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*, *Scapulariopsis*, *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*

**Article published online:** 19 February 2014

**Clin Microbiol Infect 2014; 20 (Suppl. 3): 27–46**

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This guideline was presented in part at ECCMID 2013, Berlin, Germany.

**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**

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>AMB</th>
<th>Flucytosine</th>
<th>Echinocandins</th>
<th>Fluconazole</th>
<th>Itraconazole</th>
<th>Voriconazole</th>
<th>Posaconazole</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Fusarium solani</em></td>
<td>I-R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>S-I-R</td>
<td>S-I-R</td>
</tr>
<tr>
<td><em>Scedosporium apiospermum</em></td>
<td>I-R</td>
<td>R</td>
<td>S</td>
<td>I-R</td>
<td>S-R</td>
<td>S-R</td>
<td>S-R</td>
</tr>
<tr>
<td><em>Scedosporium boydii</em></td>
<td>I-R</td>
<td>R</td>
<td>S</td>
<td>I-R</td>
<td>S-R</td>
<td>S-R</td>
<td>S-R</td>
</tr>
<tr>
<td><em>Scedosporium aurantiacum</em></td>
<td>R</td>
<td>NT</td>
<td>R</td>
<td>NT</td>
<td>R</td>
<td>S-R</td>
<td>S-R</td>
</tr>
<tr>
<td><em>Scedosporium prolificans</em></td>
<td>R</td>
<td>R</td>
<td>S-I-R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
</tr>
<tr>
<td><em>Paecilomyces species</em></td>
<td>S</td>
<td>I</td>
<td>R</td>
<td>R</td>
<td>S</td>
<td>I-S</td>
<td>S</td>
</tr>
<tr>
<td><em>Purpureocillium lilacinum</em></td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td><em>Acremonium species</em></td>
<td>S-R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>S-R</td>
<td>S-R</td>
<td>S-R</td>
</tr>
<tr>
<td><em>Scopulariopsis species</em></td>
<td>I-R</td>
<td>R</td>
<td>NT</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>I-R</td>
</tr>
</tbody>
</table>

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* dosages of systemic antifungal agents

<table>
<thead>
<tr>
<th>Agent</th>
<th>Daily dosage per age group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&gt;18 years</td>
</tr>
<tr>
<td>Amphotericin B deoxycholate&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1–1.5 mg/kg QD</td>
</tr>
<tr>
<td>Liposomal amphotericin B&lt;sup&gt;b&lt;/sup&gt;</td>
<td>3 (5) mg/kg QD</td>
</tr>
<tr>
<td>Amphotericin B lipid complex</td>
<td>5 mg/kg QD</td>
</tr>
<tr>
<td>Amphotericin B colloidal dispersion</td>
<td>3–4 mg/kg QD</td>
</tr>
<tr>
<td>Itraconazole IV</td>
<td>200 mg BID (for 2 days), followed by 200 mg daily</td>
</tr>
<tr>
<td>Itraconazole oral suspension/ capsules&lt;sup&gt;c&lt;/sup&gt;</td>
<td>600 mg/day (for 3 days), followed 400 mg/day</td>
</tr>
<tr>
<td>Voriconazole IV&lt;sup&gt;d&lt;/sup&gt;</td>
<td>6 mg/KG IV q 12 h on day 1 4 mg/kg BID</td>
</tr>
<tr>
<td>Voriconazole oral suspension/ capsules&lt;sup&gt;e&lt;/sup&gt;</td>
<td>200 mg BID</td>
</tr>
<tr>
<td>Posaconazole&lt;sup&gt;e&lt;/sup&gt;</td>
<td>200 mg QID or 400 mg BID</td>
</tr>
<tr>
<td>Caspofungin</td>
<td>50 mg/day (day 1: 70 mg) IV</td>
</tr>
<tr>
<td>Anidulafungin</td>
<td>100 mg/day (1: 200 mg) IV</td>
</tr>
<tr>
<td>Micafungin</td>
<td>100 mg/day</td>
</tr>
</tbody>
</table>

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].

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 verticilloides* (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 commonly found opportunistic pathogenic species. In contrast, *Fusarium chlamydosporum*, *Fusarium anthophilum*, *Fusarium dimereum*, *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

### 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

<table>
<thead>
<tr>
<th>Strength of a recommendation (SoR)</th>
<th>ESCMID</th>
<th>ECMM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade A</td>
<td>Strongly support a recommendation for use</td>
<td>ESCMID and ECMM</td>
</tr>
<tr>
<td>Grade B</td>
<td>Moderately support a recommendation for use</td>
<td>ESCMID and ECMM</td>
</tr>
<tr>
<td>Grade C</td>
<td>Marginally support a recommendation for use</td>
<td>ESCMID and ECMM</td>
</tr>
<tr>
<td>Grade D</td>
<td>Support a recommendation against use</td>
<td>ESCMID and ECMM</td>
</tr>
</tbody>
</table>

**Quality of evidence (QoE)**

<table>
<thead>
<tr>
<th>Level</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level I</td>
<td>Evidence from at least one properly designed randomized controlled trial</td>
</tr>
<tr>
<td>Level II</td>
<td>Evidence from at least one well-designed clinical trial, without randomization, from cohort or case-controlled studies (preferably from more than one centre); from multiple time series; or from dramatic results of uncontrolled experiments</td>
</tr>
<tr>
<td>Level III</td>
<td>Evidence from opinions of respected authorities, based on clinical experience, descriptive case studies, or reports of expert committees</td>
</tr>
</tbody>
</table>

* Added index.
  - a: Published abstract (presented at an international symposium or meeting).
  - u: Uncontrolled trial.
  - h: Comparator group is a historical control.
  - r: Transferred evidence, that is, results from different patients' cohorts, or similar immune-status situation.
  - v: Comparator group is a historical control.
  - t: Transferred evidence, that is, results from different patients' cohorts, or similar immune-status situation.
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 (All) 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 β1,3-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

<table>
<thead>
<tr>
<th>Fusarium infection/ Population</th>
<th>Test</th>
<th>SoR</th>
<th>QoE</th>
<th>Comment</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any population</td>
<td>Direct microscopy</td>
<td>A</td>
<td>III</td>
<td>Essential investigation</td>
<td>[2]</td>
</tr>
<tr>
<td></td>
<td>Culture (species identification)</td>
<td>A</td>
<td>III</td>
<td>Essential investigation</td>
<td>[2,190]</td>
</tr>
<tr>
<td></td>
<td>Histopathology</td>
<td>A</td>
<td>IIu</td>
<td>Features of hyaline septate hyphae (with acute angle branching) are similar to those seen with aspergillosis</td>
<td>[120]</td>
</tr>
<tr>
<td></td>
<td>Immunohistochemistry</td>
<td>C</td>
<td>III</td>
<td>Not yet evaluated</td>
<td>[120]</td>
</tr>
<tr>
<td></td>
<td>β-D-Glucan test/ Galactomannan</td>
<td>B</td>
<td>III</td>
<td>Glucan usually positive in case of invasive fusariosis. Aspergillus galactomannan sometimes positive in patients with fusariosis</td>
<td>[46]</td>
</tr>
<tr>
<td></td>
<td>Pan-fungal PCRs for identification</td>
<td>C</td>
<td>II</td>
<td>In combination with conventional methods</td>
<td>[36–38]</td>
</tr>
<tr>
<td></td>
<td>Multiplex PCRs *</td>
<td>C</td>
<td>III</td>
<td>Not yet validated</td>
<td>[30,37,39]</td>
</tr>
<tr>
<td></td>
<td>In situ hybridization</td>
<td>C</td>
<td>III</td>
<td>Not yet evaluated</td>
<td>[191,192]</td>
</tr>
<tr>
<td></td>
<td>Susceptibility testing</td>
<td>C</td>
<td>III</td>
<td>In-house tests</td>
<td>[33,76]</td>
</tr>
<tr>
<td></td>
<td>Environmental sampling (and fungal typing)</td>
<td>A</td>
<td>III</td>
<td>In case of an outbreak situation</td>
<td>[33,76]</td>
</tr>
<tr>
<td></td>
<td>Chest computed tomography (CT) scan</td>
<td>A</td>
<td>IIu</td>
<td>Pulmonary nodules in 82% of patients</td>
<td>[26]</td>
</tr>
</tbody>
</table>

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

*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 fusariosis remains unclear. Reversal of immunosuppression is recommended (AII) [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 (BIIu). 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) (AII) [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

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

<table>
<thead>
<tr>
<th>Population</th>
<th>Intention</th>
<th>SoR</th>
<th>QoE</th>
<th>Comment</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immunocompromised patients</td>
<td>First-line treatment</td>
<td>Voriconazole</td>
<td>A</td>
<td>Ilt,r</td>
<td>Therapeutic drug monitoring required [23,24,60,196,197]</td>
</tr>
<tr>
<td>Liposomal amphotericin B</td>
<td>B</td>
<td>Amphotericin B lipid complex</td>
<td>C</td>
<td>III</td>
<td>Fungi may be resistant to amphotericin B [4,198,199]</td>
</tr>
<tr>
<td>Amphotericin B deoxycholate</td>
<td>D</td>
<td></td>
<td>D</td>
<td>Ilt,u</td>
<td>Fungi often resistant to amphotericin B [4,198,199]</td>
</tr>
<tr>
<td>Any echinocandin</td>
<td>D</td>
<td>Any combination therapy</td>
<td>C</td>
<td>III</td>
<td>Excessive toxicity [21]</td>
</tr>
<tr>
<td>Salvage treatment</td>
<td>Posaconazole</td>
<td></td>
<td>A</td>
<td>II</td>
<td>Overall success rate 50% [23,61]</td>
</tr>
<tr>
<td>Voriconazole</td>
<td>A</td>
<td></td>
<td>A</td>
<td>III</td>
<td>Therapeutic drug monitoring required [62]</td>
</tr>
</tbody>
</table>

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 (AII), 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 apiospermum_ (teleomorphic state, _Pseudallescheria apiosperma_), _Scedosporium aurantiscum_ and _Scedosporium prolificans_. While _S. aurantiscum_ 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 sepsate, branching, hyaline hyphae are similar to those of aspergillosis, although sometimes annelloconidia (conidia that develop from the extruded end of a conidium) may be seen in tissue sections [97,118–120]. Similarly to _Fusarium_, blood cultures may be positive in >50% of

---

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

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

HSCT, haematopoietic stem cell transplant; QoE, quality of evidence; SoR, strength of recommendation.
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 I; 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-γ 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. Luangs-Ard et al. [137] revised the genus and the latter species now officially holds the name Purpureocillium...
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.

### Acremonium Infections

Acremonium species are ubiquitous in the environment and typically found in soil [8, 147]. Recently, Summerbell et al. [148]...
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 roseagriséum (currently Gliomastix roseagrisera), 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 (AII) 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]. 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 (AII), 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 (telemorphs in Microascus species) is phylogenetically close to Scedosporium. Scopulariopsis species are in vitro usually quite resistant to antifungal agents including itraconazole, fluconazole and fluocytosine 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 this organism [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 (AII). In otherwise healthy individuals this organism has been reported to cause onychomycosis [163,164], keratitis [165], otoomycosis [166], invasive sinusitis [167] and prosthetic valve endocarditis [168,169] as well as

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

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

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

---

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

<table>
<thead>
<tr>
<th>Population</th>
<th>Intention</th>
<th>SoR</th>
<th>Qoe</th>
<th>Comment</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immunocompromised patients</td>
<td>Surgery</td>
<td>B</td>
<td>III</td>
<td>Subcutaneous skin infections cure faster with surgery</td>
<td>[288–293]</td>
</tr>
<tr>
<td></td>
<td>Amphotericin B deoxycholate*</td>
<td>A</td>
<td>III</td>
<td>75% cure for P. variotii</td>
<td>[294,295,296]</td>
</tr>
<tr>
<td></td>
<td>Amphotericin B deoxycholate* and itraconazole</td>
<td>C</td>
<td>III</td>
<td>P. variotii; case report: cure</td>
<td>[297,298]</td>
</tr>
<tr>
<td></td>
<td>Ketoconazole</td>
<td>C</td>
<td>III</td>
<td>P. lilacinum; case report: cure</td>
<td>[299]</td>
</tr>
<tr>
<td></td>
<td>Second-line treatment with itraconazole</td>
<td>C</td>
<td>III</td>
<td>obsolete drug when second-generation azoles are available</td>
<td>[299]</td>
</tr>
<tr>
<td></td>
<td>Amphotericin B deoxycholate and 5-Fluorocytosine</td>
<td>C</td>
<td>III</td>
<td>P. variotii; case report: cure</td>
<td>[295]</td>
</tr>
<tr>
<td></td>
<td>Amphotericin B deoxycholate and 5-Fluorocytosine</td>
<td>C</td>
<td>III</td>
<td>P. lilacinum; case report: cure</td>
<td>[299]</td>
</tr>
<tr>
<td>Any population (mixed patients)</td>
<td>Amphotericin B deoxycholate*</td>
<td>B</td>
<td>IIr</td>
<td>Cases and case series</td>
<td>[7,300,301]</td>
</tr>
<tr>
<td></td>
<td>Voriconazole</td>
<td></td>
<td></td>
<td>P. lilacinum and P. variotii most frequently associated with cutaneous disease.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Posaconazole</td>
<td></td>
<td></td>
<td>P. lilacinum usually susceptible to voriconazole and posaconazole, but amphotericin B resistant</td>
<td></td>
</tr>
</tbody>
</table>

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

*the use of amphotericin B-lipid-preparation is recommended
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-Floërl chaired the guideline group with Malcolm Richardson, Emmanuel Rolides, 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 Freiberger are experts on medical mycology and contributed to systematic review, interpretation and writing.


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-Floërl 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 12. Summary of recommendations for treatment of Acremonium species infection

<table>
<thead>
<tr>
<th>Population</th>
<th>Intention</th>
<th>SoR</th>
<th>QoE</th>
<th>Comment</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mycetoma</td>
<td>Amphotericin B deoxycholate plus surgery</td>
<td>B</td>
<td>II</td>
<td>Few cases only</td>
<td>[150,302,303]</td>
</tr>
<tr>
<td></td>
<td>Amphotericin B deoxycholate plus itraconazole or voriconazole</td>
<td></td>
<td></td>
<td>1: the use of amphotericin-lipid-preparation is recommended</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Terbinafine</td>
<td></td>
<td></td>
<td>2: Obsolete drug when second-generation azoles are available because of side effects [304]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Posaconazole</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Surgery</td>
<td>A</td>
<td>III</td>
<td>Surgical intervention is highly recommended</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Amphotericin B deoxycholate</td>
<td>C</td>
<td>III</td>
<td>Recommendations are inconsistent, few cases</td>
<td>[147,149,151,152]</td>
</tr>
<tr>
<td></td>
<td>Nystatin</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Posaconazole</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Voriconazole</td>
<td>A</td>
<td>III</td>
<td>guided by susceptibility testing</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Antifungals and surgery</td>
<td>C</td>
<td>III</td>
<td>Early surgical intervention recommended with excision or aggressive debridement</td>
<td></td>
</tr>
</tbody>
</table>

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

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

<table>
<thead>
<tr>
<th>Population</th>
<th>Intention</th>
<th>SoR</th>
<th>QoE</th>
<th>Comment</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any population</td>
<td>Itraconazole</td>
<td>C</td>
<td>II</td>
<td>Cured, single case</td>
<td>[172]</td>
</tr>
<tr>
<td></td>
<td>Liposomal amphotericin B</td>
<td>C</td>
<td>III</td>
<td>Single case, died</td>
<td>[173]</td>
</tr>
<tr>
<td></td>
<td>Any antifungal and surgery</td>
<td>A</td>
<td>III</td>
<td>Invasive infections may require surgical and medical treatment. Infections are frequently fatal</td>
<td>[180]</td>
</tr>
</tbody>
</table>

QoE, quality of evidence; SoR, strength of recommendation.
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. 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. JoMe has received research grants from Gilead, Merck/Schering and Pfizer, and received lecture honoraria from Gilead, Pfizer and Liofilchem. ZDP has no conflicts of interest to declare. ML has received grants from Forest Pharma and received payment for the development of educational presentation from Forest Pharma. 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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. GP has received research grants from Pfizer, Gilead, AstraZeneca, Novartis, Astellas and GSK, is a consultant to AstraZeneca, Astellas and GSK, is a consultant to MSD, received travel support from Gilead, Astellas and Pfizer and received lecture honoraria from MSD and Astellas. 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.
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