporiosis and others) was nominated to provide and present the results of the discussion of this subgroup to the plenary sessions. The subgroups were set up by EFISG and ESCMID. The expert group reviewed all the available literature and documents and views were shared by email, teleconferences and face-to face meetings during 2012–2013. Once a first consensus was reached, the preliminary recommendations were presented to the whole group and discussed, developed further and finalized as a group consensus.

## Grading Criteria of Evidence

The appraisal of the available evidence was performed following the same lines of reasoning used in the previously developed guidelines for the management of *Candida* infections [10]. Studies were evaluated according to their design as well as their potential bias or validity, to define the strength of evidence they provided. A checklist for the critical appraisal of each selected publication was used to assess the validity of selected studies, the definition of the strength of recommendations and their level of evidence were summarized using criteria described in Table 3.

Certain recommendations were originally controversial (e.g. the need for susceptibility testing in rare fungi to guide antifungal treatment), a majority vote was a necessity to formulate a recommendation. The guideline follows the principles of the 'Grades of Recommendations, Assessment, Development and Evaluation' (GRADE) [11]. These guidelines also adopted the 'Appraisal of Guidelines, Research and Evaluation' (AGREE) items for the development of guidelines and all domains of AGREE were addressed [12].

## Fusariosis

The genus *Fusarium* contains mainly saprophytes and plant pathogens; only a few species cause infections in humans [2]. Among these are the species complexes encompassing *Fusarium solani*, *Fusarium oxysporum*, *Fusarium verticillioides* (including the obsolete species *Fusarium moniliforme*) and *Fusarium proliferatum*—the latter two are part of the *Fusarium* (*Gibberella*) *fujikuroi* species complex [13–18], which present the most

**TABLE 3.** Strength of the European Fungal Infection Study Group of the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) and European Confederation of Medical Mycology (ECMM) recommendation and quality of evidence

Strength of a recommendation (SoR)	
Grade A	ESCMID and ECMM strongly support a recommendation for use
Grade B	ESCMID and ECMM moderately support a recommendation for use
Grade C	ESCMID and ECMM marginally support a recommendation for use
Grade D	ESCMID and ECMM support a recommendation against use
Quality of evidence (QoE)	
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-controlled 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
*Added index:	
⊕	Meta-analysis or systematic review of randomized controlled trials.
⊖	Transferred evidence, that is, results from different patients' cohorts, or similar immune-status situation.
⊞	Comparator group is a historical control.
⊘	Uncontrolled trial.
⊡	Published abstract (presented at an international symposium or meeting).

commonly found opportunistic pathogenic species. In contrast, *Fusarium chlamydosporum*, *Fusarium anthophilum*, *Fusarium dimerum*, *Fusarium subglutinans* and *Fusarium sacchari* have been occasionally implicated in human diseases [13–18]. The most pathogenic species are found within the *F. solani* species complex [19], which include *Fusarium falciforme* (formerly known as *Acremonium falciforme*) and *Fusarium lichenicola* (formerly known as *Cylindrocarpon lichenicola*).

Opportunistic human pathogens of the genus *Fusarium* cause a broad spectrum of infections predominantly in immunocompromised individuals ranging from superficial, locally invasive to disseminated infections. Direct inoculation and airborne uptake are the most common routes of infections [20]. The clinical manifestation of fusariosis depends largely on the immune status of the host and the portal of entry [2], which include paranasal sinuses, lungs and skin. Neutropenia is one of the most important risk factors for acquiring disseminated fusariosis. Disseminated infections occur mainly in patients with haematological malignancies and in haematopoietic stem cell transplant recipients [21] and the incidence varies in different geographic regions. For example, in Brazil it was recently reported as the leading invasive fungal disease followed by aspergillosis and invasive candidosis [1].

## Clinical Spectrum

The typical manifestation of fusariosis in the immunocompromised population is invasive disease, often with haematogenous dissemination [22]. In patients with underlying

haematological diseases, infections occur most frequently in neutropenic patients with acute leukaemia, particularly acute myeloid leukaemia [4]. The features of patients with disseminated infection are similar in many respects to those of patients with disseminated aspergillosis [3,14]. Invasive *Fusarium* infection often involves skin as well as lung or sinus lesions [11] and usually can be isolated from blood cultures in up to 40–60% [3,14]. Skin lesions caused by *Fusarium* appear in 60–80% of the patients. They include erythematous macula or papula, are usually indurated and painful with a central area of necrosis. The mortality attributable to *Fusarium* infections in immunocompromised patients ranges from 50% to 70% [2,14,23,24]. Persistence of severe immunosuppression and particularly neutropenia is the most important factor associated with the poor outcome of patients with invasive fusariosis [4,21,25].

## Diagnosis

Radiological findings of pulmonary *Fusarium* infections are suggestive of angioinvasion [26,27]. Chest radiographs showed non-specific findings in 30% and in chest computed tomography (CT) scans nodules or masses were the most common findings with a halo sign being absent in 80% of patients investigated [26,27]. A CT scan is more sensitive (AII) than a chest X-ray [26] and therefore is the method of choice in imaging procedures. The definitive diagnosis requires isolation of *Fusarium* spp. from infected sites (skin, sinuses, lungs, blood or others) [22] (AIII), see Table 4. These fungi may invade blood vessels and histopathological findings include acute

branching septate hyaline hyphae with optional sporulation, resulting in haematogenous spread. Culture identification is important because of the histopathological similarities between *Fusarium* and other hyalohyphomycetes. Although the genus *Fusarium* can be identified by culture by the production of hyaline, crescent or banana-shaped, multicellular macroconidia, species identification is difficult and may require molecular methods. Molecular-based identification systems based on multilocus sequence typing methodology [28], genus-specific PCR and 28S rRNA gene sequencing [29], multiplex tandem PCR [30], multiplex suspension array [31,32] and the commercially available DiversiLab system [33], which uses automated repetitive sequence-based PCR (rep-PCR) and web-based data analyses, appear promising, but have as yet not been fully evaluated for the routine diagnostic setting. Species identification by matrix-assisted laser desorption ionization time-of-flight mass spectrometry also appears promising, but remains to be formally standardized and validated [34,35] (CIII).

Several developed in-house PCR assays (pan-fungal quantitative PCR screening tests, pan-fungal semi-nested PCR followed by fragment length analysis or sequencing, multiplex PCR, nested PCR, specific PCR and duplex quantitative PCR) have been applied to the direct diagnosis of *Fusarium* infection with varying specificity and sensitivity [36–43]. Molecular tests may be helpful, but should be used only to supplement conventional laboratory tests (CIII).

The  $\beta$ 1,3-D-glucan test is usually positive in patients suffering from invasive *Fusarium* infections [43] (BIII). However, the test is not able to distinguish *Fusarium* from many other agents of fungal infection, e.g. *Candida* spp., *Aspergillus* spp. and

**TABLE 4.** Summary of recommendations for diagnosis of *Fusarium* infection

<i>Fusarium</i> infection/ Population	Test	SoR	QoE	Comment	References
Any population	Direct microscopy	A	III	Essential investigation	[2]
	Culture (species identification)	A	III	Essential investigation Easily recovered on routine mycological media without cycloheximide Accurate species assignment is important for guiding clinical management	[2,190]
	Histopathology	A	IIu	Essential investigation Features of hyaline septate hyphae (with acute angle branching) are similar to those seen with aspergillosis	[120]
	Immunohistochemistry	C	III	Not yet evaluated	[120]
	$\beta$ -D-Glucan test/ Galactomannan	B	III	Glucan usually positive in case of invasive fusariosis. <i>Aspergillus</i> galactomannan sometimes positive in patients with fusariosis	[46]
	Pan-fungal PCRs for identification <sup>a</sup>	C	II	In combination with conventional methods	[36–38]
	Multiplex PCRs <sup>a</sup>	C	III	High negative predictive values Not yet validated	[30,37,39]
	<i>In situ</i> hybridization	C	III	Cover limited number of species/genera Not yet evaluated	[191,192]
	Susceptibility testing	C	III	In-house tests	[191,192]
	Environmental sampling (and fungal typing)	A	III	Gives an overview of drug activity and may be helpful in selecting antifungals In case of an outbreak situation	[2,181,182,193–195] [33,76]
Haematological patients	Chest computed tomography (CT) scan	A	IIu	None of patients had normal CT Pulmonary nodules in 82% of patients	[26]

QoE, quality of evidence; SoR, strength of recommendation.

<sup>a</sup>Third-party appraisal of results and harmonization of PCR-based techniques are necessary before any clear recommendations can be made regarding clinical utility.

*Trichosporon* spp. [44,45]. The *Aspergillus* galactomannan test may also produce positive results in approximately half of patients suffering from fusariosis [46].

Antifungal susceptibility testing is recommended (CIII) for epidemiological reasons and under certain circumstances to guide antifungal therapy. However, clinical breakpoints need to be defined, and *in vitro* and *in vivo* correlation may be absent. *Fusarium* spp. may display resistance towards numerous antifungal agents (Table 1), with *F. solani* complex frequently showing pan-azole resistance. Other species show a wide range of MICs when tested against voriconazole, posaconazole and amphotericin B [18,47–55].

## Therapy

Due to the lack of clinical trials and the critical role of immune reconstitution in the outcome of fusariosis, the optimal treatment strategy for patients with severe *Fusarium* infection remains unclear. Reversal of immunosuppression is recommended (AIII) [1,21] whenever possible.

Early therapy of localized disease is important to prevent progression to a more aggressive or disseminated infection (AII). This therapy should include surgical debridement and systemic antifungal therapy [2,14,56–59].

In immunocompromised patients, voriconazole, amphotericin B deoxycholate, lipid-based amphotericin B formulations and various combinations have been reported with varying success (Table 5). Based on the data available, we recommend voriconazole (AII) and lipid-based amphotericin B formulations (BII<sub>r</sub>). Lipid-based amphotericin B preparations exhibit fewer side-effects when compared with amphotericin B deoxycholate and should be favoured. The response rate to a lipid formulation of amphotericin B appeared superior to that of

deoxycholate amphotericin B [4]. Posaconazole is recommended as salvage therapy (AII) [23,60–62]. Data on combination therapy for fusariosis are limited to a few case reports (CIII); caspofungin plus amphotericin B deoxycholate [63], amphotericin B deoxycholate plus voriconazole [64–66], amphotericin B deoxycholate plus terbinafine [67] and voriconazole plus terbinafine [68] have been reported.

In addition to antifungal treatment, the optimal management of patients with fusariosis includes surgical debridement of infected tissues (AIII) [58], removal of venous catheters in confirmed catheter-related fusariosis and reversal of the immunocompromised state (AII) (Table 6) [69]. The role of granulocyte colony-stimulating factor or granulocyte-macrophage colony-stimulating factor in the adjuvant treatment of fusariosis is not established. Few cases report successful treatment of invasive fusariosis with a combination of antifungal and such adjuvant treatment [70–73] (CIII) (Table 6).

Because of the risk of relapse in immunosuppressed patients with prior fusarial infections [4], secondary prophylaxis should be considered (voriconazole, posaconazole, amphotericin B lipid formulation) (AIII) [4,74]. Consideration should be given to postponing cytotoxic therapy or using granulocyte colony-stimulating factor to shorten the period of neutropenia. A thorough evaluation and treatment of skin lesions should be undertaken before antineoplastic therapy [22]. The skin may be the primary source of these life-threatening infections.

## Prevention of Hospital-Acquired Infection

Airborne fusariosis is thought to be acquired by inhalation of airborne conidia [20]. In severely immunocompromised patients, every effort should be made to protect the patient from exposure to the pathogen [75] (AII). *Fusarium* reservoirs

**TABLE 5. Summary of recommendations for treatment of *Fusarium* infection**

Population	Intention	SoR	QoE	Comment	References
Immunocompromised patients	First-line treatment Voriconazole	A	II <sub>r</sub>	Therapeutic drug monitoring required Response rate was associated with underlying condition and infection site	[23,24,60,196,197]
	Liposomal amphotericin B Amphotericin B lipid complex Amphotericin B deoxycholate	B	II <sub>r</sub>	Fungi may be resistant to amphotericin B	[4,198,199]
		C	III	Limited case reports	[200]
		D	II <sub>u</sub>	Fungi often resistant to amphotericin B Breakthrough infections may occur Excessive toxicity	[4,198,199]
	Any echinocandin Any combination therapy	D	III	Intrinsically resistant	[21]
		C	III	Limited reports Combination not better than voriconazole alone	[23,24,63–65,67,68,196]
Salvage treatment Posaconazole	A	II	Overall success rate 50% Breakthrough infections Therapeutic drug monitoring required	[23,61]	
Voriconazole	A	III	Substantial efficacy Therapeutic drug monitoring required	[62]	

QoE, quality of evidence; SoR, strength of recommendation.

**TABLE 6.** Summary of recommendations for *Fusarium* disease and adjunctive treatment

Population	Intention	SoR	QoE	Comment	References
Haematological, cancer and neutropenic patients	Granulocyte transfusion (be cautious if allogeneic HSCT is indicated)	C	III	Limited number of patients who recovered from myelosuppression	[14] [71–73]
Acute leukaemia	Surgical debridement (localized infection)	A	IIc	Successful outcome	[58]
Bone marrow transplant patients	Surgical debridement (localized infection)	A	IIc	Independent protective factor	[59]
Any population	Surgical debridement	A	III	Solitary pulmonary nodules Aggressive surgical debridement of necrotic tissue Independent protective factor	[2,201–205]

HSCT, haematopoietic stem cell transplant; QoE, quality of evidence; SoR, strength of recommendation.

include tap water [76], sinks [77] and other wet areas such as showers and steam baths [75]. For outbreak control, identifying the source of infection is essential (All), see Table 4. There have also been cases where onychomycosis has been the source of a subsequent disseminated infection in an immunocompromised patient [78]. Careful evaluation for onychomycosis and removal of the focus is mandatory in those known to be or likely to become immunocompromised.

## Scedosporiosis

*Scedosporium* spp. are commonly isolated from rural soils, polluted waters, composts and from manure of cattle and fowl. As with *Fusarium*, members of the genus *Scedosporium* are saprophytes that mainly cause opportunistic infections in immunocompromised patients [79]. However, disseminated infections—often with central nervous system involvement—can follow near drowning accidents in previously healthy individuals [80–83]. *Scedosporium* infections are caused mainly by *Scedosporium boydii* (teleomorphic state, *Pseudallescheria boydii*), *Scedosporium apiospermium* (teleomorphic state, *Pseudallescheria apiosperma*), *Scedosporium aurantiacum* and *Scedosporium prolificans*. While *S. aurantiacum* and *S. prolificans* are predominant in hot and arid countries such as Spain and Australia, *S. boydii* and *S. apiosperma* are predominant in temperate areas such as central Europe. In general, all *Scedosporium* spp. are cosmopolitan, being ubiquitously present in the environment. They cause a wide spectrum of infections ranging from classical subcutaneous infections, like mycetoma with spread via the lymphatic system, to disseminated infections with central nervous system involvement [84–86]. These moulds are in particular known for their special neurotropic nature and their high rate of therapeutic failures and relapses [87]. In particular, *S. prolificans* represents a pan-antifungal-resistant species with mortality rates of up to 95% in immunocompromised patients [88]. *Scedosporium prolificans* grows greyish-white, to olive-grey to black and therefore in proper meaning is excluded from the hyalohyphomycetes; for the sake of simplicity and because they phylogenetically belong

to the *Scedosporium* species complex, *S. prolificans* is dealt with herein.

## Clinical Presentation

The clinical spectrum of infection in immunocompetent hosts includes keratitis, endophthalmitis, otitis, sinusitis, central nervous system infections, osteoarticular and soft tissue infections and pneumonia after near drowning [89–95]. In the setting of severe immunosuppression, deep-seated infections can involve any organ with a predilection for skin, sinuses, lungs and central nervous system [6,80,81,84,91,96–106]. In healthy individuals cerebral infection is secondary to contiguous spread from sinuses [107], penetrating trauma [89] or pulmonary infection following near drowning in polluted water [108,109]. In immunocompromised patients including those after lung transplantation, central nervous system infections tend to occur following haematogenous dissemination [80–83,91]. Patients with cystic fibrosis may be either colonized or suffering from lung infection [110–112]. Delayed treatment of brain abscesses due to *P. boydii* is associated with a high mortality rate (>75%) [106,108,113].

## Diagnosis

Few imaging descriptions have been reported and the radiographic findings of pulmonary infections show multiple bilateral patchy nodular condensations, alveolar infiltrates or, most commonly, consolidation without cavitation [114–116]. The rapid and fatal evolution of *S. prolificans* could account for the lack of cavities or crescent signs [117]. Laboratory diagnosis (Table 7) includes conventional methods such as culture, direct microscopy and histopathology (AIII). Histopathological findings of septate, branching, hyaline hyphae are similar to those of aspergillosis, although sometimes annelloconidia (conidia that develop from the extruded end of a conidiophore) may be seen in tissue sections [97,118–120]. Similarly to *Fusarium*, blood cultures may be positive in >50% of

**TABLE 7. Summary of recommendations for diagnosis of *Scedosporium* infections**

Population	Test	SoR	QoE	Comment	References
Any population	Direct microscopy	A	III	Essential investigation	[85]
	Culture (species identification by morphology and physiological characteristics)	A	III	Essential investigation Selective media supplemented with cycloheximide or benomyl (10 mg/L, Sce <sup>-</sup> Sel <sup>+</sup> ) allows growth of <i>Scedosporium</i> over other filamentous fungi from bronchial secretions.	[85,122,123,136,206–210]
	Molecular-based identification methods	C	III	Accurate species assignment is important for guiding clinical management	[121–123,211]
	Histopathology	A	III	Hyaline thin-walled septate hyphae, 2–5 µm wide similar to those seen with aspergillosis and other hyalohyphomycoses Irregular branching	[120,212,213]
	Pan-fungal PCR <sup>a</sup>	C	III	Molecular tests could be used in combination with conventional laboratory tests.	[36–38]
	Multiplex PCR <sup>a</sup>	C	III	Molecular tests could be used in combination with conventional laboratory tests.	[30,31,37,39]
	<i>In situ</i> hybridization	C	III	Low sensitivity Not yet validated	[191,192]
	Species identification (MALDI TOF and PCR)	C	III	Not yet validated	[124,214–219]
	Physiological typing	C	III	In case of an outbreak situation	[220]
	<i>In vitro</i> susceptibility testing	C	III	Gives an overview of drug activity and therefore may support choice of antifungals	[221–223]

MALDI-TOF, matrix-assisted laser desorption ionization time-of-flight mass spectrometry; QoE, quality of evidence; SoR, strength of recommendation.  
<sup>a</sup>Third-party appraisal of results and harmonization of PCR-based techniques are necessary before any clear recommendations can be made regarding clinical utility.

*S. prolificans* infections as a result of its ability to sporulate in tissue allowing haematogenous spread. A range of diagnostic molecular methods have been employed but are not yet validated and should be used only as an adjunct to conventional laboratory tests (CIII).

Isolation of the fungus is important because of the variable susceptibility of these fungi to amphotericin B and other antifungal agents, especially recent triazoles (AIII). Molecular-based methods for identification such as rolling circle amplification on cultures [121], amplified fragment length polymorphism analysis [122], loop-mediated isothermal amplification PCR [123] and semi-automated repetitive sequence--based PCR [124] appear promising, but have yet to be evaluated in the routine clinical setting (CIII). Particularly within the *P. boydii* complex, identification is complicated by low interspecies diversity and high intraspecies variability.

## Therapy

Given the scarcity of data and the potential publication bias, no solid recommendations can be provided. *In vitro* and *in vivo* data show that *P. apiospermum* is resistant to amphotericin B and flucytosine and demonstrates variable susceptibility to itraconazole, voriconazole, posaconazole and micafungin. Voriconazole is the only compound with good activity *in vitro* against *S. aurantiacum* [125], and *S. prolificans* is resistant to caspofungin, azoles and polyenes [48], see Table 1; voriconazole demonstrated the strongest *in vitro* activity [126]. A recent study suggests synergistic activity of the antibacterial agent colistin with voriconazole against *Scedosporium* spp. [127].

The management of infections due to members of the genus *Scedosporium* depends on the underlying condition of the host

and voriconazole represents the first-line treatment (All) [96,99,100,114], see Table 8. Surgical resection remains the key to a successful outcome if the lesions are localized (AIII). The therapeutic outcome is usually poor in the setting of persistent immunosuppression. A combination of interferon- $\gamma$  and antifungal therapy in a patient with chronic granulomatous disease helped to control disseminated infection [128]; however, due to the lack of additional data, no solid recommendations can be provided.

The outcome of *S. prolificans* infection is very poor, because no drug appears to be effective [96,129], see Table 9. Surgical debridement of infected tissue and recovery of immunosuppression appear to be the major means of halting progression of the infection [105,130]. A few reports of successful treatment with voriconazole plus terbinafine have been published [68,91,131–133], we moderately recommend this combination (BII). Also, case series of *S. apiospermum* infections demonstrated efficacy of combinations of azoles and terbinafine [134], sequential azole and terbinafine [135], or voriconazole and caspofungin [136]. The use of miltefosine as an antifungal agent for severe infection with *S. prolificans* needs to be clarified in detail, up to now only one case report is available [111].

Indications for surgical removal of tissue infected with *Fusarium* and *Scedosporium* species are given in Table 10.

## *Paecilomyces* and *Purpureocillium* Infections

Until recently, the genus *Paecilomyces* harboured two known human pathogenic species: *Paecilomyces variotii* and *Paecilomyces lilacinus*. Luangsa-Ard *et al.* [137] revised the genus and the latter species now officially holds the name *Purpureocillium*

**TABLE 8. Summary of recommendations for treatment of *Scedosporium* spp. infections**

Population	Intention	SoR	QoE	Comment	References
Immunocompromised patients	First-line treatment				
	Voriconazole	A	II <sub>r,t</sub>	Therapeutic drug monitoring required Success in 66%	[6,87,96,224–228]
	Itraconazole	D	III	Only one case, failed	[229]
	Any combination	C	III	Unclear whether combination is more effective than either drug alone	[6,196,225,230–233]
	Liposomal amphotericin B	C	III	Variable activity	[96,225]
Near drowning victims	Amphotericin B deoxycholate	D	III	<i>S. apiospermum</i> may be resistant	[225]
	Posaconazole	C	III	Only case reports	[234]
	Voriconazole	A	II	Good penetration into central nervous system	[89,235–239]
	Any combination of antifungals	C	III	Therapeutic drug monitoring	[227,240,241]
	Case reports				[242,243]
Cystic fibrosis patients	First-line therapy				
	Voriconazole	B	III	Therapeutic drug monitoring	[100,102,227,240,244–246]
	Salvage therapy				
	Voriconazole plus caspofungin	C	III		
	Caspofungin plus terbinafine	C	III		
Lung transplantation in cystic fibrosis patients	Posaconazole	C	III		
	Voriconazole	A	III	Surgery if possible Good central nervous system penetration	[236–238]
	Any combination	C	III	Unclear	[247–249]
Cerebral abscess	Granulocyte transfusion combined with antifungals	C	III	Independent protective factor, lack of solid data	[130,250–252]
	Haematopoietic stem cell transplantation				
Neutropenic patients	Chronic granulomatous disease				
	Osteomyelitis and/or soft tissue infections	A	III	Case reports only	[253–257]
Immunocompromised patients	Surgical debridement	A	III	Surgical drainage and debridement of necrotic tissues is essential to the success of therapy	[96,258,259]

QoE, quality of evidence; SoR, strength of recommendation.

**TABLE 9. Summary of recommendations for treatment of *Scedosporium prolificans* infection**

Population	Intention	SoR	QoE	Comment	References
Immunocompromised patients	Voriconazole	A	II <sub>c,r</sub>	40% survival Therapeutic drug monitoring	[96,260,261]
	Voriconazole plus terbinafine	B	III	Case reports, 50% survival	[68,91,131,133,262–269]
	Itraconazole	C	III	Case reports, 15% survival	[97,129,263,270]
	Amphotericin B deoxycholate	D	III	Case reports, 4% survival	[118,271–276]
	Any combination	C	III	Case reports only	[86,119,130,277–281]
	Fluconazole	D	III	Case reports	[98,263,275]
	Voriconazole or Posaconazole plus terbinafine (plus granulocyte colony-stimulating factor)	B	III	Case reports	[68,131,269]
Dissemination	Voriconazole	B	II		[261]
	Voriconazole plus terbinafine or posaconazole	B	III	Review of case series	[68,261,267,282]
Skin and subcutaneous infections	Surgery	A	III		[119,283]
	Voriconazole	B	II	91% success rate	[261]
Cerebral abscess	Surgery plus antifungals	A	III	Improved outcome with voriconazole-itraconazole failed	[251,284]
	Osteomyelitis/septic arthritis				
Osteomyelitis/septic arthritis	Voriconazole	B	III	Extensive surgical debridement enhances recovery rates; one case even without antifungals	[261,285]
	Fluconazole	D	III		[275]
	Combination of voriconazole and terbinafine or caspofungin	B	III		[111,132,286]
	Surgery	A	III		[111,119,251,275,282,285,286]

QoE, quality of evidence; SoR, strength of recommendation.

*lilacinum*. Both representatives are rarely pathogenic in humans and are isolated from soil and decaying plant material [138–141]. The definitive diagnosis requires isolation of the pathogens from infected sites. Disseminated infection, pneumonia, cellulitis, fungaemia and pyelonephritis have been reported in immunosuppressed patients [138–140,142–144], and cutaneous infection in an immunocompetent patient [145]. The portal of entry involves breakdown of skin or mucous membranes and inhalation. Infections associated with contamination of fluids and air conditioning systems have been reported [141,146]. The optimal antifungal treatment has not

been established. Clinical management consists of antifungal treatment (AIII), surgery (BIII) or a combination of both, see Table 11. Usually, *in vitro* *P. lilacinum* are highly resistant to amphotericin B but susceptible to azoles and *P. variotii* is usually amphotericin B susceptible.

### Acronium Infections

*Acronium* species are ubiquitous in the environment and typically found in soil [8,147]. Recently, Summerbell et al. [148]

**TABLE 10.** Indications for surgical removal of tissue infected with *Fusarium* and *Scedosporium* species

Surgical intervention	SoR	Qoe	References
Haemoptysis from a single cavitary lung lesion (always perform a computerized chest scan to search for other lesions)	A	III	[2,5,57–59]
Progressive cavitary lung lesion (always perform a computerized chest scan to search for other lesions)	A	III	[2,5,57–59]
Infiltration into the pericardium, great vessels, bone or thoracic soft tissue	A	III	[2,5,57–59]
Osteomyelitis, septic arthritis	A	IIr	[2,46,47,155–159,257,287]
Resection of infected/colonized tissue before commencing immunosuppressive agents to prevent dissemination in case of cytotoxic therapy	A	III	[2]

QoE, quality of evidence; SoR, strength of recommendation.

have reviewed the genus and some species of clinical interest have been transferred to the genera *Sarocladium* and *Gliomastix*. Species that have been reported to cause infections in humans are *Acremonium alabamensis*, *Acremonium kiliense* (currently *Sarocladium kiliense*), *Acremonium roseogriseum* (currently *Gliomastix roseogrisea*), *Acremonium strictum* (currently *Sarocladium strictum*), *Acremonium potronii* and *Acremonium recifei*. *Acremonium falciforme* is nowadays *Fusarium falciforme*, a member of the *Fusarium solani* species complex. Members of this genus are recognized as aetiological agents of nail and corneal infections, mycetoma, peritonitis and dialysis fistula infection, osteomyelitis, meningitis following spinal anaesthesia in a healthy person, cerebritis in an intravenous drug abuser, endocarditis in a prosthetic valve operation, and a pulmonary infection in a child [147,149–154]. Occasionally, deep *Acremonium* infections have been reported in patients with serious underlying diseases [8].

The definitive diagnosis requires isolation of *Acremonium* from infected sites (All) and blood cultures may become positive only once the disease has progressed. Members of the

genus *Acremonium* grow slowly; therefore, culture plates need to be incubated for at least 2 weeks for detection. *In vitro*, *Acremonium* spp. may be susceptible to amphotericin B and the azoles [8,155,156], Table 1. However, a recent study demonstrated high MICs for all agents tested, except for terbinafine [157].

Clinical data on treatment of infections by *Acremonium* spp. are limited to case reports, Table 12. Based on the clinical outcomes observed we recommend treatment with voriconazole (All), amphotericin B (BII) and posaconazole (BII) [153,158–160]. Surgery and catheter removal have also been reported as part of the successful management of these infections (CIII) [153,161]; however, a standard therapy is lacking.

### Scopulariopsis Infections

Among the human-pathogenic fungi, the genus *Scopulariopsis* (teleomorphs in *Microascus* species) is phylogenetically close to *Scedosporium*. *Scopulariopsis* species are *in vitro* usually quite resistant to antifungal agents including itraconazole, fluconazole and flucytosine and variously susceptible to amphotericin B, miconazole and ketoconazole [162]. Oral itraconazole and terbinafine and topical natamycin were reportedly effective in treating onychomycosis due to these organisms [163,164].

*Scopulariopsis brevicaulis* rarely causes human infection and is the most common species of the genus in clinical specimens. The definitive diagnosis requires isolation of *Scopulariopsis* from infected sites (All). In otherwise healthy individuals this organism has been reported to cause onychomycosis [163,164], keratitis [165], otomycosis [166], invasive sinusitis [167] and prosthetic valve endocarditis [168,169] as well as

**TABLE 11.** Summary of recommendations for treatment of *Paecilomyces variotii* and *Purpureocillium lilacinum* infections

Population	Intention	SoR	QoE	Comment	References
Immunocompromised patients	Surgery	B	III	Subcutaneous skin infections cure faster with surgery	[288–293]
	Amphotericin B deoxycholate <sup>a</sup>	A	III	<i>P. variotii</i> , deep infections	[294]
	Amphotericin B deoxycholate <sup>a</sup> and itraconazole	C	III	75% cure for <i>P. variotii</i>	[142,295,296]
	Ketoconazole	C	III	<sup>a</sup> the use of amphotericin B-lipid-preparation is recommended	[297,298]
	Amphotericin B deoxycholate <sup>a</sup> and 5-Fluorocytosine	C	III	<i>P. lilacinum</i> ; case report: cure	[292]
Any population (mixed patients)	Second-line treatment with itraconazole	C	III	Obsolete drug when second-generation azoles are available	[295]
	Amphotericin B deoxycholate and Itraconazole	C	III	<i>P. variotii</i> ; case report: cure	[299]
	Amphotericin B deoxycholate <sup>a</sup>	B	IIr	<i>P. lilacinum</i> ; case report: cure	[7,300,301]
	Voriconazole			Cases and case series.	
	Posaconazole			<i>P. lilacinum</i> and <i>P. variotii</i> most frequently associated with cutaneous disease.	
				<i>P. lilacinum</i> usually susceptible to voriconazole and posaconazole, but amphotericin B resistant	
				<sup>a</sup> the use of amphotericin B-lipid-preparation is recommended	

QoE, quality of evidence; SoR, strength of recommendation.



**TABLE 12. Summary of recommendations for treatment of *Acremonium* species infection**

Population	Intention	SoR	QoE	Comment	References
Mycetoma	Amphotericin B <sup>a</sup> deoxycholate plus surgery			Few cases only	[150,302,303]
	Amphotericin B <sup>a</sup> deoxycholate plus itraconazole or voriconazole	B	II	<sup>a</sup> the use of amphotericin-lipid-preparation is recommended	
	Terbinafine <sup>b</sup>			<sup>b</sup> Obsolete drug when second-generation azoles are available because of side effects [304]	
	Posaconazole				
Disseminated infections	Surgery	A	III	Surgical intervention is highly recommended	[147,149,151,152]
	Amphotericin B deoxycholate	C	IIc	Recommendations are inconsistent, few cases	
	Nystatin				
	Posaconazole				
	Voriconazole <sup>a</sup>	A	III	<sup>a</sup> guided by susceptibility testing	
	Antifungals and surgery	C	III	Early surgical intervention recommended with excision or aggressive debridement	

QoE, quality of evidence; SoR, strength of recommendation.

invasive infections in patients with cystic fibrosis [170]. Invasive infections have been reported among immunocompromised patients [171]. These infections involve mainly soft tissues and lungs [172–179] and are associated with a high mortality. The optimal antifungal treatment has not been established. Invasive infections may require surgical and medical treatment (AIII); infections are frequently fatal [172,173,180], Table 13.

### Authors Contributions

Anna Maria Tortorano and Cornelia Lass-Flörl chaired the guideline group with Malcolm Richardson, Emmanuel Roilides, Patricia Munoz and Paul Verweij representing as subgroup coordinators. All contributed to systematic review, interpretation and writing, organization of teleconferences and voting. Anne van Diepeningen, Morena Caira, Elisabeth Johnson, Joseph Meletiadis, Zoi-Dorothea Pana, Michaela Lackner and Tomas Freiburger are experts on medical mycology and contributed to systematic review, interpretation and writing.

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Lortholary, Jacques F. Meis, Andrew J. Ullmann and George Petrikos contributed to review and interpretation.

No other experts have been asked to externally review this guideline.

### Transparency Declarations

Competing interests of guideline development group members have been recorded by Lass-Flörl Cornelia displaying all relevant issues to the whole group. Members were asked to provide the ICMJE Form for Disclosure of Potential Conflicts of Interest, which is stored electronically. AT has received research grants from Astellas and MSD, and received lecture honoraria from Astellas, Gilead and MSD. MR has received payment for development of educational presentations from Pfizer, received royalties from Blackwell Publishing, received travel support from Astellas, is a consultant to Gilead and MSD, and received lecture honoraria from Astellas and Pfizer. ER has received research grants from Enzon, Gilead, Pfizer and Schering, is a consultant to Astellas, Gilead, Merck, Pfizer and Schering, and received lecture honoraria from Astellas, Aventis, Cephalon, Gilead, Merck, Pfizer, Schering and Wyeth. AvD has no conflicts of interest to declare. MoCa is a consultant to Gilead and Merck/Schering, is a board member of Merck, received payment for the development of educational presentations from Gilead and Merck, and received lecture honoraria from Astellas, Gilead, Merck and Pfizer. PM

**TABLE 13. Summary of recommendations for treatment of *Scopulariopsis* species infections**

Population	Intention	SoR	QoE	Comment	References
Any population	Itraconazole	C	IIc	Cured, single case	[172]
	Liposomal amphotericin B	C	III	Single case, died	[173]
	Any antifungal and surgery	A	III	Invasive infections may require surgical and medical treatment Infections are frequently fatal	[180]

QoE, quality of evidence; SoR, strength of recommendation.

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## 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.

**Keywords:** Clinical presentation, diagnosis, guideline, mycosis, phaeohyphomycosis, prophylaxis, treatment

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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.agreertrust.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 I. 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 I.** 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**

		In vitro susceptibility (MIC range, mg/L) <sup>a</sup>									
Aetiological agents [references]	Most common described infections	Species	AMB	ITC	VRC	POS	ISA	FC	FLU	ECHINO	TERB
<i>Alternaria</i> [38,55,167]	Cutaneous and subcutaneous infection, sinusitis, keratitis, ABPM, disseminated disease	<i>A. alternata</i> <i>A. infectoria</i>	0.25–1.0 0.25–1.0	0.25–1.0 0.25–1.0	1.0–4.0 1.0–4.0	0.12–0.50 0.06–0.12	–	8.0–>64.0 16.0–>64.0	8.0–32.0 16.0–32.0	0.50–1.0 1.0	>16.0 >8.0
<i>Acrophialophora</i> [183–185]	Brain abscess, ocular and lung infection	<i>Alternaria</i> spp.	0.03–4.0	1.0	2.0	1.0	–	16.0–>64.0	16.0–>64.0	>16.0	16.0
<i>Aureobasidium</i> [211]	Brain abscess, ocular and lung infection	<i>A. fusispora</i>	0.25–4.0	0.06–0.25	0.12–2.0	0.125–2.0	–	>64.0	8.0–32.0	–	–
<i>Bipolaris</i> [213,242]	Cutaneous and subcutaneous infection, ocular infection, rare deep infection, fungaemia	<i>A. pullulans</i>	0.01–16.0	0.01–2.0	0.01–16.0	0.01–4.0	–	–	4.0–64.0	0.06–8.0	–
<i>Chaetomium</i> [143,257,258]	Cutaneous and subcutaneous infection, pneumonia, brain abscess	<i>B. hawaiiensis</i> <i>B. australiensis</i>	0.12–0.25 0.06–0.12	0.03–0.5 0.25–0.5	0.25–2.0 0.05–1.0	0.03–0.5 0.06	–	>64.0 >64.0	2.0–32.0 8.0–16.0	0.50–1.0 1.0	–
<i>Cladophialophora</i> [87,123]	Cutaneous and subcutaneous infection, brain abscess	<i>B. spicifera</i> <i>C. globosum</i>	0.03–4.0 0.50–8.0	0.03–8.0 0.03–0.50	0.25–4.0 0.50	0.03–2.0 –	–	>64.0 32.0–>64.0	4.0–>64.0 >64.0	0.25–2.0 –	–
<i>Curvularia</i> [277,284]	Cutaneous and subcutaneous infection, keratitis, ABPM, peritonitis, cerebral infection, disseminated disease	<i>C. perflouidum</i> <i>C. carlinii</i> <i>C. banitana</i>	0.25 0.5–8.0 0.12–2.0	0.01–0.06 0.01–0.12 0.01–0.25	0.01–16.0 0.12–4.0 0.12–4.0	0.06–0.12 0.01–0.06 0.01–0.25	0.01–1.0 0.01–1.0 0.01–1.0	–	4.0–64.0 16.0–64.0 2.0–16.0	8.0–>16.0 0.25–4.0 0.50–>16.0	0.01–1.0 – –
<i>Exophiala</i> [334–338]	Cutaneous and subcutaneous infection, pneumonia, brain abscess, disseminated disease	<i>C. senegalensis</i> <i>C. lunata</i> <i>Curvularia</i> spp.	0.06–0.50 0.12–>16.0 0.06–>16.0	0.06–1.0 0.12–>16.0 0.03–>16.0	0.12–4.0 0.25–1.0 0.15–>16.0	0.03–0.50 0.03–4.0 0.03–4.0	–	>64.0 64.0–>64.0 1.0–>64.0	2.0–64.0 8.0–32.0 2.0–32.0	0.50–>16.0 0.06–8.0 0.25–8.00	– – 0.03–2.0
<i>Eserohilum</i> [340,375]	Cutaneous and subcutaneous infection, keratitis, meningitis and spinal infection, arthritis, disseminated disease	<i>E. jeanselmei</i> <i>E. dermatitidis</i> <i>E. spinifera</i> <i>E. rostratum</i>	0.01–0.50 0.25–4.0 0.03–0.12	0.03–0.5 0.01–0.12 0.03–0.12	0.06–1.0 0.03–1.0 0.03–1.0	0.03–0.25 0.01–0.06 0.01–0.06 2.0	–	0.12–>64.0 –	16.0–>64.0 –	1.0–8.0 0.25 >16.0	0.03–1.0 – 0.50–2.0
<i>Fonsecaea</i> [83,378]	Cutaneous and subcutaneous infections brain abscess	<i>F. monophora</i> <i>F. pedrosoi</i>	0.50–2.0 0.50–2.0	0.03–0.25 0.03–0.25	0.12–1.0 0.12–0.50	0.01–0.06 0.03–0.06	0.06–1.0 0.06–0.25	–	8.0–64.0 8.0–32.0	1.0–4.0 2.0–4.0	– 0.06–0.25
<i>Hortaea</i> [396]	Tinea nigra, very rare deep mycosis	<i>Fonsecaea</i> 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	–
<i>Neoscydium</i> [103,400,401,409]	Cutaneous infections and onychomycosis, very rare deep mycosis	<i>H. werneckii</i> <i>N. dimidiatum</i>	0.12–2.0 0.06–1.0	0.03–0.50 0.03–>16.0	0.06–0.25 0.03–4	0.01–0.12 0.06–32	–	–	8.0–64.0 0.25–32.0	1.0–8.0 0.06–>16.0	– 0.06–2.0
<i>Ochroconis</i> [434,437]	Subcutaneous infection, disseminated infection	<i>O. gallapova</i>	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
<i>Phaeoacremonium</i> [445,446]	Pneumonia, brain abscess, disseminated disease	<i>O. tshawytschae</i> <i>P. parasiticum</i>	4.0 2.0	0.50 0.12–8.0	0.12 0.06–0.25	–	–	>64.0 8.0	>64.0 8.0	0.25 >16.0	– 0.50–2.0
<i>Phoma</i> [457,459]	Cutaneous and subcutaneous infection, ocular infection, rare deep mycosis	<i>Phoma</i> spp.	0.5–1.0	0.25–8.0	0.25–8.0	–	–	–	–	–	–
<i>Pyrenochaeta</i> [462]	Cutaneous and subcutaneous infection, keratitis	<i>P. ramerei</i>	4.0	0.50	4.0	0.50	0.12	–	>64.0	8.0	–
<i>Rhinoctadiella</i> [130,478,480,485]	Brain abscess	<i>R. mackenziei</i> <i>R. aquaspersa</i>	1.0–>16.0 1.0–2.0	0.01–0.25 0.06–0.12	0.01–2.0 2.0	0.01–0.25 0.06–0.12	–	4.0–16.0	16.0–64.0 32.0–64.0	1.0–8.0 8.0	– –
<i>Varanaea</i> [494]	Cutaneous and subcutaneous infection, disseminated disease	<i>V. baryosa</i>	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, fluconazole; FLU, fluconazole; ECHINO, echinocandins; TERB, terbinafine; ABPM, allergic bronchopulmonary mycosis.  
<sup>a</sup>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 [9–13,23,27]	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
Cerebral abscess and other localized infections [9–13,23,27]	Definitive diagnosis and species identification	As above and specimen taken at the sources of infection	A	III	Conventional isolation media for species identification (BHI for some strains)
Disseminated infections [9–13]	Definitive diagnosis and species identification	As above and specimen taken at the sources of infection	A	III	<i>Candida</i> / <i>Aspergillus</i> / <i>Trichosporon</i> and <i>Rhinodactyla mackenziei</i> (most common species in cerebral abscess)
All cases [9–13]	To know local species distribution	As above and blood cultures and other specimens when possible	A	III	None
Cases by isolates difficult to identify and sibling/cryptic species [14]	Definitive species identification	Periodical epidemiological surveys	A	III	None
All cases with deep infections [15–17]	To detect high MIC values <i>in vitro</i> and recommend the best therapy	Molecular identification (DNA target sequencing)	B	III	May be essential investigation for some rare species
All cases [18,19]	To detect local resistance <i>in vitro</i>	MIC determination	A	III	Use reference procedure
All cases with deep infection [20–22]	Detect infection	Periodical epidemiological MIC determination surveys	A	III	Use reference procedures
All cases with deep infection [9]	Detect infection	$\beta$ -D-glucan quantification	C	III	Panfungal detection. Insufficient data
Infections by <i>F. pedrosoi</i> and <i>C. carrionii</i> [12]	Detect infection	<i>Aspergillus</i> galactomannan quantification	D	III	Cross-reactivity in some cases
All cases [23,24]	Detect infection in tissues	In-house ELISA techniques	C	III	Not validated
All cases [12,25]	Detect infection in blood, serum or other sterile fluids	PCR-based methods	C	III	Insufficient data
		PCR-based methods	C	III	No data

BHI, brain–heart infusion; H&amp;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 <sup>a</sup>	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
	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), 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 <sup>b</sup> 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
	Cure	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
Mycetoma	Cure or reduce infections in advanced cases	Voriconazole (400 mg), posaconazole (800 mg) or terbinafine (250 mg) PLUS surgery [66–69]	A	III	Dramatic results of uncontrolled few cases
	As above	Ketoconazole (400 mg) [59,63,64]	D	III	Side effects
	As above	Amphotericin B (1 mg/kg) [12]	B	III	Impractical given the therapy duration
Refractory mycetoma	Reduce lesions	Combination antifungal therapy (azoles PLUS terbinafine or flucytosine) [65,67]	B	III	Descriptive case studies
	Cure or reduced infections in advanced cases	Itraconazole (400 mg) for months to years PLUS surgery [72–74,76]	A	II	Surgery when possible
Chromoblastomycosis	Cure or reduced infections in advanced cases	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
	As above	Combination antifungal therapy (itraconazole plus terbinafine) [72,74,75,82–84]	B	III	Descriptive case studies
Refractory chromoblastomycosis	Reduce lesions	Natamycin alone or PLUS other topical agents [89,90,92–94]	A	II	Surgery when possible
	Cure	Topical azoles alone [95–97]	B	III	Multiple time series
	Cure	Oral triazoles (conventional doses) PLUS surgery if needed [89,91–93]	B	III	Descriptive case studies
Pulmonary infection	Cure	Intrastromal voriconazole injection [96,98]	C	III	Descriptive case studies
	Cure or control of infection	Systemic liposomal amphotericin B (3 mg/kg), itraconazole (400 mg), voriconazole (400 mg) or posaconazole (800 mg) [12,102–107]	B	III	Insufficient data
	Cure	Surgery [12,99,108]	B	III	Descriptive case studies in immunocompromised or with underlying pulmonary disease (few cases for posaconazole)
Solitary pulmonary nodule in immunocompetent	Cure	Complete excision (when possible) [109,112,117–120]	A	II	Dramatic results of uncontrolled cases
	Cure	Voriconazole (400 mg) or posaconazole (800 mg) [121–128]	C	II	Multiple time series and animal model and <i>in vitro</i> data
	Cure when surgery is not possible	Amphotericin B (several doses) [122–124,129]	D	III	Descriptive case studies, failures and results from animal models and <i>in vitro</i> data
Cerebral abscess	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)
	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
Bone and joint infections	Cure	Catheter removal PLUS systemic antifungal therapy [133–137]	A	II	Dramatic results of uncontrolled cases removing the catheter
	Cure (associated with peritoneal dialysis)	Liposomal amphotericin B (3 mg/kg), itraconazole (400 mg), voriconazole (400 mg), or posaconazole (800 mg) [138,141–147]	C	III	Descriptive case studies
Disseminated infection	Cure or infection control	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 <i>Scedosporium</i> infections)
	As above	Surgery PLUS systemic steroids [151–154]	A	II	Prospective, randomized, placebo-controlled trial (24 patients only) and reviews
	Remove the mucin and reduce symptoms	Add itraconazole (several doses) [152,153,155]	C	III	Descriptive case studies
Allergic sinusitis	Reduce requirements of steroids	Add itraconazole (several doses) or voriconazole (400 mg) [156–158]	C	III	Descriptive case studies
	Reduce symptoms	Surgery [159]	A	II	Dramatic results of uncontrolled cases
Refractory allergic sinusitis	Cure	Liposomal amphotericin B (3 mg/kg) 2 weeks followed by voriconazole (400 mg) 3 months [159]	C	III	Insufficient evidence
	Cure	Steroids [12,151,161,162]	B	III	Descriptive case studies
Invasive sinusitis	Reduce symptoms	Add itraconazole (several doses) [160,163]	D	III	Expert opinion
	Reduce symptoms				

QoE, quality of evidence; SoR, strength of recommendation.

<sup>a</sup>The population to whom the recommendations are meant to apply is any patient suffering from phaeohyphomycosis.

<sup>b</sup>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 All) [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 All) [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 All) 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 fuispora* is of clinical interest. *Acrophialophora fuispora* 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 fuispora* 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 mansonii*, 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 aerea*, *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 salt pans [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 keratolytic 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 dermatophytosis [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 *Natrassia mangiferae* (formerly *Hendersonula toruloidea*) [405]. However, molecular studies have demonstrated that they are two different species, and *Natrassia 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 barrel-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  $\beta$ -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 krajdienii*, *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,  $\beta$ -tubulin and chitin synthase I 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 *Rhinoctadiella 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 *Rhinoctadiella 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

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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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AnC has no conflicts of interest to declare. JaM has received research grants from Astellas, Merck and MSD, is a consultant to Astellas, Basilea, Merck and MSD, received travel support from Astellas, and received lecture honoraria from Merck. JoG has no conflicts of interest to declare. SdH has no conflicts of interest to declare. SK has no conflicts of interest to declare.

MCA has received research grants from Astellas, Gilead, Merck/Schering and Pfizer, is a consultant to Merck, Gilead, Pfizer, received travel support from Astellas, Merck/Schering and Pfizer and received lecture honoraria from Astellas, Gilead, Merck/Schering, and Pfizer. SAA has received research grants from Pfizer, is a consultant to Pfizer, and received lecture honoraria from Merck, and Pfizer. MA has received research grants from Gilead, Merck and Pfizer, is a consultant to Gilead, Merck and Pfizer, has received travel support from Merck, Gilead, and Pfizer, and received lecture honoraria from Gilead, Merck, and Pfizer. TB has received royalties from Elsevier. MoC has no conflicts of interest to declare. JeG has received research grants from Basilea, BioMerieux, Astellas, Pfizer, Fundacion Mutua Madrilenia, Fondo de Investigacion Sanitaria (FIS), and received lecture honoraria from Astellas, Pfizer, Gilead, MSD, and Hickma Pharma. ArC has no conflict of interest to declare. ED has received research grants from BioRad, Gilead and Pfizer, is a consultant to Astellas and Innothera, received travel support from Merck/Schering, Astellas and Gilead, and received lecture honoraria from Gilead and Merck/Schering. AvD has no conflict of interest to declare. TF is a consultant to Hutman AG. AHG has received research grants from Gilead and Merck Sharp & Dohme, is a consultant to Astellas, Gilead, Merck Sharp & Dohme and Schering-Plough, and received lecture honoraria from Astellas, Gilead, Merck Sharp & Dohme, Schering-Plough, and Zeneus/Cephalon. WH has received research grants from Pfizer, Astellas, Gilead and F2G, is a consultant to Pfizer, Astellas, Gilead and F2G, and received lecture honoraria from Astellas, Gilead, Merck/Schering, and Pfizer. EJ is a consultant to Astellas, Gilead, Merck/Schering and Pfizer, received travel support from Astellas, Merck/Schering and Pfizer, received payment for development of educational presentations from Astellas, Merck/Schering and Pfizer, and received lecture honoraria from Astellas, Gilead, Merck/Schering, and Pfizer. ML has no conflicts of interest to declare. KL has received research grants from Gilead, MSD and Pfizer, has given expert testimony for Merck/Schering and Pfizer, is a consultant to Gilead, Merck/Schering and Pfizer, received travel support from MSD, Pfizer and Gilead and received lecture honoraria from Gilead, Merck/Schering, and Pfizer. FL has received research grants from Gilead, received travel support from Gilead, MSD and Schering, and received lecture honoraria from Gilead. CLF has received research grants from Astellas, Gilead, Pfizer, Schering-Plough and MSD, is a consultant to Gilead, MSD, Pfizer and Schering-Plough, received payment for development of educational presentations from Pfizer, received travel support from Gilead, MSD, Pfizer, Astellas and Schering-Plough, and received lecture honoraria from Astellas, Gilead, Merck/Schering, and Pfizer. OL is a consultant

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# ESCMID<sup>†</sup> and ECMM<sup>‡</sup> joint clinical guidelines for the diagnosis and management of rare invasive yeast infections

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## Abstract

The mortality associated with invasive fungal infections remains high with that involving rare yeast pathogens other than *Candida* being no exception. This is in part due to the severe underlying conditions typically predisposing patients to these healthcare-related infections (most often severe neutropenia in patients with haematological malignancies), and in part due to the often challenging intrinsic susceptibility pattern of the pathogens that potentially leads to delayed appropriate antifungal treatment. A panel of experts of the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) Fungal Infection Study Group (EFISG) and the European Confederation of Medical Mycology (ECMM) undertook a data review and compiled guidelines for the diagnostic tests and procedures for detection and management of rare invasive yeast infections. The rare yeast pathogens were defined and limited to the following genera/species: *Cryptococcus adeliensis*, *Cryptococcus albidus*, *Cryptococcus curvatus*, *Cryptococcus flavescens*, *Cryptococcus laurentii* and *Cryptococcus uniguttulatus* (often published under the name *Filobasidium uniguttulatum*), *Malassezia furfur*, *Malassezia globosa*, *Malassezia pachydermatis* and *Malassezia restricta*, *Pseudozyma* spp., *Rhodotorula glutinis*, *Rhodotorula minuta* and *Rhodotorula mucilaginosa*, *Sporobolomyces* spp., *Trichosporon asahii*, *Trichosporon asteroides*, *Trichosporon dermatis*, *Trichosporon inkin*, *Trichosporon jirovecii*, *Trichosporon loubieri*, *Trichosporon mucoides* and *Trichosporon mycotoxinivorans* and ascomycetous ones: *Geotrichum candidum*, *Kodamaea ohmeri*, *Saccharomyces cerevisiae* (incl. *S. boulardii*) and *Saprochaete capitatae* (*Magnusiomyces* (*Blastoschizomyces*) *capitatus* formerly named *Trichosporon capitatum* or *Geotrichum* (*Dipodascus*) *capitatum*) and *Saprochaete clavata*. Recommendations about the microbiological investigation and detection of invasive infection were made and current knowledge on the most appropriate antifungal and supportive treatment was reviewed. In addition, remarks about antifungal susceptibility testing were made.

**Keywords:** Clinical guideline, *cryptococcus*, *Geotrichum*, *Kodamaea*, *Malassezia*, *Pseudozyma*, *Rhodotorula*, *Saccharomyces*, *Saprochaete*, *Sporobolomyces*, *Trichosporon*

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## Introduction

In 2012 the first official European Society for Clinical Microbiology and Infectious Diseases (ESCMID) guideline on the diagnosis and treatment of a fungal infection was published [1–6]. Mucosal and invasive candidosis were covered and a comprehensive consensus guideline was developed with the participation of many experts from the ESCMID Fungal Infection Study Group (EFISG) representing many European countries. Before publication the recommendations were presented for discussion at a European Congress for Clinical Microbiology and Infectious Diseases (ECCMID) workshop and the subsequent manuscripts underwent peer-review before publication in the ESCMID journal, *Clinical Microbiology and Infection*.

Following the same rigorous procedure, EFISG continued the ESCMID guideline development process—this time in collaboration with the European Confederation of Medical Mycology (ECMM) and focusing on rare invasive fungal infections. The definition of such pathogens is somewhat pragmatic but yeasts other than *Candida*, mucorales, hyalohyphomycetous and dematiaceous fungi that are not common causes of invasive infections were included. This guideline presents the diagnostic and management guideline for ‘rare invasive yeast infections’ including several basidiomycetous yeasts: *Cryptococcus adeliensis*, *Cryptococcus albidus*, *Cryptococcus curvatus*, *Cryptococcus flavescens*, *Cryptococcus laurentii* and *Cryptococcus uniguttulatus* (often published under the name *Filobasidium uniguttulatum*), *Malassezia furfur*, *Malassezia globosa*, *Malassezia pachydermatis* and *Malassezia restricta*, *Pseudozyma* spp., *Rhodotorula glutinis*, *Rhodotorula minuta* and *Rhodotorula mucilaginosa*, *Sporobolomyces* spp., *Trichosporon asahii*, *Trichosporon asteroides*, *Trichosporon dermatis*, *Trichosporon inkin*, *Trichosporon jirovecii*, *Trichosporon loubieri*, *Trichosporon mucoides* and *Trichosporon mycotoxinivorans* and ascomycetous ones: *Geotrichum candidum*, *Kodamaea ohmeri*, *Saccharomyces cerevisiae* (incl. *S. boulardii*) and *Saprochaete capitatae* (*Magnusiomyces* (*Blastoschizomyces*) *capitatus* formerly named *Trichosporon capitatum* or *Geotrichum* (*Dipodascus*) *capitatum*) and *Saprochaete clavata*.

The selection of organisms has been based on the following criteria: (i) species were only included if they were documented as a cause of human invasive infections and (ii) rare *Candida* species were excluded because we anticipate that readers would probably refer to the ESCMID *Candida* guidelines rather than a rare invasive yeast infection guideline concerning species like *Candida palmiophila* etc. although such species fulfil the term of being a rare cause of invasive infections. The species not considered being documented as

cause of invasive human disease included *Cryptococcus albidosimilis*, *Cryptococcus diffluens*, *Cryptococcus humicola* and *Cryptococcus uzbekistanensis*, *Trichosporon* spp. others than those mentioned above, *Blastobotrys proliferans*, *Millerozyma farinosa*, *Ogataea polymorpha* and *Guehomyces pullulans*. Finally, the guideline was limited to true yeasts and hence the unicellular algae *Prototheca wickerhamii* and *Prototheca zopfii* var. *zopfii* were excluded although we realize they have been misidentified as yeasts on occasion.

For the uncommon *Candida* species we refer the reader to the general recommendations regarding diagnosis and treatment as described in the ESCMID *Candida* guideline [1–6]. However, as some of these species are characterized by unique intrinsic susceptibility patterns, which are not specifically addressed in the *Candida* guidelines, a table summarizing this information has been elaborated and included here (Table 1, [7–19]). This table also includes names used in the anamorphic and teleomorphic states, despite this distinction recently being made superfluous [20].

General recommendations regarding collection, transport and storage of clinical specimens, direct examination, isolation and identification procedures, which are valid for all yeast-associated human infections, can be found in appropriate textbooks (e.g. Barnett et al. [21]) and are not mentioned here. Only specific features regarding genus identifications for the specific yeasts discussed herein were considered. The methods to evaluate the quality of evidence and to reach consensus recommendations were described previously [1]. Strength of recommendations’ quality of evidence was graded according to the criteria outlined in Table 2.

## Rare Invasive Yeast Infections

It is important to underscore that the fungal organisms covered in this guideline are not rare *per se*. A number of the ‘rare yeasts’ are encountered as frequent colonizers of human skin, mucosal surfaces, in food items or in the environment. In the normal host, infections are typically limited to various superficial infections like pityriasis versicolor, white piedra and occasionally onychomycosis, the management of which are dealt with in dermatology guidelines [22–25]. However, in the immunosuppressed or otherwise compromised host, invasive infections may occur, some being related to the presence of a central venous catheter (CVC) and a few reported as nosocomial clusters that require molecular approaches to be properly documented. As predicted from their low pathogenicity, invasive infections are still reported at low numbers in severely immunocompromised hosts (Table 3) [26–30]. For example, these organisms together constituted 1.1% of the

**TABLE 1.** Summary of rare *Candida* species that have been associated with human infection (by anamorphic and teleomorphic name). Remarks that may be relevant in the clinical context are included. References are kept to a minimum as these species are not the topic of this guideline

Anamorphic state	Teleomorphic state	Specific comment relevant in clinical context
<i>C. africana</i>	Not described	Closely related to <i>C. albicans</i> . Intrinsic susceptibility pattern as for this species. Probably less pathogenic than <i>C. albicans</i> and almost exclusively found in female genital tract specimens [7]
<i>C. auris</i>	Not described	Related to <i>C. haemulonii</i> . Fluconazole MICs higher than for <i>C. albicans</i> [8]
<i>C. bracarensis</i>	Not described	Closely related to <i>C. glabrata</i> . Susceptibility pattern as for <i>C. glabrata</i> (azole MICs elevated compared with <i>C. albicans</i> ) [9]
<i>C. ciferrii</i>	<i>Trichomonascus ciferrii</i>	Clinical significance uncertain. Inherent resistance to several antifungal compounds described [10]
<i>C. dubliniensis</i>	Not described	Closely related to <i>C. albicans</i> . Intrinsic susceptibility pattern as for this species. However, potential for acquired resistance to fluconazole appears to be greater than for <i>C. albicans</i> [11]
<i>C. fabianii</i>	<i>Cyberlindnera fabianii</i>	Clinical significance uncertain. Fluconazole MICs higher than for <i>C. albicans</i> [12]
<i>C. famata</i>	<i>Debaromyces hansenii</i>	This species has been reported as an infrequent cause of fungaemia. However, recent data questions if this species is actually human pathogenic (lack of growth at 37°C and no cases confirmed by sequencing [13])
<i>C. guilliermondii</i>	<i>Meyerozyma guilliermondii</i>	Closely related to <i>C. fermentati</i> and <i>C. palmiophila</i> . High echinocandin and azole MICs [13]
<i>C. haemulonii</i> (incl. <i>C. duobushaemulonii</i> )	Not described	Emerging evidence suggests that it may be a human pathogen related to superficial infections and central venous catheter-related fungaemia, particularly in Brazil, the Caribbean and Asian regions. Elevated azole and amphotericin MICs are reported. Related to <i>C. auris</i> [14]
<i>C. hellenica</i>	<i>Zygoascus meyeriae</i>	Fungaemia and respiratory infection has been reported. Decreased susceptibility to fluconazole, itraconazole, caspofungin, susceptible to voriconazole [15]
<i>C. inconspicua</i>	Not described	Closely related to <i>C. norvegensis</i> . Susceptibility pattern similar to <i>C. krusei</i> (intrinsically resistant to fluconazole) [16]
<i>C. intermedia</i>	Not described	Oropharyngeal colonizer, bloodstream infections, peritonitis. Susceptible to antifungal drugs except flucytosine [13]
<i>C. kefyr</i>	<i>Kluyveromyces marxianus</i>	No inherent resistance to antifungals described
<i>C. lipolytica</i>	<i>Yarrowia lipolytica</i>	Clinical significance uncertain. Fluconazole MICs higher than for <i>C. albicans</i> .
<i>C. lusitanae</i>	<i>Clavispora lusitanae</i>	Not a good target for amphotericin B even if MICs are in the susceptible range ( $\leq 1$ mg/L) [17]
<i>C. metapsilosis</i>	Not described	Closely related to <i>C. parapsilosis</i> . Susceptibility pattern similar to this species (high echinocandin MICs) [18]
<i>C. nivariensis</i>	Not described	Closely related to <i>C. glabrata</i> . Susceptibility pattern as for <i>C. glabrata</i> (decreased susceptibility to azoles) [9]
<i>C. norvegensis</i>	<i>Pichia norvegensis</i>	Closely related to <i>C. inconspicua</i> . Susceptibility pattern similar to <i>C. krusei</i> (intrinsically resistant to fluconazole) [16]
<i>C. orthopsilosis</i>	Not described	Closely related to <i>C. parapsilosis</i> . Susceptibility pattern similar to this species (high echinocandin MICs) [18]
<i>C. palmiophila</i>	Not described	Phenotypically related to <i>C. guilliermondii</i> . High azole MICs (but low echinocandin MICs in contrast to those for <i>C. guilliermondii</i> ) [13]
<i>C. pelliculosa</i>	<i>Wickerhamomyces anomalus</i> (prev. <i>Pichia anomala</i> , <i>Hansenula anomala</i> )	Fluconazole MICs higher than for <i>C. albicans</i> [19]
<i>C. pulcherrima</i>	<i>Pichia kudriavzevii</i> (prev. <i>Metschnikowia pulcherrima</i> )	Clinical significance uncertain
<i>C. rugosa</i>	Not described	Fluconazole MICs higher than for <i>C. albicans</i> [19]
<i>C. subhashii</i>	Not described	Clinical significance uncertain
<i>C. viswanathii</i>	Not described	Clinical significance uncertain
<i>C. zeylanoides</i>	Not described	Clinical significance uncertain

**TABLE 2.** Strength of the EFISG and ECMM recommendation and quality of evidence

Strength of a recommendation (SoR)	
Grade A	ESCMID and ECMM strongly support a recommendation for use
Grade B	ESCMID and ECMM moderately support a recommendation for use
Grade C	ESCMID and ECMM marginally support a recommendation for use
Grade D	ESCMID and ECMM support a recommendation against use
Quality of evidence (QoE)	
Level I	Evidence from at least one properly designed randomized, controlled trial
Level II <sup>a</sup>	Evidence from at least one well-designed clinical trial, without randomization; from cohort or case–controlled 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
<sup>a</sup> Added index: ∙: Meta-analysis or systematic review of randomized controlled trials. ∙: Transferred evidence, that is, results from different patients' cohorts, or similar immune-status situation. ∙: Comparator group is a historical control. ∙: Uncontrolled trial. ∙: Published abstract (presented at an international symposium or meeting).	

almost 4000 fungaemia isolates in an 8-year national surveillance programme in Denmark [26,27]. In Paris, they represented 5.1% of the 3668 fungaemia isolates in a prospective surveillance programme from 2002 to 2012 (YEASTS Network, National Reference Centre for Invasive Mycoses and Antifungals, Paris, France (O. Lortholary, unpublished data), Table 3).

*Saccharomyces cerevisiae* is a biotechnologically highly important fungus with a broad use in the production of food and alcoholic beverages etc. Phylogenetically, the species is relatively closely related to *Candida glabrata* [31].

As most of these rare invasive yeast infections occur in the haematology and Intensive Care Unit (ICU) settings, clinicians should be aware that all of the responsible fungal species, presumably except *Saccharomyces* spp. and *Kodamaea ohmeri*, are regarded as intrinsically resistant to echinocandins. As a result of the rare nature of these pathogens, controlled prospective and comparative clinical trials are not feasible so solid data on treatment efficacy cannot be compiled. Moreover, clinical susceptibility breakpoints have not been established. Hence, management recommendations derive from clinical experience (cohort or case–controlled analytical studies, from multiple time series), pragmatic interpretations of susceptibility data and limited animal studies when available. Also because of their rare incidence, primary prophylaxis is not indicated unless specific local epidemiology suggests otherwise. As specific diagnostic surrogate markers have not been developed for these organisms (apart from the antigen test for *Cryptococcus* but mainly evaluated for *Cryptococcus*

**TABLE 3.** Summary of rare yeast isolates collected during the national surveillance programme in Denmark 2004–2011 and the surveillance programme in Paris hospitals, France October 2002–May 2012. Only unique isolates are included. For comparison and representing other parts of the world data from a US cancer centre, the Artemis study and a Brazilian study are included

	DK (national) [26,27]	Paris Hosp. <sup>a</sup>	US (cancer centre) [28]	Artemis study 1997–2007 [29]	Sao Paulo Brazil [30]
Fungaemia isolates (total)	3982	3668	3382	NA	1195
Rare yeasts other than <i>Candida</i>	44 (1.1%)	188 (5.1%)	94 (2.8%)	11,240	174 (14.5%)
<i>Cryptococcus neoformans</i>	13 (29.5%)	137 (72.8%)	NA	3,512 (31.2%)	79 (45.4%)
<i>Cryptococcus</i> spp.	1 (2.3%)	1 (0.5%)	NA	113 (1.0%)	NA
<i>Geotrichum</i> spp.	2 (4.5%)	19 (10.1%)	2 (5%)	NA	NA
<i>Rhodotorula</i> spp.	4 (9.1%)	5 (2.7%)	21 (51%)	462 (4.1%)	28 (16.1%)
<i>Saccharomyces</i> spp. <sup>b</sup>	22 (50.0%)	14 (7.4%)	8 (20%)	1,321 (11.8%)	NA
<i>Trichosporon</i> spp.	2 (4.5%)	11 (5.9%)	8 (20%)	1,196 (10.6%)	NA
<i>Malassezia</i> spp.	0	1	1 (2%)	NA	NA
<i>Pichia anomala</i>	0	NA	1 (2%)	28 (0.2%)	32 (18.4%)
<i>Saprochaete capitata</i>	0	NA	NA	109 (1.0%)	NA

NA, Not available.

<sup>a</sup>YEASTS Network, National Reference Centre for Invasive Mycoses and Antifungals, Paris, France (unpublished data).

<sup>b</sup>Taxonomically also a *Candida* species (*C. robusta*).

*neoformans*), blood culture remains an essential investigation for the detection of invasive infection and the general recommendations concerning volume and sampling frequency should be followed [32–34]. Emerging evidence has highlighted the additional yield obtained for candidaemia when a fungal blood culture bottle is included to specifically support the growth of fungi and at the same time avoid suppression by concomitant faster growing microorganisms [35–38]. It remains to be demonstrated if this applies to the detection of fungaemia due to the yeasts described herein. In the following sections the general characteristics for the different pathogens will be reviewed (in alphabetical order). Specific characteristics concerning the epidemiology and species identification are summarized in Tables 2 and 3. In most cases, identification to the species level requires the adoption of new tools including matrix-assisted laser desorption/ionization time of flight mass spectrometry (MALDI-TOF-MS) or DNA sequencing. In this context it is important to underline that the performance of these techniques depends on the quality of the databases employed. However, these approaches appear promising for most of these species and are expected to play an important role in the future (Table 4). Recommendations regarding use of blood culture and surrogate markers are summarized in Table 5. Finally, recommendations regarding appropriate first-line antifungal treatment options are summarized in Table 6.

## Cryptococcus

### Introduction

*Cryptococcus* is an anamorphic basidiomycetous yeast genus that comprises 70 species [39] but only two species *C. gattii* and *C. neoformans* are regularly causing infections. The diagnosis and

management of these have been described in detail elsewhere and are not included in the present guideline because they are not uncommon or rare infections [40–43].

Other *Cryptococcus* species (e.g. *C. albidus*, *C. curvatus*, *C. laurentii*) are prevalent worldwide and have been identified from various environmental sources including air, soil, water, pigeon droppings and food items such as cheese, milk, beans and wine [39]. The species are able to grow at 37°C and have been described as a cause of invasive human infections, with *C. albidus* and *C. laurentii* accounting for 80% of the non-*neoformans*/non-*gattii* cryptococcal infections [44]. *Cryptococcus uniguttulatus*, *C. adeliensis* and *C. flavescens* have also been implicated in cases of meningitis, albeit less frequently [45–48]. The clinical presentation is similar to that for *C. neoformans* but the cryptococcal antigen test is often negative and intrinsic susceptibility patterns are characterized by higher MICs for several agents [49]. Therefore, diagnosis and optimal management depend on a high index of suspicion and a skilled mycology laboratory service. In the literature, cultures were not always performed and species identifications were in many cases based solely on phenotypic methods. Therefore, reports on infections caused by the individual species should be interpreted with caution unless coming from reference laboratories.

### Risk factors and clinical presentation

*Cryptococcus adeliensis*, *C. albidus*, *C. curvatus*, *C. flavescens*, *C. laurentii* and *C. uniguttulatus* have been recovered from various clinical specimens [44–48,50]. The most common underlying risk factor is impaired cellular immunity, of which 16% was related to human immunodeficiency virus infection in a recent review of 44 previously published cases [44]. In addition, *C. laurentii* has been linked to the presence of invasive devices [44]. Clinical presentation involves bloodstream infection in 33–55% of the cases, neurological manifestations in 20–33%

**TABLE 4.** Identification of the rare yeasts; laboratory characteristics and tools for identification to the species level

Organism	Pseudo-hyphae	Hyphae	Blastoconidia	Anelloconidia	Chlamydoconidia	Cap-sule	Monopolar budding	Arthroconidia	Urease	Appearance on CHROMagar	Specific comments regarding morphology	Identification to the species level requires <sup>a</sup>
<i>Cryptococcus</i> spp. other than <i>C. gattii</i> & <i>Geotrichum</i>	-	-	+	-	-	+	-	-	+	No data	India ink may visualize the capsule in clinical specimens	ITS 1 + 2 (2nd option D1/D2 domain) MALDI-TOF promising
<i>Kodamaea ohmeri</i>	+	-	+	-	-	-	-	+	-	Variable, probably species dependent	White colonies, arthroconidia	ITS 1 + 2 (2nd option D1/D2 domain) MALDI-TOF promising
<i>Milaszezia</i>	-	-	+	-	+/(-)	-	+	-	+	Gradually pink to blue No growth except <i>M. pachydermatis</i>	Colour change on CHROMagar within 48 h Lipid dependent except <i>M. pachydermatis</i> white/cream colonies, monopolar budding Fusiform spindle-shaped elongated blastoconidia	Phenotypically or ITS 1 + 2 MALDI-TOF promising
<i>Pseudozyma</i>	-	+	+	-	-	-	-	-	+	<i>P. aphidis</i> forms rough green colonies. No data for the other species. No data		ITS 1 + 2 (2nd option D1/D2 domain)
<i>Rhodotorula</i>	-/(+)	-/(+)	+	-	-	(+)	-	-	+	Dark pink	Red, orange-salmon coloured colonies Larger cells compared with <i>C. glabrata</i> , poor growth on blood agar	ITS 1 + 2 (2nd option D1/D2 domain) Biochemical tests or MALDI-TOF
<i>Saprocete capitata</i>	-	+	+/-	-	-	-	-	+	-	No data	Whitish, butyrous colonies, arthroconidia	ITS 1 + 2 (2nd option D1/D2 domain) MALDI-TOF promising
<i>Sporobolomyces</i>	-/(+)	-/(+)	+	-	-	-	-	-	+	No data	Red, orange-salmon coloured colonies; satellite colonies due to ballistoconidia	ITS 1 + 2 (2nd option D1/D2 domain)
<i>Trichosporon</i>	-	+	+	-	-	-	-	+	+	<i>T. asahii</i> ; dirty green (others variable)	Colony becoming dry, arthroconidia	ITS 1 + 2 (2nd option D1/D2 domain) IGS1 necessary for some species MALDI-TOF promising

<sup>a</sup>ITS 1 + 2: Sequencing of the Internal transcribed spacer 1 and 2 of the rDNA. 2nd option D1/D2 domain: Sequencing of the D1/D2 domain of the large subunit (LSU) ribosomal DNA 09FDNA recommended if species identification is not obtained by ITS 1 + 2 sequencing. IGS1: Sequencing of the intergenic spacer 1 region of the rDNA is necessary for correct species identification of some *Trichosporon* species. Biochemical tests: correct species identification can be obtained by biochemical tests such as the Vitek 2 and API ID32C. MALDI-TOF: matrix-assisted laser desorption/ionization time of flight mass spectrometry.

**TABLE 5.** Summary of and recommendations regarding use of blood culture and surrogate markers

Species	Surrogate markers	Strength of recommendation	Quality of evidence	Comment	References
All	Blood culture	A	II	Volume of blood is essential. Adults: 40–60 mL either one venepuncture or separate immediately after each other. Repeated if signs and symptoms of fungaemia persist.	[32–34]
	Blood culture fungal medium	B	II <sup>c</sup>	Several studies have documented better yield for <i>Candida</i> and BACTEC and BacT/ALERT BC systems if a mycosis medium is included. Not shown specifically for rare yeasts.	[26,35–38]
<i>Cryptococcus</i> other than <i>C. neoformans</i> and <i>C. gattii</i>	Cryptococcus antigen	C	III	Cerebrospinal fluid and serum. Sensitivity lower than for <i>C. neoformans</i> . (4/17 in one study). Negative result does not exclude cryptococcosis.	[44,45]
	Asp GM	D	III	Cross-reaction due to galactomannan in the fungal cell wall. However, sensitivity not examined.	[65]
<i>Geotrichum</i> <i>Kodamaea ohmeri</i> <i>Malassezia</i>	$\beta$ -D-glucan	D	II	$\beta$ -D-glucan is not part of the cryptococcal cell wall.	[63]
	No data on surrogate markers	No recommendation	No data		
	No data on surrogate markers	No recommendation	No data		
<i>Pseudozyma</i> <i>Rhodotorula</i>	Isolator 10 Lysis centrifugation or BC bottle suppl. with palmitic acid with prolonged incubation (2 weeks)	B	III	Positive microscopy and negative culture may be suggestive, due to the lipid dependence of most species. Subculture: Sabouraud overlaid with sterile olive oil, Dixon agar or other lipid-containing agar.	[107,108]
	No data on surrogate markers	No recommendation	No data		
<i>Saccharomyces</i>	$\beta$ -D-glucan	C	III	$\beta$ -D-glucan present in culture supernatant but in lower amount and but no clinical data.	[63]
	<i>Candida</i> mannan antigen	C	III	$\beta$ -D-glucan present in culture supernatant but no clinical data.	[63,180]
<i>Saprochaete capitata</i>	Asp GM	C	III	Single clinical case and antigen similarity	[179]
	Asp GM	C	III	Cross-reaction due to galactomannan in the fungal cell wall. However, sensitivity not examined.	[208,209]
<i>Trichosporon</i>	$\beta$ -D-glucan	C	III	$\beta$ -D-glucan present in culture supernatant but no clinical data.	[63]
	Cryptococcus antigen	B	II <sup>u</sup>	Cross-reaction with cryptococcal polysaccharide and galactomannan Ags. Dual positivity may be suggestive for <i>Trichosporon</i> infection. However, sensitivity not examined.	[57,58,246–249]
	Asp GM	C	III		
	$\beta$ -D-glucan	D	II	Low sensitivity	[238,250,251]

and pulmonary infection in 5–11% of the cases, but other body sites may also be involved including skin, eyes, peritoneum (secondary to peritoneal dialysis) and lymph nodes (5–10% each). *Cryptococcus laurentii* was associated with no mortality in contrast to *C. albidus* (28% mortality) [44].

### Diagnosis

Cryptococci are budding, encapsulated, round to oval yeast cells with a size from 3 to 8  $\mu$ m in fluids or tissues. The cells can be visualized by mixing the pellet (cerebrospinal fluid, pleural fluid or bronchoalveolar lavage) with India ink. The capsule surrounding the cell will appear transparent as a halo resembling an egg-white around the yolk. Tissue sections can be stained with mucicarmine or Alcian blue to highlight the capsule and so exclude other yeasts with similar morphology. Clinical specimens should be incubated on Sabouraud or other selective fungal agar at 30–35°C (for up to 4 weeks in case of prior antifungal treatment). Lysis centrifugation or culture of the buffy coat improves the yield of fungaemia detection [40]. Creamy mucoid colonies are obtained and the colour may darken with age. The genus is non-fermentative and identified by the presence of a capsule, urease production and assimilation pattern using commercial kits [39]. When cultured on bird seed agar most species do not form brown to black colonies (and can therefore be differentiated from *C. neoformans* and

*C. gattii*). There are few exceptions such as *Cryptotrichosporon anacardii* [51] and *Cryptococcus podzolicus* [52]. Species identification requires sequencing of internal transcribed spacer (ITS) 1 + 2 regions of rDNA and/or D1/D2 domains [39,47,48,53]; MALDI-TOF-MS is a promising tool for future identification of uncommon yeasts including *Cryptococcus* species; however, its performance will depend on the quality of the database (T. Boekhout, unpublished observations) [54–56].

Despite sharing several capsular antigens with *C. neoformans*, cryptococcal antigen detection is not a reliable diagnostic test for non-*neoformans*/non-*gattii* cryptococcal species with only 4/17 bloodstream cases being positive and at low titres [44,45]. Whether the poor sensitivity is attributable to differences in capsule structure (versus *C. neoformans*) or lower fungal burden remains to be clarified. False-positive results have been reported during invasive *Trichosporon* infections [57,58] and in the case of rheumatoid factor [59], *Capnocytophaga canimorsus* septicaemia [60], *Stomatococcus mucilaginosus* bacteraemia [61], soaps and disinfectants [62]. The amount of  $\beta$ -1-3-D-glucan in the cryptococcal cell wall is much lower than in for example *Candida albicans* and the  $\beta$ -1-3-D-glucan test has not been found useful in the diagnosis of cryptococcal disease, as exemplified by only two of 12 patients with cryptococcosis positive at a cut-off value of 80 pg/mL [63,64]. Therefore the test is not recommended in this context. Finally, cross-reaction with the

**TABLE 6. Targeted antifungal treatment of emerging invasive yeast infections. Note: intention is to cure manifest infection**

	Population/ manifestation	Antifungal	Strength of recommendation – quality of evidence	Comments	References
<i>Cryptococcus</i> other than <i>C. neoformans</i> and <i>C. gattii</i>	CNS and severe inf. Induction	Amphotericin <sup>a</sup> (±flucytosine <sup>b</sup> )	B-III	MICs of 5-FC, fluconazole and other azoles often elevated and particularly so for <i>C. albidus</i> , <i>C. laurentii</i> and <i>C. uniguttulatum</i> [29,30,33,54–59] If <i>in vitro</i> susceptible	[44–46,49,69–74]
	CNS and severe inf. Consolidation	Fluconazole ≥400 mg/day	C-III		
	Non-CNS, not severe inf.	Fluconazole ≥400 mg/day	C-III	MICs of 5-FC, fluconazole and other azoles often elevated and particularly so for <i>C. albidus</i> , <i>C. laurentii</i> and <i>C. uniguttulatum</i> [29,30,33,54–59]	
<i>Geotrichum</i> <i>candidum</i>	Non-CNS, not severe inf.	Amphotericin <sup>a</sup>	B-III	May be preferable to fluconazole for the less azole-susceptible species	
	Any	Echinocandins	D-II	Intrinsically resistant	
	Any	Amphotericin <sup>a</sup> (±flucytosine <sup>b</sup> )	B-III	Preferred agent is amphotericin B (w/wo 5-FC).	[77–80]
	Any	Fluconazole	D-III	No human data and high MIC values	[77,82]
<i>Kodamaea</i> <i>ohmeri</i>	Any	Voriconazole	NR	Low MIC values. One breakthrough failure case (while on micafungin), but voriconazole TDM levels not reported.	[77,78,81]
	Any	Echinocandins	D-II	<i>In vitro</i> resistant	[77]
	Any	Amphotericin <sup>a</sup>	B-III	Most (but limited) clinical experience w amphotericin B;	[83,85,86,92,95,96]
<i>Malassezia</i>	Any	Fluconazole	C-III	Elevated MICs for some isolates. Fluconazole successful in 5/6 paediatric cases, in 1/1 adult immunocompromised patient case (fluconazole followed by itraconazole) unsuccessful in one adult case of cellulitis [70,74,78].	[84,88,92]
	Any	Echinocandins	C-III	Two case reports showed successful outcome for one patient each on micafungin and caspofungin respectively (MICs higher than for <i>C. albicans</i> ) No data	[91,93]
	Any	Voriconazole	NR		
	Severe cases	Amphotericin <sup>a</sup>	B-III		[97,106]
	Non-severe cases	Fluconazole	B-III	<i>M. pachydermatis</i> may be less susceptible <i>in vitro</i> <i>In vitro</i> activity, no clinical data, exposure issues particularly in the paediatric population	[97,106]
Any	Voriconazole	C-III	No reference susceptibility test for <i>Malassezia</i> ; modified susceptibility tests suggest intrinsic resistance	[97,106]	
<i>Pseudozyma</i> spp.	Any	Echinocandins	D-III	No reference susceptibility test for <i>Malassezia</i> ; modified susceptibility tests suggest intrinsic resistance	
	Any	Flucytosine <sup>b</sup>	D-III		
	Any, fungaemia	Amphotericin <sup>a</sup>	A-II <sup>d</sup>	Low MICs of amphotericin B, case stories reporting success.	[121–124]
	Any, fungaemia	Fluconazole	D-II	5/6 clinical isolates had high MICs of fluconazole	[121–124]
<i>Rhodotorula</i>	Any, fungaemia	Echinocandins	D-II	<i>In vitro</i> resistant	[123,124]
	Any, fungaemia	Flucytosine <sup>b</sup>	D-II	<i>In vitro</i> resistant (MIC >64 mg/L)	[121,123]
	Any, fungaemia	Voriconazole	C-III	<i>In vitro</i> activity, no clinical data, exposure issues	[123,124]
	Any	Amphotericin <sup>a</sup> (±flucytosine <sup>b</sup> )	A-II	<i>In vitro</i> susceptible only to these two agents. Good response in the case reports available.	[131,153,154]
<i>Saccharomyces</i>	Any	Azoles	D-II <sup>d</sup>	Breakthrough cases on fluconazole and echinocandins. <i>In vitro</i> resistant to all azoles and echinocandins	[131,147,148,153,154]
	Any	Echinocandins	D-II	Breakthrough cases on azoles and echinocandins. <i>In vitro</i> resistant	[147,153,154]
	Any	Amphotericin <sup>a</sup>	B-III	Most clinical experience; toxicity risk higher than for echinocandins	[178,182,183]
	Any	Echinocandins	C-III	Two successful cases in the literature (± neutropenic), no emergence of <i>S. cerevisiae</i> after intro of echinocandins as first line agents for candidaemia, two recent failure cases neutropenic (Arendrup MC unpublished data)	[27,182,183]
<i>Saprochaete</i> <i>capitata</i>	Any	Amphotericin B <sup>a</sup> + Flucytosine <sup>b</sup>	B-III	Excellent <i>in vitro</i> susceptibility. May be used in severe cases or when penetration into an infected focus is challenging.	[70,170,181,184,185]
	Any	Fluconazole	D-III	Increased occurrence in patients exposed to fluconazole; high fluconazole MICs (similar to those for <i>C. glabrata</i> )	[26,178]
	Any	Discontinuation of probiotics	A-III	Probiotic containing <i>S. boulardii</i> has been documented to be the origin of systemic infections.	[175,176]
	Any	Amphotericin <sup>a</sup> (±flucytosine <sup>b</sup> )	B-III	Most (but limited) experience. <i>In vitro</i> susceptibility of amphotericin B in the intermediate range, failures in hepatosplenic infections reported on amphotericin B monotherapy.	[186,194,196]
<i>Sporobolomyces</i>	Any	Voriconazole	B-III	Less data available, but promising <i>in vitro</i> susceptibility	[186]
	Any	Echinocandins	D-II	<i>In vitro</i> resistant and a case report document breakthrough infections on an echinocandin.	[211,212]
	Any	Fluconazole	NR	<i>In vitro</i> resistant – but animal model data suggest activity	[211–213]
	Any	CSF or interferon- $\gamma$ in combination w antifungal treatment	C-III	Improved <i>in vitro</i> phagocytic activity has been observed	[194,195,206]
<i>Sporobolomyces</i>	Any	Amphotericin <sup>a</sup>	C-III	Possibly a treatment option but insufficient clinical data	[69,222,223,230]
	Any	Voriconazole	C-III	Possibly a treatment option but insufficient clinical data	[69,225,230]

Table 6 (Continued)

	Population/ manifestation	Antifungal	Strength of recommendation – quality of evidence	Comments	References
Trichosporon	Any	Echinocandins	D-II	<i>In vitro</i> resistant	[69,230]
	Any	Fluconazole	D-II	<i>In vitro</i> resistant	[69,230]
	Any	Voriconazole	B-III	Preferred therapy, but as data are scarce	[233,237,238,259,260]
	Any	Fluconazole	C-III	Some clinical evidence for usefulness, but also some isolates with higher MICs	[192,232,238]
	Any	Echinocandins	D-II	<i>In vitro</i> resistant	[237–239,256,262]
	Any	Amphotericin <sup>a</sup>	D-III	Low success rates on amphotericin B and <i>in vitro</i> resistance reported	[192,232,261,265–267,270]
	Any	Flucytosine <sup>b</sup>	D-III	<i>In vitro</i> resistant	

5-FC, flucytosine; CNS, central nervous system; inf., infection; TDM, therapeutic drug monitoring; w/wo, with/without.  
<sup>a</sup>Amphotericin, wherever mentioned, includes amphotericin B deoxycholate and its lipid formulations. Lipid formulations are preferred due to lower toxicity and liposomal amphotericin B specifically whenever central nervous system penetration is warranted.  
<sup>b</sup>Flucytosine, wherever mentioned, is a possible option particularly in cases where penetration issues (e.g. central nervous system infection) or severity, suggest combination therapy may improve outcome. Flucytosine should only be used in combination due to the risk of selection of resistance and therapeutic drug monitoring is highly recommended due to the narrow therapeutic index.

*Aspergillus* galactomannan antigen test (Platelia *Aspergillus*; BioRad, Marnes la Coquette, France) has been observed due to the presence of galactoxylomannan in the cryptococcal capsule [65]. A commercially available cryptococcal lateral flow antigen detection device (IMMY; Immuno-Mycologics, Inc., Norman, OK, USA), has recently been introduced as a point-of-care test for the early diagnosis of cryptococcosis. The test has proven effective both for serum, cerebrospinal fluid and urine samples in comparison with conventional techniques of antigen detection but the performance for the detection of infections due to cryptococci other than *C. neoformans* has not been evaluated [66–68].

#### Susceptibility testing and treatment

Cryptococci are intrinsically resistant to echinocandins. The optimal treatment for invasive infections due to other *Cryptococcus* species has not been established. Amphotericin B alone or in combination with flucytosine and fluconazole either alone or after induction therapy with amphotericin B has been used. Predictors for mortality were infection with *C. albidus* (rather than *C. laurentii*), age above 45 years and central nervous system involvement [44]. *In vitro* susceptibility testing suggests that *C. albidus*, *C. curvatus* and *C. laurentii* are susceptible to amphotericin B with MICs comparable to those for *C. neoformans* [49]. On the contrary, MICs of flucytosine, fluconazole and other azoles are in most studies elevated and particularly so for *C. albidus*, *C. laurentii* and *C. uniguttulatus*, suggesting that these organisms may be less susceptible [45,46,49,69–74]. Moreover, fluconazole resistance has been reported more frequently in patients with previous azole exposure (83% versus 50%) [44]. The clinical implication of these observations remains to be understood. However, initial induction therapy with amphotericin B until clear clinical improvement and careful evaluation of fluconazole susceptibility if step-down to this agent is considered appears to be a sound and safe strategy.

### *Geotrichum candidum*

*Geotrichum candidum* (*Galactomyces candidus*) is a filamentous ascomycetous yeast that forms arthroconidia and that has rarely been reported to be responsible for disseminated infections in the haemato-oncology setting [75–77]. It is closely related to *Saprochaete capitata* (*Magnusiomyces capitatus*) and *Saprochaete clavata* (see below). A recent literature review of 12 invasive cases reported since 1971 revealed that 8/12 patients had underlying malignancy [77]. It has been anecdotally reported as a cause of invasive skin infection [78]. The preferred agent for invasive infections is amphotericin B with or without concomitant flucytosine as most experience exists with this agent [77,79,80]. Voriconazole may be a promising agent, as suggested by good *in vitro* susceptibility, but only a single case is reported in the literature with an unsuccessful outcome of a breakthrough infection (while on micafungin) [77,78,81]. Neither echinocandins nor fluconazole can be recommended because of high MICs and no clinical support for efficacy [77,82].

### *Kodamaea ohmeri*

#### Introduction

*Kodamaea (Pichia) ohmeri* is a rarely occurring yeast that has recently been identified as a cause of fungaemia, endocarditis, cellulitis, funguria and peritonitis in neonates and children [83–87], and in both immunocompromised [88–91] and immunocompetent [92,93] adult patients. The anamorphic state is *Candida guilliermondii* var. *membranaefaciens*, and has been confused with *Candida guilliermondii* (for which the teleomorphic state is *Meyerozyma guilliermondii*). Recent literature invariably does not acknowledge the anamorphic state (and readers may therefore not recognize this species as a *Candida* sp.), so we have included *K. ohmeri* in this guideline. *Kodamaea ohmeri* may be

misidentified as *Candida tropicalis* [84], *Candida haemulonii* or *Candida parapsilosis* [94] by traditional methods and molecular identification is mandatory.

#### Risk factors/clinical presentation

There are <30 cases described in the world literature, which are mainly sporadic reports but also include two Asian series with several cases [84,94]. In one of these, the hands of a healthcare worker at a surgical ward were colonized with *K. ohmeri*, suggesting a nosocomial outbreak [84].

#### Diagnosis

Blood culture remains the cornerstone in the diagnosis of invasive infection. On solid media, *K. ohmeri* forms *Candida*-like colonies, which on CHROMagar (BioMérieux, Marcy l'Etoile, France) change colour from pink to blue within 48 h [88]. Although mis-classification as *Candida tropicalis* has been reported, correct species identification can be obtained by biochemical tests such as the Vitek 2 and API ID32C or sequencing of the rDNA loci [84,88].

#### Susceptibility testing and treatment

Susceptibility testing suggests that the susceptibility pattern mirrors that for *Candida glabrata* with azole MICs higher than those for *Candida albicans* (fluconazole: 2–64 mg/L; voriconazole: 0.03–8 mg/L, posaconazole 0.06–4 mg/L, respectively), but amphotericin B and echinocandin MICs in the range that would be interpreted as susceptible for *Candida albicans* (amphotericin B: 0.25–1 mg/L, caspofungin: 0.125–1 mg/L, micafungin: 0.03–0.06 mg/L, respectively) [84,94]. Most cases have been treated with liposomal amphotericin B (or amphotericin B deoxycholate) and with good response [83,85,86,92,95,96]. Fluconazole was successful in 5/6 paediatric cases, in 1/1 adult immunocompromised patient (fluconazole followed by itraconazole) and was associated with failure in one adult case of cellulitis [84,88,92]. Finally, caspofungin or micafungin treatment has been successful in one case each [91,93]. Hence, although there are insufficient data to support a firm treatment recommendation, amphotericin B appears to be an attractive first-line agent and echinocandins are possibly promising alternative candidates. Susceptibility testing is recommended not only to guide treatment but also to provide MIC–outcome relationships and hence data for future optimized treatment recommendations.

## Malassezia

### Introduction

*Malassezia* species are basidiomycetous yeasts and part of our normal skin microbiota. The genus includes 14 species of

which 13 are lipid dependent. These include *M. furfur*, *M. sympodialis*, *M. globosa*, *M. obtusa*, *M. restricta*, *M. slooffiae*, *M. dermatitis*, *M. japonica*, *M. nana*, *M. yamatoensis*, *M. equina*, *M. caprae* and *M. cuniculi*. *Malassezia pachydermatis*, however, is able to grow on routine media without the addition of oil or other sources of lipid. *Malassezia sympodialis*, *M. globosa*, *M. slooffiae* and *M. restricta* are the most frequently found species responsible for colonization of humans.

#### Risk factors/clinical presentation

*Malassezia* species may cause various skin manifestations including pityriasis versicolor, seborrhoeic dermatitis, dandruff, atopic eczema and folliculitis and less commonly onychomycosis [97]. These skin manifestations are common and are typically diagnosed and managed in the primary healthcare sector or by dermatologists [97]. For their management, we would refer the reader to local and international guidelines. However, skin colonization and infection may be a source for transmission to vulnerable patient groups susceptible to invasive infections [97]. Both the non-lipid-dependent species *M. pachydermatis* and the lipid-dependent *Malassezia* spp. (almost all reported as caused by *M. furfur*) have been reported to cause systemic infections [97–99]. As an example, *M. pachydermatis*, which is known to cause external otitis in dogs, has been isolated from the hands of dog owners, including healthcare providers such as nurses, and associated with clusters of infections in neonates [98,100–102]. Apart from contact with a potential carrier, other risk factors for *M. pachydermatis* include increased median neonatal acute physiology score and more than 9 days of arterial catheterization [98]. Notably, *M. pachydermatis* can persist for a long time on surfaces of incubators, which may serve as a source of infection for neonates [103].

Systemic infections due to lipid-dependent *Malassezia* species mainly occur in the following host groups: (i) infants on lipid-containing parenteral nutrition and (ii) children and adults with various forms of immunosuppression and underlying diseases [97,104]. Risk factors for fungaemia related to non-lipid total parenteral nutrition are the following: chronic ambulatory peritoneal dialysis (due to lipids leaking from the gastrointestinal tract), haematological malignancy, cancer and Crohn's disease and most cases arise in patients with a CVC [97,105,106].

#### Diagnosis

The diagnosis of invasive *Malassezia* infections is challenging because of the lipid-dependent nature of most species. Hence, special media, such as modified Dixon or modified Leeming and Notham agar, or the use of Sabouraud agar with the addition of a few drops of sterile olive oil is required. The



performance of the various modern automated blood culture systems for the detection of *Malassezia* species has not been systematically studied, however, the use of the Isolator 10 system (with subculture of lipid-containing agar) or supplementation of the blood culture flask with palmitic acid has been shown to be required for the detection of lipid-dependent species in earlier blood culture systems [107,108]. Inoculated blood culture media should be incubated for up to 2 weeks. Colonies on solid agar are cream to beige. Yeast cells are round or oval with thick walls with a size varying from 2 to 8 µm. Cell division is via monopolar budding with buds that may be nearly as broad as the mother cell in many cases, leading to a flask-like appearance of the cells.

*Malassezia* species may be distinguished phenotypically using morphology and a series of biochemical tests as well as using molecular tools [109–111] and by MALDI-TOF-MS (T. Boekhout, unpublished observation). Full protocols for phenotypic identification are provided by Guého-Kellermann et al. [112]. For clinical management at the level of the individual patient, species identification is less important, although it is obviously needed for epidemiological surveillance and outbreak investigation.

#### Susceptibility testing and treatment

Susceptibility testing of *Malassezia* has not been standardized because growth is not supported on the standard RPMI growth medium recommended for yeast and mould testing by CLSI and EUCAST. Significant variation and broad range MICs have been reported in various publications depending on the medium used, which may result in random/erroneous susceptibility classification [113]. Some reports suggest that *in vitro* fluconazole resistance may be encountered more often in *M. pachydermatis* [114,115]. The clinical implication of this finding remains unclear. So far susceptibility testing for guiding treatment cannot be recommended. As for the other rare invasive yeast infections, larger patient series are lacking, and hence evidence-based treatment recommendations cannot be made. The key factors in the management of invasive *Malassezia* infection are removal of the CVC, discontinuation of the parenteral lipid and institution of systemic antifungal treatment. Most experience is with fluconazole and amphotericin B, which are the preferred agents [106,116,117]. In general MICs are lower for voriconazole than for fluconazole for most species, however, so is the voriconazole exposure, particularly in the paediatric population, which is a reason to strongly consider therapeutic drug monitoring if voriconazole is prescribed [118–120]. Additionally, voriconazole is associated with more side-effects and drug–drug interactions and is not licensed for neonates or children <2 years old. Future studies are

warranted to elucidate which antifungal treatment is optimal. *In vitro* resistance to flucytosine and echinocandins appears to be a consistent finding and therefore these drug classes are not recommended [101,116].

## *Pseudozyma*

#### Introduction

*Pseudozyma* species are basidiomycetous plant pathogens, which belong to the Ustilaginales. The genus today contains at least 20 species and was not recognized as a human pathogen until 2003 when three *Pseudozyma* species—*Pseudozyma antarctica*, *Pseudozyma parantarctica* and *Pseudozyma thailandica*—were isolated from the blood of three Thai patients [121]. Fungaemia due to *Pseudozyma aphidis* was subsequently reported from the USA in 2008 [122] and recently in a neonate from India [123].

#### Risk factors/clinical presentation

So far infections due to *Pseudozyma* have been reported from Asia (Korea, China, India, Thailand), Brazil and the USA [123]. Risk factors associated with invasive *Pseudozyma* infections are similar to those of non-*albicans* *Candida* spp., i.e. extremes of age, cancer chemotherapy, neutropenia (<3000 cells/µL), presence of a CVC and severe thrombocytopenia [121–124]. Invasive *Pseudozyma* spp. infection most often presents with fungaemia. Moreover, deep-seated focal infections including brain abscess [125] and pleural cavity have been reported [124]. Finally, a single case of a mycetoma due to co-infection with *Nocardia* after traumatic inoculation in an Asian farmer has been described [126].

#### Diagnosis

The main stay in the diagnosis of invasive *Pseudozyma* spp. infection is blood culturing and when, focal infection is suspected, culture of relevant tissue samples. On Sabouraud agar *Pseudozyma* species form rapidly expanding moist, tan-yellow and wrinkled yeast colonies [122,124] and on CHROMagar *Candida* medium *P. aphidis* forms rough green colonies after 48–72 h of incubation at 37°C (no data for the other species). Microscopic examination shows fusiform spindle-shaped elongated blastoconidia and the presence of hyphae. Germ tube test and chlamydoconidia formation are negative. Isolates show positive test for diazonium blue B and hydrolyse urea. Growth is inhibited on 0.1% cycloheximide-containing medium. API ID 32C and VITEK2 compact generally give non-conclusive profile(s). Amplification and sequencing of the ITS and/or D1/D2 domain is necessary for a proper identification [121–123,125,126].

### Susceptibility testing and treatment

Low MIC values of amphotericin B, posaconazole (0.03 mg/L), voriconazole (0.06 mg/L) and isavuconazole (0.25 mg/L) have been reported. Susceptibility of itraconazole was variable and 5/6 isolates had MICs of fluconazole in the range of 4 to greater than 64 mg/L. The echinocandins (>4 mg/L) and flucytosine (>64 mg/L) are not active against *Pseudozyma* [123]. Although the available data are too limited to provide firm treatment recommendations, first-line options may be amphotericin B or voriconazole whereas echinocandins, fluconazole and flucytosine should be avoided.

## Rhodotorula

### Introduction

Clinically relevant red yeasts belong to two genera: *Rhodotorula* and *Sporobolomyces* (see below). *Rhodotorula* species are common environmental basidiomycetous yeasts, which can be found in soil, ocean and lake water, fruit juice and milk, and on shower curtains and toothbrushes [30,127]. Today, the genus contains 46 species [128] of which three have been described as rare human pathogens: *R. mucilaginosa* (also known as *R. rubra*), *R. glutinis* and *R. minuta* [30,129,130]. The association of *R. mucilaginosa* with humans is well documented and this yeast has been isolated from skin, sputum and digestive tract samples including faeces, forming part of the normal human microbiota. This species accounts for the majority of the infections (74–79%) followed by *R. glutinis* (7.7%) [130,131]. In a significant proportion of the reported cases the species identification is not available (17%); furthermore, species identification is not reliable by methods normally available in the routine microbiology laboratory, and identification using sequence analysis of the DID2 domains of the large subunit ribosomal DNA (rDNA) and the ITS 1 + 2 regions of the rDNA is needed [30,130].

### Risk factors/clinical presentation

Opportunistic fungal infections due to *Rhodotorula* have emerged after the first case was reported in 1985, and the most common predisposing factor appears to be the presence of a CVC and underlying haematological disease [28,127,130–135]. However, *Rhodotorula* fungaemia, peritonitis, endocarditis or meningitis have also been reported in other vulnerable patient groups, including patients with AIDS, extensive burns, continuous ambulatory peritoneal dialysis, cirrhosis, those who have undergone intra-abdominal surgery, intravenous drug abusers and critically ill ICU patients [130,136–146]. Notably, a significant number of cases are breakthrough infections during fluconazole or echinocandin treatment [131,134,135,147,148]. Infections appear to be less common in Nordic countries

compared with the warmer regions [26,28,149]. Moreover, *Rhodotorula* has also been found on the hands of healthcare workers in Egypt [150], and it has a high affinity to adhere to plastic surfaces and can form biofilms [28,151]. Hence, medical equipment including flexible endoscopes, various utensils and furniture in the patient's room can easily become colonized. These observations suggest geographical differences in the epidemiology and possibly a potential role of differences in hygiene procedures [30,148,150].

### Diagnosis

The mainstay in the diagnosis of invasive *Rhodotorula* spp. infection is blood culture as 79% of the systemic infections presents as fungaemia [130]. Of note, isolates of *Rhodotorula* have been found to cross react with the *Candida glabrata*/*Candida krusei* probe in the commercially available fluorescence *in situ* hybridization test for presumptive species identification of positive blood cultures, which might lead to inappropriate echinocandin treatment [152]. A CVC is often involved and therefore the catheter tip should be cultured when the CVC is removed to capture cases where blood cultures are falsely negative [127]. *Rhodotorula* isolates are easily recognizable in the laboratory by their distinctive orange to salmon-coloured mucoid colonies. Cells of *Rhodotorula* spp. are subglobose, oval to elongate, with or without small capsules, may sometimes form rudimentary hyphae but not ballistoconidia, produce urease but fail to ferment carbohydrates.

Antigen detection has not been reported in clinical cases of systemic *Rhodotorula* infections.  $\beta$ -1-3-D-glucan has been detected in the supernatant from three isolates of *R. mucilaginosa* (syn. *R. rubra*) at an average concentration of two-thirds of that of *Candida* spp. [63]. Whether the  $\beta$ -1-3-D-glucan test would be useful as a surrogate marker for invasive *Rhodotorula* infection remains to be investigated.

### Susceptibility testing and treatment

Susceptibility testing has yielded amphotericin B MICs of <1 mg/L and flucytosine MICs of <0.5 mg/L, but fluconazole MICs of >32 mg/L and voriconazole, itraconazole and posaconazole median MICs of 2 mg/L, which is above the breakpoints for not only *Candida albicans* but also *Aspergillus fumigatus* [153–157]. Hence, *Rhodotorula* species are regarded as intrinsically resistant to azoles and echinocandins, but susceptible to amphotericin B and flucytosine [153,158,159]. This is further supported by the finding that many cases have been breakthrough infections during fluconazole or echinocandin treatment [131,147,148]. Consequently, the preferred treatment of choice is with any kind of amphotericin B preparation. With such treatment, an overall mortality was reported as 13.8% in the haematological setting and ranges

from 0% in patients with non-Hodgkin's lymphoma to 21% in patients with acute leukaemia [30,127,131,160]. If present, withdrawal of CVC is strongly recommended [130–133,135,147] and sometimes reported to be efficacious without any accompanying antifungal treatment [28,161]. Furthermore, cases of chronic ambulatory peritoneal dialysis-associated *Rhodotorula* peritonitis have been diagnosed and successfully treated (5/6 patients cured) with catheter removal (5/6 patients) and systemic or intraperitoneal antifungal therapy (amphotericin B in 5/6 patients or ketoconazole 1/6 patients, which is today regarded as an obsolete compound for oral administration, in one case) [130,138,162,163]. There are anecdotal reports indicating improvement of fungal infection under fluconazole and miconazole treatment despite *in vitro* resistance and in patients without antifungal treatment [130,164]. However, since there are no confirmatory trials for treatment of *Rhodotorula* infections, such practice should be avoided, especially in seriously ill patients.

## Saccharomyces

### Introduction

*Saccharomyces cerevisiae*, also known as baker's or brewer's yeast, is a low pathogenic ascomycetous yeast. *Saccharomyces boulardii*, a genetically similar subtype [165,166], is used as a probiotic for prevention and treatment of various sorts of diarrhoea and recurrent *Clostridium difficile*-associated diarrhoea [167–169] and should be avoided in immunocompromised hosts. The anamorphic state of *S. cerevisiae* is sometimes referred to as *Candida robusta*. As the species is closely related to *Candida glabrata* phylogenetically it is not surprising that the clinical and microbiological characteristics are similar to this species.

### Risk factors/clinical presentation

*Saccharomyces cerevisiae* may be found as a harmless and transient digestive commensal and colonizer of mucosal surfaces of normal individuals. It can, however, also be involved in mucosal infections like vaginitis, particularly in fluconazole-exposed women with recurrent vulvo-vaginal candidiasis, and in bloodstream infections, again particularly in fluconazole-exposed patients [35,170]. Cases of fungaemia and disseminated infection have been described in vulnerable patients after treatment with the *S. boulardii* probiotic compound [171–176], and also as nosocomial infection in a patient that shared a room with a patient receiving probiotic, suggesting transfer via contaminated hands of the nursing staff [177]. In a recent review of 92 cases of invasive *Saccharomyces* infections, *S. boulardii* accounted for half of these, was less often associated with an underlying immunocompromised

condition and more often associated with a favourable outcome [178]. Use of probiotics in debilitated patients, in ICU, in neutropenic patients, in preterm newborns or in patients with central lines should be carefully considered.

### Diagnosis

Invasive infection is most often diagnosed by microscopy and culture. Yeast cells are round to oval and larger than *Candida glabrata* cells. Ascospores are occasionally seen and short pseudohyphae may be formed but are not typical; urease activity is absent. *Candida* mannan antigen positivity has been anecdotally reported in patients with fungaemia but it remains unclear if this test can be used for diagnosis [179]. Similarly,  $\beta$ -1-3-D-glucan has been found in culture supernatant from *S. cerevisiae* at quantities of approximately 85% compared with that from *Candida* cultures and this test has been reported positive in case reports of *Saccharomyces* bloodstream infection and on culture supernatants from *S. cerevisiae* cultures, but the diagnostic performance has not been systematically studied [63,180].

### Susceptibility testing and treatment

The *in vitro* susceptibility pattern is similar to that of *Candida glabrata*, with elevated azole MICs, but echinocandin MICs only a few dilutions higher than for *Candida albicans* and low amphotericin B and flucytosine MICs [70,170,181]. Most clinical experience exists with fluconazole and amphotericin B, for which favourable outcome was observed for 60% and 77.7%, respectively [178]. The clinical experience with the echinocandin class of drugs is limited. Two cases have been reported in the literature and were successfully treated [182,183]. However, two recent failures, one of which with autopsy documented multi-organ dissemination, have also been observed (M. C. Arendrup, unpublished observations). Finally, amphotericin B with or without flucytosine has been used in severe or recurrent cases [184,185] but the role of this combination remains to be established. In addition to the systemic antifungal therapy, it is strongly recommended that probiotics containing *S. boulardii* are discontinued and indwelling foreign bodies are removed, when possible, because this organism, like many other yeasts, is capable of forming biofilms [176].

## Saprochaete

### Introduction

*Saprochaete capitata* (Teleomorph: *Magnusiomyces capitatus*, previously named *Geotrichum capitatum*, *Trichosporon capitatum* or *Blastoschizomyces capitatus*) is a non-fermentative, non-encapsulated, urease-negative ascomycetous yeast. It is found in environmental sources such as wood and soil, in

animals (including bovine mastitis and poultry faeces) and has been found in dishwashers [133,186–188]. In addition, *S. capitata* is part of the normal microbiota of human skin and is frequently isolated from sputum and the digestive tract of healthy people [186].

#### Risk factors/clinical presentation

*Saprochaete capitata* is a rare, but emerging yeast mostly responsible for often lethal fungaemia in patients with profound neutropenia in the haematology setting [186,189–191]. This patient category represents up to 92% of reported cases and 75% of them have been reported from Italy, Spain and France [192]. Mortality associated with disseminated infections has been estimated to be 57% in the haematology population [192,193]. Of note, *Geotrichum* spp. represented 5% (2/41) of non-*Candida*, non-*Cryptococcus* fungaemia cases among haematological patients in a tertiary cancer centre in Houston, suggesting that this species is still a rare invasive pathogen [28]. In the haemato-oncology setting, 60–80% of patients present with deep organ involvement [193]. Indeed, it has been recognized as a cause of skin lesions similar to those observed during disseminated candidiasis, hepatosplenic abscesses [194,195], pancreatic infections [196], brain abscesses [195], funguria [197], acute renal failure due to fungal occlusion of glomeruli [198] and osteomyelitis, mostly with vertebral involvement [199–201]. Central venous catheters have been recognized as a potential portal of entry [193].

A common hospital source has been advocated for several clusters [186,202] and more recently, it has been confirmed by sequencing that *S. capitata* in milk vacuum flasks was the origin of an outbreak in four patients in Barcelona [203]. No subsequent cases occurred when the identified contaminated source was withdrawn [203].

Outside the oncology context, *S. capitata* has been responsible for prosthetic valve endocarditis [204], pneumonia [205], fungaemia due to contaminated intravenous fluid [206] and meningitis [207].

#### Diagnosis

Most cases of *S. capitata* fungaemia have been diagnosed by means of blood culture. On solid media, *S. capitata* colonies are white to cream and isolates produce true hyphae, pseudohyphae, blastoconidia, arthroconidia and annelloconidia. *In vitro* and *in vivo* studies have revealed that *Magnusiomyces capitatus* antigens may cross-react with the *Aspergillus* galactomannan assay [208,209].  $\beta$ -1-3-D-glucan can be detected *in vitro* in culture supernatant at amounts of 88% compared with that for *Candida* spp. [63], but there is no experience of glucan detection during invasive human cases. The species can also be identified by MALDI-TOF-MS (T. Boekhout, unpublished observation).

#### Susceptibility testing and treatment

*In vitro* susceptibility data suggest that *S. capitata* is susceptible to flucytosine (MIC values 0.25–0.5 mg/L), itraconazole, voriconazole and posaconazole (MIC ranges: 0.12–0.50, 0.25–0.5 and 0.03–0.25 mg/L, respectively), but not to fluconazole (MIC between 16 and 32 mg/L) [193,202,210]. The MICs for amphotericin B ranged between 0.5 and 2.0 [186]. *Saprochaete capitata* can be considered intrinsically resistant to echinocandins and *S. capitata* was the cause of at least five reported episodes of breakthrough infection in neutropenic patients receiving echinocandins [211,212]. Finally, various combination regimens were not superior to high-dose fluconazole in an experimental animal model of *Blastoschizomyces capitatus* infection (MICs of 8 and 16 mg/L) [213]. The clinical implication of the conflicting observations regarding *in vitro* and *in vivo* activity of fluconazole remains to be understood.

There are not enough clinical data to assess the optimal treatment for *S. capitata* in haematology patients. However, based on *in vitro* data and the limited clinical data available, any amphotericin B formulation with or without flucytosine can be recommended [186,196]. Failure despite high-dose liposomal amphotericin B (7 mg/kg) has been reported in the context of hepatosplenic infection and neutropenic sepsis [191,194]. Voriconazole exhibits a promising activity *in vitro* [186] and some authors have suggested the use of voriconazole and amphotericin B combination therapy [193,214]. Of note, in the above-mentioned animal model, high-dose fluconazole was more efficacious than amphotericin B, flucytosine or voriconazole monotherapy [213]. Although echinocandin MIC values are elevated, isolated case reports have suggested the potential interest of the combination of caspofungin and voriconazole [215,216]. The role of echinocandins as part of combination therapy for *S. capitata* infections remains to be clarified.

Early removal of the catheter is an important complementary treatment as it has been the likely source of the infection in some cases [186,189] and as removal was shown as a prognostic indicator for success in one study [193]. Other adjuvant therapies to improve the phagocytic activity such as colony-stimulating factors, granulocyte transfusions and interferon- $\gamma$  have been combined with antifungal drugs with some success [194,195,217].

*Saprochaete clavata* (*Geotrichum clavatum*), which is closely related to *S. capitata*, has only very infrequently been described as involved in invasive human infection. However, 33 cases of *S. clavata* invasive infections were recently reported in France from January 2009 to August 2012, of which 17 cases were diagnosed within 2 months as part of an outbreak in haematology wards in 2012 (Vaux, ECCMID 2013,

O 505). It remains to be determined if the low number of reported cases is the result of difficult species identification and confusion with related species or if it is indeed a very uncommon infection outside isolated outbreaks.

## Sporobolomyces

### Introduction

*Sporobolomyces* species are usually red-to-orange pigmented basidiomycetous yeasts, that, next to regular budding cells, form ballistoconidia. Phylogenetically, they are closely related to *Rhodotorula* species. The 53 species occur widely in nature, especially on leaf surfaces, but also in soil, fruits etc. and *Sporobolomyces* is detected in indoor air, particularly in the summer season [218–221].

### Risk factors/clinical presentation

*Sporobolomyces* have been reported as the cause of sporadic invasive bloodstream infections particularly in AIDS patients [222,223]. A single case of meningitis due to *Sporobolomyces roseus* has been described in an immunocompetent cocaine abuser presenting with a 1-week history of severe headache and neck stiffness but no cerebrospinal fluid pleocytosis [224]. The cerebrospinal fluid was culture negative but the yeast was detected by molecular assays in two separate cerebrospinal fluid specimens. Amphotericin B has been efficacious in fungaemic and meningitis cases [222,224]. A single case of endogenous endophthalmitis due to *Sporobolomyces salmonicolor* in a patient with a history of pelvic inflammatory disease 2 years earlier has been reported [225]. The patient recovered following intravitreal amphotericin B (5 µg) and systemic voriconazole 200 mg twice daily. Finally, dermatitis due to *Sporobolomyces holsaticus* and allergic respiratory disease linked to *Sporobolomyces* exposure have been reported [226–228].

### Diagnosis

Colonies of *Sporobolomyces* species are usually red or orange in colour and are similar to those of *Rhodotorula* species. They differ from the latter by the formation of ballistoconidia that are actively discharged, which usually lead to the formation of many small satellite colonies. The optimal growth temperature is 25–30°C. Some isolates may fail to grow well at 35–37°C [218]. Species identification requires sequence analysis of the D1/D2 domains and the ITS1 + 2 regions of the rDNA. The performance of indirect tests such as  $\beta$ -1-3-D-glucan has not been investigated. Due to the ubiquitous presence of *Sporobolomyces* contamination, transient colonization or pseudoinfection should be considered [223,224,229].

### Susceptibility testing and treatment

*In vitro* susceptibility testing has been investigated for a limited number of *Sporobolomyces salmonicolor* isolates and suggests that this species is intrinsically resistant to fluconazole and echinocandins (MIC ranges 8–256 and  $\geq 128$  mg/L of fluconazole and micafungin, respectively), but susceptible to voriconazole and terbinafine (0.03–2 and 0.06–0.12 mg/L, respectively) [69]. The MIC range of amphotericin B and itraconazole was 0.5–8 and 0.03–4 mg/L, respectively, suggesting variable susceptibility [69,230]. Although the available data are too limited to provide firm treatment recommendations, first-line options may be amphotericin B or voriconazole whereas echinocandins and fluconazole should be avoided [69,222,223,225,230]. Susceptibility testing is recommended.

## Trichosporon

### Introduction

*Trichosporon* species are urease-positive, non-encapsulated basidiomycetous yeasts with no known sexual state. They are widely distributed in the environment and regularly found on normal skin, particularly in the peri-genital areas, and occasionally as part of the normal gastrointestinal or upper respiratory microflora [133,231]. The most characteristic morphological feature is the formation of cylinder-shaped arthroconidia in addition to pseudohyphae, septate hyphae and blastoconidia. The genus has undergone a major taxonomic reclassification and today 37 species are described that belong to at least five phylogenetic clades [231]. However, only 16 species have been associated with human infection [231]. The vast majority of cases is caused by *Trichosporon asahii* (74%), followed by *T. dermatis* (12%) [232]. An obvious challenge in this respect is that a significant part of the existing literature does not provide a correct or unique species identification and hence species-specific data are limited.

### Risk factors/clinical presentation

In humans, *Trichosporon* has been associated with white piedra and hypersensitivity pneumonia particularly in hot and humid climates (16–30%). In the immunocompromised host, invasive infections such as fungaemia, endocarditis, peritonitis and meningitis have also been reported. Most common risk factors for invasive infections are underlying malignant haematological disease with long-term neutropenia [192,232,233] or with neutrophil dysfunction such as chronic granulomatous disease [234]. Finally, a recent report suggests that *T. mycotoxinivorans* may be an emerging pulmonary pathogen in patients with cystic fibrosis [235]. Males more often contract the infection and predisposing factors are the presence of a CVC, ICU stay,

peritoneal dialysis, steroid use and cytotoxic chemotherapy [192,231,232,236]. Previous other fungal systemic infection is not uncommon and breakthrough cases in patients receiving fluconazole or echinocandin have been described [237–239]. The infection most commonly presents as fungaemia (75%), in approximately 50% of the cases associated with metastatic skin lesions [232,233]. Renal involvement may occur and be associated with haematuria and funguria [232]. In immunocompromised patients, *Trichosporon* is increasingly seen at some centres among invasive yeast infections other than *Candida* and *Cryptococcus* and associated with a mortality rate of up to 80% [236,240,241], though 55% has been reported in a more recent report from Taiwan [232]. Of note, rare clinical cases have been reported in neonates and in intravenous drug abusers [242–244].

### Diagnosis

The cornerstone in the diagnosis of invasive infection is microscopy (for the detection of fungal disease) and culture. On solid media, colonies are white, but on CHROMagar *T. asahii* forms characteristic dirty green colonies. *Trichosporon* species share antigens with *Cryptococcus* and *Aspergillus* and a number of reports have demonstrated cross-reaction for the cryptococcal antigen and/or galactomannan antigen kits [57,58,245–249]. Therefore, dual positivity in these tests may be an indicator of invasive trichosporonosis; however, the sensitivity and specificity of this approach has not been defined [57,231,245]. On the other hand the  $\beta$ -1-3-D-glucan tests have been associated with a low diagnostic sensitivity for trichosporonosis [245,250,251]. Molecular tests, including direct detection on blood or formalin-fixed paraffin-embedded tissue samples, are being developed but are not yet standardized [252–255]. Reliable species identification requires molecular identification with sequencing of the ITS 1 + 2 ( $\pm$ D1/D2 domain) or even the intergenic spacer region (IGS1) of the rDNA [256–258]. MALDI-TOF-MS appears to be a promising identification tool (with an extensive database) [259].

### Susceptibility testing and treatment

Emerging experience suggests that azoles are the primary drug class for the treatment of invasive trichosporonosis [192,232,233,237,238,260,261]. Several of the species are resistant *in vitro* to amphotericin B with MICs  $\geq 2$  mg/L, including *T. asahii* [256,257,262,263]. *Trichosporon* species are resistant to flucytosine (MICs 4–128 mg/L) and to the echinocandins (MICs  $>16$  mg/L) [239,263,264]. In patients with systemic trichosporonosis and underlying haematological disease poor response rates (i.e. between 16% and 24%) on amphotericin B have been reported and therefore this agent is not recommended for invasive infections [192,231,265–267].

Triazoles on the other hand have been found to be superior to other antifungal drug classes in prophylaxis and treatment [232,238,268]. Most published experience concerns the use of fluconazole. However, variations in susceptibility *in vitro* may suggest that not all species and isolates are equally susceptible to this agent [257]. Voriconazole is the preferred agent because it displays good *in vitro* activity against most *Trichosporon* species and isolates and has been associated with good *in vivo* outcome in most cases of clinical and animal studies [232,233,256,261,263,269–271]. In addition to triazole treatment, resolution of myelosuppression and removal of vascular catheters are other confounders related with increased survival [28,192,231,237,238].

### Conclusion

Rare yeasts other than *Candida* and *Cryptococcus neoformans/gattii* are commonly found in the environment and as skin or mucosal colonizers in humans. Some of them may be considered as true emergent opportunistic pathogens in Europe, although the number of reported episodes remains low because of their low pathogenicity even in patients with severely compromised immunity, particularly those with haematological malignancies and a CVC.

Several of these rare yeasts possess intrinsic or variable resistance to antifungals including echinocandins (to which only *Saccharomyces* spp. and *K. ohmeri* are presumably susceptible) and even polyenes (*Trichosporon* spp.) or azoles (*Rhodotorula* spp.; some *M. capitatus* isolates). This may explain the occurrence of breakthrough infections during empiric antifungal therapy in neutropenic patients. Amphotericin B is among the recommended first-line treatment options for these infections except for *Trichosporon*. Combination with flucytosine may be considered particularly in severe cases or cases where drug penetration may be suboptimal provided the infecting organism is susceptible. In agreement with the recommendations provided in the *Candida* guideline amphotericin B lipid formulations may be considered preferable to conventional deoxycholate amphotericin B for toxicity reasons and liposomal amphotericin B particularly for infections involving the CNS [3,5,6,272,273].

Genus identification is mandatory for clinical management and should be performed and provided in a timely manner. Species identification of these rare yeasts, however, remains difficult and often requires reference expertise and adoption of modern techniques including molecular analysis or MALDI-TOF-MS (with an extensive database). Whether or not the precise species identification (outside cryptococcosis) may

have an impact on the individual clinical management remains to be documented; however, its use and value for epidemiological surveillance and outbreak investigation has been documented beyond doubt.

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TB has no conflict of interest to declare.

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OL is a consultant for Novartis, Fab Pharma and Gilead Sciences, and received grants or speaker's fees from MSD, Roche, Astellas, Gilead Sciences and Pfizer.

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