Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Global guideline for the diagnosis and management of rare mold infections: An initiative of the ECMM in cooperation with ISHAM and ASM*

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Introduction and Methods

Invasive aspergillosis and mucormycosis have been the most commonly documented invasive mold infections over recent decades\textsuperscript{1-4}, but mycoses caused by rare molds are on the rise\textsuperscript{5}. Mold-active antifungal prophylaxis in those at highest risk for invasive aspergillosis has proven effective in preventing invasive aspergillosis, and to a lesser extent also mucormycosis\textsuperscript{6,7}. However, the selective pressure of antifungal prophylaxis also may be contributing to the emergence of less common invasive mold infections, caused by molds that are often intrinsically resistant against classes of antifungals, and include \textit{Fusarium}, \textit{Lomentospora} and \textit{Scedosporium} species as well as even less common emerging molds such as \textit{Rasamsonia}, \textit{Scopulariopsis} and \textit{Paecilomyces} spp., which have been described as opportunistic pathogens in patients with a variety of underlying diseases\textsuperscript{8-10}. Intrinsic resistance of the fungal pathogens to many of the available antifungals limits successful therapeutic options. The prevalence of infection due to these fungal pathogens varies widely among geographic regions\textsuperscript{11}. Readily available guidance on recognizing different disease patterns and the diagnostic and therapeutic options available, which differ across the regions of the world, is important to optimize patient management\textsuperscript{12}. Current guidelines are limited to individual rare mold pathogens\textsuperscript{13-15}, focusing on specific groups of patients such as those with hematological malignancies\textsuperscript{15}, or are missing altogether for infections caused by many of the very rare, but emerging pathogenic molds.

Therefore, the European Confederation of Medical Mycology (ECMM)\textsuperscript{16}, together with the International Society for Human and Animal Mycology (ISHAM) and the American Society for Microbiology (ASM), issue this comprehensive guidance document as part of their “One World – One Guideline” initiative\textsuperscript{12,17}, to facilitate clinical decision-making, and simultaneously provide an overview of the areas of uncertainty for invasive mold infections caused by \textit{Fusarium} spp., \textit{Lomentospora} spp., \textit{Scedosporium} spp., dematiaceous molds causing phaeohyphomycosis, \textit{Rasamsonia} spp., \textit{Scopulariopsis} spp., \textit{Penicillium} spp., non-\textit{marneffei Talaromyces} spp., \textit{Paecilomyces} spp., \textit{Purpureocillium} spp., and \textit{Schizophyllum} spp. as well as other basidiomycetes. We aimed to address the limitations of previous recommendations by engaging physicians and scientists involved in all aspects of the management of rare mold infection, representing the fields of
microbiology, mycology, pathology, radiology, infectious diseases, pharmacology, surgery, pediatrics, haematology, intensive care, and dermatology.

Panel: How the guideline group worked

In January 2018, experts were identified based on their publication activity in the field of rare mold infections in the previous five years, their involvement in patient management, and their distribution across the world regions as defined by the United Nations (Figure 1).

Figure 1. Worldwide distribution of the authors of the Rare Mold Guideline

Experts were invited in February 2018 to develop this guideline. From February to March 2018, videoconferences on the methodology were held, and a mandatory video tutorial added in March 2018. Supervision of the group was provided by the coordinators (MH, DS, OAC). Documents were shared among the authors on a password-protected OneDrive (Microsoft Corp, Redmond, WA, USA) repository, and were centrally managed and kept up-to-date with any new developments. Updates on PICO (population, intervention, comparison, and outcome) tables were written in red font; after spelling check and formatting, font color was changed to blue for evaluation by the group. Following discussion of contents and consensus, the font was changed to black. Once all tables were finalized, a writing group (MH, JSG, TJW, MN, CFN, JDJ, ML, MB, FC, TF, PK, TL, AK, JP, MR, SR, MS, JSt, BS, RS, ST, AW, PW, JY, DS, and OAC) contributed
the first draft, which was circulated to all participants for approval in January 2020. Recommendations were consensus-based. If no consensus was found, the majority vote was used.

In April 2020, a four-week public consultation phase ensued. Comments received were evaluated, and used to modify the manuscript as appropriate, resulting in a final author review in July 2020. 54 scientific societies, including national societies from 38 countries and several international societies reviewed and endorsed the guidance document.

The following societies have endorsed the guideline:

International
- International Immunocompromised Host Society (ICHS)
- The International Society for Human & Animal Mycology (ISHAM)

Africa
- Ghana Medical Mycology Group
- Federation of Infectious Diseases Societies of Southern Africa (FIDSSA)

Americas
- Medical Mycology Society of the Americas (MMSA)

Americas, Canada
- Association of Medical Microbiology and Infectious Disease (AMMI)

Americas, Latin America/Caribbean
- Asociación Argentina de Microbiología (AAM), Subcomisión de Micología Clínica
- Brazilian Association of Hematology, Hemotherapy and Cell Therapy (ABHH)
- Brazilian Society of Infectious Diseases
- Latin American Forum for Fungal Infections

Americas, United States
- American Society for Microbiology (ASM)

Asia
- Asia Fungal Working Group (AFWG)

Asia Central/Southern
- Medical Microbiology & Infectious Diseases Society of Pakistan (MMIDSP)
- Indian Society of Medical Mycologist (MSI)
- Iranian Society of Infectious Diseases and Tropical Medicine (ISIDTM)
- Iranian Society for Medical Mycology (ISMM)

Asia, Eastern/South-Eastern
- Indonesia Society for Medical Mycology
- Malaysian Society of Infectious Diseases and Chemotherapy (MSIDC)
- Infectious Diseases Society of Taiwan (IDST)
- Infectious Diseases Society of Thailand (IDAT) with Thai Medical Mycology Forum (TMMF)
Asia, Western
- Israeli Society for Infectious Diseases (ISID)
- Lebanese Society of Infectious Diseases and Clinical Microbiology (LSIDCM)
- Omani Society of Medical Microbiology and Infectious Diseases
- Infectious Diseases and Clinical Microbiology Specialty Society of Turkey (EKMUD)
- Turkish Society of Hospital Infection and Control (TSHIC)
- Turkish Febrile Neutropenia Society
- Turkish Society of Medical Mycology

Europe
- European Hematology Association (EHA)
- European Paediatric Mycology Network (EPMyN)

Europe, Eastern
- Czech Society for Medical Microbiology (SPLM)
- Hungarian Society of Infectious Diseases and Clinical Microbiology (MIFKMT)
- Romanian Society for Medical Mycology and Mycotoxicology (SRMMM)
- The Interregional Association for Clinical Microbiology and Antimicrobial Chemotherapy (IAC-MAC)
- Serbian Society of Medical Mycology (SSMM)
- Slovak Society of Chemotherapy
- Slovenian Society for Clinical Microbiology and Hospital Infections of SMC

Europe, Northern
- Nordic Society for Medical Mycology (NSMM)
- Finnish Society for Medical Mycology (FSMM)
- Irish Fungal Society (IFS)
- Swedish Society for Clinical Mycology (SSKM)
- British Infection Association (BIA)
- British Society for Medical Mycology (BSMM)

Europe, Southern
- Hellenic Society of Medical Mycology (HSMM)
- La Federazione Italiana di Micopatologia Umana ed Animale (FIMUA)
- Sorveglianza Epidemiologica Infezioni nelle Emopatie (SEIFEM)
- Società Italiana Terapia Antinfettiva (SITA)
- Associação Portuguesa de Micologia Médica (ASPMOM)
- Asociación Española de Micología (AEM), Sección de Micología Médica

Europe, Western
- Austrian Society for Medical Mycology (ÖGMM)
- Belgian Society for Human and Animal Mycology (BSHAM)
- French Society for Medical Mycology (SFMM)
- German Society for Hematology and Medical Oncology (AGIHO)
- German Speaking Mycological Society (DMykG)
- Paul-Ehrlich-Society for Chemotherapy (PEG)

Oceania
- ASID Australasian Society for Infectious Diseases
This guideline follows the structure and definitions of previous guidelines on invasive fungal infections which are in accordance with the Grading of Recommendations Assessment, Development and Evaluation (GRADE) and Appraisal of Guidelines for Research & Evaluation (AGREE) systems. The tables reflect the PICO approach, and the methodology including strength of recommendation (SoR), quality of evidence (QoE), and indexes (t, transferred evidence; h comparator group: historical controls; u, uncontrolled trials) as previously described\textsuperscript{12,17}.

1. Fusariosis

**Epidemiology of fusariosis**

Only a relatively small proportion of the more than 300 *Fusarium* species are opportunistic pathogens in humans\textsuperscript{19}. *Fusarium solani* and *Fusarium oxysporum* spp. complexes are especially important, causing more than 50% and about 20% of severe fusariosis cases, respectively\textsuperscript{18,20}. Other species causing infections are those from the *Fusarium fujikuroi* spp. complex [mainly *Fusarium verticillioides* (formerly *Fusarium moniliforme*), *F. fujikuroi*, *Fusarium subglutinans*, *Fusarium proliferatum*], and *Fusarium dimerum* spp. complex\textsuperscript{20}. The main routes of infection are inhalation of airborne microconidia or direct inoculation through traumatic injury, including burns. In immunocompetent patients, fusariosis mostly results from direct contact with contaminated material and frequently presents as superficial infection, such as onychomycosis or fungal keratitis, that may become locally invasive\textsuperscript{21-23}. Eye infections are mainly caused by species of the *F. solani* complex\textsuperscript{24}. *Fusarium* spp. can adhere to plastic substrates such as catheters and soft contact lenses, predisposing those exposed to contaminated devices and material to associated infections\textsuperscript{25}. Hospital water distribution systems may harbor *Fusarium* spp. and serve as a potential source of nosocomial transmission to hospitalized immunocompromised patients\textsuperscript{26}. Outbreaks of *Fusarium*-related keratitis in contact lens wearers have been associated with contaminated lens cleaning solution\textsuperscript{27}. In immunocompromised hosts, especially neutropenic patients with hematological malignancy or those undergoing hematopoietic stem cell transplantation (HSCT) or solid organ transplantation (SOT), fusariosis manifests as invasive infection mainly affecting skin and deep soft tissue, lungs and sinuses\textsuperscript{20,28}. Infections...
in SOT patients tend to be locally invasive. Fusarium spp. frequently disseminate, with positive blood cultures in as much as 70% of cases in immunocompromised patients. This is in contrast to infections caused by many other molds, where blood cultures remain negative despite disseminated infection. This distinctive clinical characteristic of positive blood cultures in disseminated fusariosis may be related to the ability of some Fusarium spp. to form in vivo adventitious conidia or aleurioconidia, which may then break away from invading hyphae and enter the blood stream. Necrotic erythematous papular or nodular skin lesions are often evident in immunocompromised patients with systemic fusariosis and are a distinctive characteristic of these infections. Dissemination to the central nervous system (CNS) and also hepatosplenic fusariosis have been described in isolated reports only. Fusarial paronychial infection in neutropenic patients may result in a painful, erythematous infection of the great toe, which may serve as an important portal of entry for disseminated fusariosis.

Incidence and prevalence of Fusarium infections vary depending on the underlying disease and geographical region. Comparable incidence of fusariosis in HSCT recipients has been identified in centers in Brazil and the United States, where ~6 cases per 1,000 transplants have been affected, ranging between 1.4 and 2 per 1,000 autologous HSCT recipients, and reaching 20 per 1,000 allogeneic HSCT recipients with HLA-mismatched related donors. In Brazil, the 1-year cumulative incidence of fusariosis after allogeneic HSCT was 3.2%, and 0.6% after autologous HSCT. In that study, fusariosis accounted for 29% of all invasive fungal infections. Similarly, an incidence of fusariosis of 14.8 cases per 1,000 patients with acute lymphoblastic leukemia and 13.1 cases per 1,000 patients with acute myeloblastic leukemia have been reported from another center in Brazil. In contrast, a Spanish multicentre study analysing respiratory, blood and tissue samples, identified Fusarium spp. in 1.2% of all clinical isolates tested. In a Spanish tertiary teaching hospital, median incidence of invasive fusariosis was 0.074 episodes per 10,000 admissions in hematological patients. The incidence increased during the study period. Other centers in Europe, Asia and South America have also reported an increase in fusariosis cases in recent years. A pediatric cancer center in Canada diagnosed five fusariosis cases over a period of 15 years.
*Fusarium* keratitis, often associated with contact lenses, is one of the most common fungal infections of the cornea\(^4^5\). In a Danish study, 20% of all cases of fungal keratitis were due to *Fusarium* spp. In this study, a mean incidence of 0.6 per million per year was estimated, ranging between 0 and 2 per million in 14 years (Figure 2)\(^4^6\).

**Figure 2. Worldwide distribution of fusariosis (reported cases between 2009 and 2019 per million population)**

Cases of *Fusarium*-related infections reported in the medical literature were identified in a PubMed search on October 30, 2019 using the search string (*Fusarium* OR fusariosis) that yielded 1,850 publications. In total, 2,435 cases were selected from 48 countries, ~80% related to eye infections. Overall, the vast majority of cases were reported from India (n>1,200, more than 95% related to eye infections), China (n=189), Brazil (n=109), the United States of America (n=100), Philippines (n=94), Argentina (n=83), Italy (n=67), Germany (n=58), and Turkey (n=52)\(^1^3,1^8,2^1,2^4,3^2,3^4,3^7,3^8,4^1,4^2,4^6,3^2^0\). Outbreaks related to contaminated contact lens solution, tap water or other causes were not included. The number of cases reported between 2009 and 2019 is presented as cases per million population per country. The resident population per country was obtained from www.worldometers.info\(^3^2^1\). Of note, the maps in this guideline document are an underestimation of the true prevalence and only reflecting the reported prevalence. Reporting of
cases and case series is highly depending on the ability diagnose those rare fungal infections and the ability to publish.

Fusarium spp. are also the cause of human and animal exposure to serious life-threatening toxins, especially in agricultural settings. For example, ingestion of trichothecene toxins may result in fatal toxic alimentary aleukia which can cause pancytopenia, gastrointestinal distress, seizures, and death.

Diagnosis of fusariosis

Figure 3. Clinical, mycologic and histologic characteristics of invasive Fusarium infections (owned by co-author S. Taj-Aldeen)

Panel A. Cutaneous lesions resulting from fungemia in a hematopoietic allogeneic stem cell transplant pediatric patient. The lesions are painful and may depict different aspects according to the clinical progression. Skin lesions with ulcerated center, crusted necrotic center and surrounded by an erythematous halo (“target lesions”) are suggestive and mostly observed on the trunk and extremities. Panel B. Immediate examination of potassium hydroxide digested cutaneous biopsies, may reveal hyaline septate 45° branching hyphae similar to other hyalohyphomycoses, although irregular branching patterns with up to 90° branching do occur. Panel C. Histopathology of skin lesions resulting from fungemia, shows vasculitis,
the proliferation of capillary vessels with ectasiated lumen and intravascular thrombi containing fibrin and hyphae (PAS staining x 200). Panel D. Colony with cottony appearance surrounded by a tan pigment. Panel E. On slide culture, characteristically curved macroconidia (“banana-shaped”) and thin hyaline hyphae are depicted (lactophenol cotton blue x400). Panel F. Histopathologic aspects are nonspecific and similar to other hyalohyphomycoses (Gomori’s methenamine silver staining x 1000).

Diagnosis – Microscopy, culture and histopathology

Evidence – Blood cultures are positive in 40% of invasive cases\(^\text{230}\), with faster detection of growth in fungal blood culture bottles compared to standard aerobic bottles\(^\text{323}\). This is true specifically for low inocula (\(10^2\) and \(10^3\) CFU/ml) which are detected earlier in fungal media than in bacteriological media (10 hours earlier for \(F.\) dimerum, 14 hours for \(F.\) solani, and 35 hours for \(F.\) verticillioides)\(^\text{230,323}\). Although members of the genus \(Fusarium\) can be identified by the production of hyaline hyphae and pigmented, banana-shaped multicellular macroconidia with a foot cell at the base, species identification is difficult morphologically\(^\text{324}\).

Microscopy has a very important role for diagnosing \(Fusarium\)-related infection particularly in many low and middle income countries, where culture may not be available and histopathology is only accessible in some tertiary facilities\(^\text{45}\).

Direct examination of tissue, especially skin biopsy, allows for a rapid evaluation prior to culture results if the tissue sample can be examined in a timely fashion\(^\text{230}\) (Figure 3). In particular, to diagnose fungal keratitis, histopathologic examination and culture of corneal scrapings are employed\(^\text{30}\). In fresh tissue, hyphae are morphologically similar to those of \(Aspergillus\) spp., \(e.g.\) appearing as hyaline septate filaments that typically dichotomize in acute to 45° and sometimes even 90° angles. Adventitious sporulation may be present and the finding presence of reniform adventitious conidia is highly suggestive of fusariosis\(^\text{324}\).
Hyphae are often difficult to visualize in tissue with routine haematoxylin-eosin (H&E) staining but can be easily identified with Grocott-Gomori’s methenamine silver (GMS) or periodic acid-Schiff (PAS) staining. In the absence of microbial growth, distinguishing fusariosis from other hyalohyphomycosis may be difficult and requires the use of in situ hybridization of paraffin-embedded tissue specimens\textsuperscript{325}. Matrix assisted laser desorption/ionization-time of flight mass spectrometry (MALDI-TOF MS) is also increasingly used for the identification of molds\textsuperscript{326,327,328,329} (Table 1).

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</tr>
</tbody>
</table>

**Imaging studies**

| Hematological malignancies | To differentiate fusariosis from aspergillosis | Chest CT | C | IIh | Nucci CMI 2018\textsuperscript{354} |
| Any | To differentiate fusariosis from other invasive mold diseases | Chest CT | C | III | Nucci SRCCM 2015\textsuperscript{354} |

**AFLP, amplified fragment-length polymorphism; BDG: Beta-D-glucan; CFU, colony-forming unit; CT, computed tomography; DNA, deoxyribonucleic acid; EF1α, elongation factor 1α; FFPE, formalin-fixed paraffin-embedded tissue; GM, galactomannan; IA, invasive aspergillosis; ITS, internal transcribed spacer; LAMP, loop-mediated isothermal amplification; LFD, Lateral Flow Device; MALDI-TOF MS, matrix assisted laser desorption ionization-time of flight mass spectrometry; MIC, minimal inhibitory concentration; MLST, multilocus sequence typing; NPV, negative predictive value; PCR, polymerase chain reaction; PPV, positive predictive value; qPCR, quantitative polymerase chain reaction; rDNA, ribosomal DNA; RPB2, ribonuclease II gene; RT-PCR, real time polymerase chain reaction; sen., sensitivity; spec., specificity; SoR, strength of recommendation; TEF1α, translation elongation factor 1α; w/o, without.**

**Recommendations** – Conventional methods are strongly recommended for the diagnosis of fusariosis and include direct microscopy, culture and histopathology. *Fusarium* spp. grow rapidly in most culture media without cycloheximide. The guideline group strongly recommends obtaining infected tissue or body fluids for histological or cytological evaluation and culture. Use of both culture and histopathology together should increase the yield of diagnostic testing.
**Diagnosis – microbiology - serological testing**

**Evidence** – Prior to establishing *Fusarium* spp. as the fungal cause of infection, other blood tests such as the *Aspergillus* galactomannan antigen test (GM; Platelia Aspergillus EIA BioRad) or (1→3)-β-D-glucan (BDG; Fungitell®, Associates of Cape Cod Diagnostics) assay, may be ordered. Knowledge of their performance in the setting of an active *Fusarium* infection is helpful. Serum GM antigen detection has 83% sensitivity and 67% specificity during *Fusarium* infection in the neutropenic immunocompromised host\(^2^{30}\), with 73% of tests positive prior to the first clinical manifestation observed \(^2^{30}\). In a later study, *Aspergillus* serum GM antigen was positive in 89% of cases of invasive aspergillosis, while it was positive in 73% of cases of fusariosis\(^3^{34}\). In any patient with fusariosis with a positive *Aspergillus* serum GM antigen test, repeated testing over time (e.g., once weekly) may help with treatment stratification and outcome prediction, as continuously positive GM test results correlate with negative outcome\(^2^{30}\). When the BDG assay is used and two sequential tests are both >80 pg/ml, sensitivity is 90% and specificity 61% for *Fusarium* infections, since positive results may also indicate infections caused by *Aspergillus*, *Candida* and other fungal pathogens\(^3^{33}\). The *Aspergillus*-specific Lateral Flow Device (LFD) Test (OLM Diagnostics) is highly specific for aspergillosis, while results have been found negative in samples from patients with invasive fusariosis, which may therefore differentiate between aspergillosis and fusariosis\(^3^{35},^{36}\).

**Recommendations** – Galactomannan (GM) testing is moderately recommended and BDG marginally recommended as part of the diagnostic evaluation for fusariosis. Monitoring serum GM during treatment is strongly recommended for those patients with positive serum GM results.

**Diagnosis – Microbiology – Molecular testing**

**Evidence** – Molecular testing is used for genotyping and species identification of clinical isolates, although this information is not usually useful in practice\(^3^{47},^{351}-^{353}\). Investigators have used murine models to develop these molecular assays\(^3^{56},^{357}\). Molecular genetic methods include amplified fragment length polymorphisms (AFLP), loop mediated isothermal amplification (LAMP), multilocus sequence typing (MLST), and real-time polymerase chain reaction (RT-PCR). Accurate identification of *Fusarium* to the species level
was often achieved by using TEF1-α sequencing, which allowed detection of various species including *F. oxysporum*, *F. solani*, *F. keratoplasticum*, *F. petroliphilum*, *F. napiforme*, *Fusarium falciforme*, *F. pseudensiforme*, *F. dimerum* and the new species *Fusarium riograndense*.21,24,342,350

When TEF1-α was used as part of a multiplex PCR and DNA microarray hybridization panel used for species identification primarily in neutropenic cancer patients, *F. solani* and *F. oxysporum* could be reliably identified, but these tests are not validated for clinical implementation.337,344 If TEF1-α was included in a panfungal semi-nested PCR (ITS2 target) and Luminex xMAP technology approach analysing various clinical specimens, *F. solani*, *F. oxysporum*, *F. verticillioides*, and *F. proliferatum* could be identified. These assays can be considered pan-*Fusarium*.339 PCR has been used with a variety of specimen sources,338–340,343,344 including blood,338,343 spinal fluid, and tissue material.341,343 Accurate identification of *Fusarium* spp. from invasive infections to species level is important not only from an epidemiological standpoint, but also for choosing the appropriate antifungal treatment. For example *F. solani* spp. complex show higher MICs to VCZ and AmB than *F. oxysporum* spp. complex. Within *F. solani* spp. complex, *F. keratoplasticum* had higher MICs than *F. falciforme* and *F. petroliphilum* in one study from Brazil.347

**Recommendations** – Molecular-based diagnostic testing is not widely available; it is mainly based on in-house tests at centers where there is expertise in this area. If available, these tests are strongly recommended for species identification, which may have implications for antifungal susceptibility, and marginally recommended directly from clinical specimens.

**Diagnosis – microbiology – susceptibility testing**

**Evidence** – Susceptibility testing of isolates recovered in culture should be used for epidemiologic purposes in defining the range of minimal inhibitory concentrations (MIC) distributions for *Fusarium* spp.331. However, studies demonstrating that susceptibility testing results should be utilized to inform antifungal drug choice are lacking.285,332 In one case series, there was a high rate of treatment failure (11/12) among patients with disseminated fusariosis who received VCZ as first-line treatment, where susceptibility testing showed a lack of *in vitro* activity of this drug (MIC ≥16 μg/mL).332 Conversely, in another study, among
nine clinical isolates tested, there was no correlation between MIC and clinical outcome, and some cases responded well to VCZ treatment despite high MICs. These discrepancies between MIC and outcome may be related to the critical role that host factors play in treatment of fusariosis in immunocompromised patients. Although there are no interpretative breakpoints for antifungal agents against *Fusarium* spp., compounds with MICs that are off-scale, such as >16 µg/ml, at the highest range of concentrations are unlikely to be active in patients. While susceptibility testing according to EUCAST or CLSI is primarily recommended, the E-test® (bioMérieux) is a good alternative method for testing of *Fusarium* spp., but unusually high MICs should be confirmed by the CLSI method.

**Recommendations** — Susceptibility testing of isolates is strongly recommended for epidemiologic purposes and marginally recommended for informing antifungal drug choice for fusariosis. Although there is little correlation between MIC and clinical success, knowing the causative species and its resistance pattern may help with some decisions such as combination therapy and duration of therapy.

**Diagnosis — Imaging**

**Evidence** — Imaging studies may produce subtle findings that help differentiate fusariosis from aspergillosis. Both fusariosis and aspergillosis present with macronodules on imaging. Cases of aspergillosis may have a halo sign, while cases of fusariosis are less likely to have a halo sign. Invasive fusariosis should be suspected if chest computed tomography (CT) imaging demonstrates pulmonary infiltrates with a hypodense sign, but without the halo or the occluded-vessel signs. Suspicion is greater in the presence of hyperdense maxillary and ethmoid sinusitis.

**Recommendations** — CT imaging is marginally to moderately recommended for differentiating fusariosis from other invasive mold diseases including aspergillosis. Proceed with imaging for any suspected lung or sinus infection, since those body sites can have fluids or tissues to be examined by both culture and histopathology. As with other invasive fungal infections, imaging studies may assist in recognizing that there is a fungal infection, and may assist in the procurement of infected tissue or body fluids for further analysis when needed. No radiological findings reliably discriminate between different mold infections.
Proceed with imaging for any suspected sinus, lung or liver involvement, since those body sites can have fluids or tissues to be examined by both culture and histopathology. Proceed with corneal scrapings of any corneal lesions. Proceed with biopsy of any skin lesions, particularly among neutropenic patients. While it is helpful to perform MIC testing of isolates recovered in culture, MIC results may not always correlate with clinical outcome. Additional molecular workup of organisms recovered from cultures will depend on the resources available at a particular center (Figure 4).
Figure 4. Optimal diagnostic pathway for fusariosis, when all imaging and assay techniques are available

Invasive infection due to *Fusarium* spp.

Any population

Hematologic / Neutropenic patients
  *Persistent fever or respiratory symptoms*

Suspected fungal keratitis
  *Ocular pain, erythema, chemosis, loss of vision, corneal ulcer*

Imaging procedures (CT scan, MRI, X-ray) on suspected sites of infection

Galactomannan
  *in serum*

1,3-β-D-Glucan
  *in serum*

Repeat galactomannan
  to monitor response if previously positive; correlates with outcome

Direct microscopy
  hyaline, septate filaments, dichotomizing in acute angles

Culture from any site / blood culture

Specific fungal blood culture
  *low inocula detected earlier in fungal medium than in aerobic bottles*

Histology
  hyaline, septate filaments; dichotomizing in acute angles; *in situ* hybridization might be required

For further species identification
  *ITS 1, ITS 2 and TEF1α sequencing*

For further species identification
  MALDI-TOF MS

Legend:
  strongly recommended
  moderately recommended
  marginally recommended
  recommended against

CT, computed tomography; ITS, internal transcribed spacer; MALDI-TOF MS, matrix-assisted laser desorption/ionization time-of-flight mass spectometry; MRI, magnetic resonance imaging; TEF1α, translational elongation factor 1α

* Serum galactomannan has been shown to have reduced sensitivity in the absence of neutropenia, and may therefore be less reliable as diagnostic in the non-neutropenic host
### Treatment approaches for infections caused by rare molds – Standard Dosing recommendations for adults

Standard dosages of antifungals recommended in this guideline for treatment of rare mold infections in adults are outlined in Table 2.

**Table 2. Standard dosing recommendations for adults with rare mold infections**

<table>
<thead>
<tr>
<th>Antifungal</th>
<th>Standard Dosage</th>
<th>Route of Administration</th>
<th>Therapeutic Drug Monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>Voriconazole (VCZ)</td>
<td>2x 6 mg/kg d1, 2x 4 mg/kg from d2</td>
<td>iv; po</td>
<td>Yes, target trough level &gt; 1.5-2 µg/ml and &lt;6mg/l</td>
</tr>
<tr>
<td>Posaconazole (PCZ)*</td>
<td>Suspension: 4x 200 mg or 2x 400 mg (lower exposure than 4x 200 mg) Delayed-release tablet/iv: 2x 300 mg on d1, 1x 300 mg from d2</td>
<td>iv; po (tablet preferable over suspension)</td>
<td>Yes (when used for treatment; target trough level &gt; 0.7 mg/l)</td>
</tr>
<tr>
<td>Isavuconazole (ISA)</td>
<td>3x 200 mg on d1+2; 1x 200 mg/d thereafter</td>
<td>iv; po</td>
<td>No</td>
</tr>
<tr>
<td>Itraconazole (ICZ)</td>
<td>iv: 200-400 mg/d po: 100-400 mg/d SUBA-ICZ: 50-100 mg/d</td>
<td>iv; po; for po consider SUBA-ICZ</td>
<td>Yes</td>
</tr>
<tr>
<td>Liposomal amphotericin B (L-AmB)</td>
<td>3-5 mg/kg qd</td>
<td>iv</td>
<td>No</td>
</tr>
<tr>
<td>Amphotericin B Lipid Complex (ABLC)</td>
<td>3-5 mg/kg qd</td>
<td>iv</td>
<td>No</td>
</tr>
<tr>
<td>Amphotericin B colloidal dispersion (ABCD)</td>
<td>6 mg/kg qd</td>
<td>iv</td>
<td>No</td>
</tr>
<tr>
<td>Amphotericin B deoxycholate (D-AmB)</td>
<td>1 mg/kg qd</td>
<td>iv</td>
<td>No</td>
</tr>
<tr>
<td>Caspofungin (CASPO)</td>
<td>70 mg on d1, 50 mg from d2 (if body weight ≤ 80 kg) or 1 x 70 mg per day from d2 (if body weight &gt; 80 kg)</td>
<td>iv</td>
<td>No</td>
</tr>
<tr>
<td>Anidulafungin (ANID)</td>
<td>200 mg on d1, 100 mg from d2</td>
<td>iv</td>
<td>No</td>
</tr>
<tr>
<td>Micafungin (MICA)</td>
<td>100 mg/d</td>
<td>iv</td>
<td>No</td>
</tr>
<tr>
<td>Terbinafine (TRB)</td>
<td>2x 250-500 mg/d</td>
<td>po</td>
<td>No</td>
</tr>
<tr>
<td>5-Flucytosine (5-FC)</td>
<td>po: 50-150 mg/kg qd in divided doses every 6 hours iv: 70-150 mg/kg qd in divided doses every 6 hours</td>
<td>iv; po</td>
<td>Yes, target trough level 25-50 µg/ml, peak level 50-100 µg/ml</td>
</tr>
</tbody>
</table>

* For definitions of conditions that may require treatment stop/salvage treatment, including persistent, refractory, relapsed or breakthrough IFI, please refer to d, day(s); iv, intravenously; po, orally; qd, once a day; SUBA, super bioavailability
Treatment approaches to fusariosis

Treatment in adults

Primary prophylaxis

Evidence – While mold active prophylaxis that covers also Fusarium spp. has become standard of care in many high-risk settings, primary prophylaxis specifically for invasive fusariosis has been evaluated in one study only, in a subset of patients\textsuperscript{802}. A previous study from the same group showed that high-risk hematological patients (acute leukemia or HSCT) with superficial skin lesions on the feet (interdigital intertrigo and/or onychomycosis) on hospital admission with positive culture for Fusarium spp. were at an increased risk of developing invasive fusariosis\textsuperscript{22}. In this non-randomized trial, mold active prophylaxis (VCZ or PCZ) was given in 20 episodes at risk (neutropenia or graft versus host disease), while fluconazole or no prophylaxis was administered in 219 episodes\textsuperscript{302}. Invasive fusariosis occurred in a similar proportion, namely 5.9% of the patients without and in 5% with anti-mold prophylaxis. However, in the subgroup of patients with superficial skin lesions with positive cultures for Fusarium spp., four out of five patients who had not received anti-mold prophylaxis developed invasive fusariosis vs. none out of six who received VCZ or PCZ (p=0.01). Cases of breakthrough invasive fusariosis have been reported in patients receiving primary mold-active prophylaxis with PCZ, VCZ or isavuconazole (ISA)\textsuperscript{9,194,370-373} (Table 3).

Recommendations – Primary prophylaxis with a mold-active triazole (VCZ or PCZ) is moderately recommended in high-risk hematological patients who present with superficial skin lesions with positive cultures for Fusarium spp. There are no data to support mold-active primary prophylaxis specifically to prevent fusariosis in other settings.

Secondary prophylaxis

Evidence – Secondary prophylaxis for invasive fusariosis was evaluated in a multicenter retrospective study of 40 patients who were successfully treated for invasive fusariosis and were exposed to subsequent periods of immunosuppression (neutropenia in 35 patients and graft versus host disease in five patients)\textsuperscript{331}. Overall, 32 patients received secondary prophylaxis (VCZ in 24 patients, PCZ in two patients and a lipid formulation of amphotericin B (AmB) in six patients). Relapse of invasive fusariosis occurred in two
of the eight patients (25%) who were not on secondary prophylaxis and in three out of 32 (9.4%) patients who received secondary prophylaxis (p=0.26). Considering only patients who had disseminated fusariosis, relapse occurred in both patients not on secondary prophylaxis and in three out of 26 (11.5%) patients who had received secondary prophylaxis (p=0.03) (Table 3).

**Recommendations** – Secondary prophylaxis with a mold-active triazole or a lipid formulation of AmB is moderately recommended in patients with prior invasive fusariosis who will be exposed to subsequent periods of immunosuppression, especially if the previous disease was disseminated.

**Diagnostic-driven treatment**

**Evidence** – Patients with invasive fusariosis may frequently present with positive serum GM or BDG. In a multicenter study, 15 out of 18 patients with invasive fusariosis had at least one positive serum GM test. In one study, serum GM was positive at a median of 10 days before the first clinical manifestation of fusariosis in 73% of patients. In another study, 12 out of 13 patients with invasive fusariosis had a positive BDG, in 11 the test was positive prior to the diagnosis of invasive fusariosis. However, the test lacked specificity and the positive predictive value for 2 consecutive positive BDG tests was 7% only. Another study evaluated the strategy of using the area over the neutrophil curve (D-index) to stratify the risk for invasive mold disease in 29 high-risk neutropenic patients. A cumulative index above 5,800 identified a group at higher risk, with a rate of invasive mold disease (including fusariosis) of 67%, 45.5% and 0% in high-, intermediate- and low-risk patients, respectively (Table 3).

**Recommendations** – Serum GM, serum BDG and the cumulative D-index may be of help to establish a diagnostic-driven approach in high risk neutropenic patients. However, these tests lack specificity for the diagnosis of invasive fusariosis. Therefore, the guideline marginally supports the use of these tools for initiating specific treatment for invasive fusariosis.

**First line treatment**

**Evidence** – There are no randomized trials evaluating antifungal drugs for the treatment of invasive fusariosis. The largest series published to date is a multicenter retrospective study of 236 patients with invasive fusariosis diagnosed between 1985 and 2011 in 44 centers from 11 countries all over the world.
Among 206 patients who received treatment for invasive fusariosis, 110 received AmB deoxycholate (D-AmB), 38 were treated with VCZ, 34 with a lipid formulation of AmB (liposomal 20, lipid complex 8, colloidal dispersion 6; in a previous study lipid complex was less well tolerated than the liposomal formulation with more acute infusion-toxicity375), 21 received combination therapy (mainly VCZ plus AmB), and three received other therapies. The 90-day probability of survival was 27% for patients treated with D-AmB, 53% for patients receiving VCZ, and 48% for those receiving a lipid formulation of AmB.

Other studies reported lower numbers of patients receiving primary treatment with a single agent for invasive fusariosis with either VCZ (55 patients, response rates ranging from 44 to 100%, including localized disease)18,201,285,376,377, AmB lipid complex (ABLC; 28 patients, 43% response rate)378, liposomal AmB (L-AmB; 10 patients, response rates 0 to 100%)371,378,380, and D-AmB (5 patients, 20% response rate)379. A few patients received treatment with either ISA, echinocandins, terbinafine (TRB) or PCZ285,381-383. Combination therapy with VCZ plus L-AmB or another agent was reported in the majority of studies, and is the preferred initial approach in many specialized centers because of high VCZ MICs, while other centers prefer monotherapy18,28,159,201,285,377,382,384,385. Response rates with combination therapy overall were similar to monotherapy, and randomised controlled trials comparing monotherapy with combination therapy are lacking. In one study, combination therapy was used in 21 out of 236 patients (including VCZ plus L-AmB in 12 cases and VCZ plus D-AmB in 5 cases). Response rates did not significantly differ from monotherapy and receipt of combination therapy was not a significant predictor of 90-day survival28. However, as combination therapy may have been used in more critically ill patients, no conclusions can be drawn from this retrospective study between combination therapy and monotherapy.

Removal of indwelling central venous catheters has been associated with improvement in observational studies and thus should be considered in all cases of fungemia386 (Table 3).

### Table 3. Prophylaxis and first line treatment of Fusarium spp. infections

<table>
<thead>
<tr>
<th>Population</th>
<th>Intention</th>
<th>Intervention</th>
<th>SoR</th>
<th>QoE</th>
<th>Reference</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prophylaxis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Varon AAC 2016160</td>
<td></td>
</tr>
<tr>
<td>HSCT with superficial</td>
<td>To prevent invasive</td>
<td>Primary prophylaxis with PCZ or VCZ</td>
<td>B</td>
<td>IIu</td>
<td>Bose JCM 2011387</td>
<td>N=2, breakthrough during PCZ</td>
</tr>
<tr>
<td>skin fusariosis</td>
<td>disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HSCT after disseminated</td>
<td>To prevent recurrence</td>
<td>Secondary prophylaxis with PCZ, VCZ or L-AmB</td>
<td>B</td>
<td>IIu</td>
<td>Nucci Mycoses 201931</td>
<td></td>
</tr>
<tr>
<td>fusariosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fever-driven treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any</td>
<td>To cure</td>
<td>Initiate treatment upon fever</td>
<td>D</td>
<td>III</td>
<td>No reference found.</td>
<td></td>
</tr>
<tr>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td></td>
</tr>
</tbody>
</table>

### Diagnosis-driven treatment

<table>
<thead>
<tr>
<th>Hematological malignancy</th>
<th>To increase survival rate</th>
<th>Apply D-Index for treatment initiation</th>
<th>C</th>
<th>I lu</th>
<th>Garnica BJID 2016</th>
</tr>
</thead>
</table>

### First-line treatment

<table>
<thead>
<tr>
<th>Any</th>
<th>To cure</th>
<th>L-AmB 3-9 mg/kg qd iv</th>
<th>A</th>
<th>I lu</th>
<th>N=20</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any</td>
<td>To cure</td>
<td>VCZ iv, switch to po when stable,</td>
<td>A</td>
<td>I lu</td>
<td>N=38, 92% hematol, 90 d survival 60%</td>
</tr>
<tr>
<td>Any</td>
<td>To cure</td>
<td>VCZ in combination with AmB lipid formulation</td>
<td>A</td>
<td>I lu</td>
<td>N=13, diverse combinations</td>
</tr>
<tr>
<td>Any</td>
<td>To cure</td>
<td>ABLC</td>
<td>A</td>
<td>I lu</td>
<td>N=34, including ABLC (N=8), and ABCD (N=6), 90 d survival 53%</td>
</tr>
<tr>
<td>Any</td>
<td>To cure</td>
<td>D-AmB</td>
<td>D</td>
<td>I lu</td>
<td>N=110, poorer response (90 d survival 28%, 95%CI 20-36%) compared with VCZ or AmB lipid formulation</td>
</tr>
<tr>
<td>Any</td>
<td>To cure</td>
<td>AmB lipid formulation + triazole/echinocandin/TRB</td>
<td>B</td>
<td>I I t</td>
<td>N=5, response in 1/5 (20%)</td>
</tr>
<tr>
<td>Hematological malignancy</td>
<td>To cure</td>
<td>VCZ</td>
<td>A</td>
<td>I I t</td>
<td>N=15, 5 success</td>
</tr>
<tr>
<td>Hematological Malignancy</td>
<td>To cure</td>
<td>SA</td>
<td>C</td>
<td>III</td>
<td>Cormely Mycoses 2018</td>
</tr>
<tr>
<td>Hematological malignancy</td>
<td>To cure</td>
<td>Echinocandin</td>
<td>D</td>
<td>III</td>
<td>Apostolidis CID 2003</td>
</tr>
<tr>
<td>Hematological malignancy</td>
<td>To cure</td>
<td>TRB</td>
<td>C</td>
<td>III</td>
<td>Stampel OFID 2015</td>
</tr>
</tbody>
</table>

### Solid organ transplant

<table>
<thead>
<tr>
<th>Hematological malignancy with endophthalmitis</th>
<th>To cure</th>
<th>VCZ for 10 d iv, switch to po +/- VCZ intravitreal +/- AmB intravitreal +/- vitrectomy</th>
<th>B</th>
<th>III</th>
<th>N=1, success</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematological malignancy with endophthalmitis</td>
<td>To cure</td>
<td>L-AmB 5-9 mg/kg qd or other AmB formulations iv +/- AmB intravitreal 5 mg/0.1 ml qw +/- vitrectomy</td>
<td>C</td>
<td>III</td>
<td>Ocampo-Garza JEADV 2016</td>
</tr>
<tr>
<td>Hematological malignancy with endophthalmitis</td>
<td>To cure</td>
<td>VCZ iv + L-AmB +/- VCZ intravitreal 100 mg/0.1 ml/wk, +/- AmB intravitreal</td>
<td>B</td>
<td>III</td>
<td>N=1, success</td>
</tr>
<tr>
<td>Treatment Type</td>
<td>Recommended Treatment</td>
<td>Grade</td>
<td>Evidence</td>
<td>Authors</td>
<td></td>
</tr>
<tr>
<td>----------------------------------------------</td>
<td>----------------------------------------------------------------------------------------</td>
<td>-------</td>
<td>----------</td>
<td>--------------------------</td>
<td></td>
</tr>
<tr>
<td>Immunecompetent patient with endophthalmitis</td>
<td>VCZ, AmB intravitreal, vitrectomy</td>
<td>C</td>
<td>III</td>
<td>Milligan AJOCR 2018</td>
<td></td>
</tr>
<tr>
<td>Liver transplantation with endophthalmitis</td>
<td>VCZ iv, intravitreal</td>
<td>C</td>
<td>III</td>
<td>Jørgensen JMCR 2014</td>
<td></td>
</tr>
<tr>
<td>Postoperative endophthalmitis</td>
<td>VCZ intravitreal, AmB intravitreal, vitrectomy</td>
<td>C</td>
<td>III</td>
<td>Mithal ClinOphthalmol</td>
<td></td>
</tr>
<tr>
<td>Postoperative endophthalmitis</td>
<td>VCZ</td>
<td>C</td>
<td>II</td>
<td>Buchta Mycopathol</td>
<td></td>
</tr>
<tr>
<td>Postoperative endophthalmitis</td>
<td>VCZ, AmB intravitreal, vitrectomy</td>
<td>C</td>
<td>III</td>
<td>Chander Mycopathol</td>
<td></td>
</tr>
<tr>
<td>Exogenous endophthalmitis</td>
<td>VCZ + VCZ intravitreal topical +/- topical + AmB intravitreal +/- topical, surgical intervention</td>
<td>B</td>
<td>II</td>
<td>Gunegel Mycoses</td>
<td></td>
</tr>
<tr>
<td>Exogenous endophthalmitis</td>
<td>AmB 5 µg/0.1 ml intravitreal +/-, vitrectomy</td>
<td>C</td>
<td>III</td>
<td>Alves da Costa Pertuiset</td>
<td></td>
</tr>
<tr>
<td>Exogenous endophthalmitis</td>
<td>VCZ iv, switch to po or VCZ po +/- VCZ intraocular</td>
<td>B</td>
<td>III</td>
<td>Troke Infection</td>
<td></td>
</tr>
<tr>
<td>Exogenous endophthalmitis</td>
<td>PCZ po, topical</td>
<td>C</td>
<td>III</td>
<td>Sponsel BJD</td>
<td></td>
</tr>
<tr>
<td>Exogenous endophthalmitis</td>
<td>AmB + VCZ topical, po</td>
<td>C</td>
<td>III</td>
<td>Barrios Andrés RIM</td>
<td></td>
</tr>
<tr>
<td>Exogenous endophthalmitis</td>
<td>Ketoconazole 200 mg/d po + natamycin topical 5% + D-AmB topical 0.15%</td>
<td>D</td>
<td>III</td>
<td>Comer ClinOphthalmol</td>
<td></td>
</tr>
</tbody>
</table>

**Standard dose unless stated otherwise:** ABLC, amphotericin B lipid complex; AmB, amphotericin B; bid, twice a day; CASPO, caspofungin, CI, confidence interval; CF, cystic fibrosis; d, day(s); D-AmB, amphotericin B deoxycholate; po, orally; H SCT, hematopoietic stem cell transplantation; I SA, isavuconazole; iv, intravenous; L-AmB, liposomal amphotericin B; PCZ, posaconazole; qd, once a day; QoE, quality of evidence; qw, once a week; SoR, strength of recommendation; TDM, therapeutic drug monitoring; tid, three times a day; TRB, terbinafine; VCZ, voriconazole; wk, week(s).

**Recommendations** — Data regarding primary therapy with a lipid formulation of AmB show similar numbers of patients treated and similar response rates with either L-AmB (doses from 3 to 9 mg/kg qd) or ABLC, which may be slightly worse tolerated than L-AmB. Likewise, data on primary therapy with VCZ show similar response rates compared to a lipid formulation of AmB. We therefore strongly recommend primary treatment for invasive fusariosis with either VCZ or a lipid formulation of AmB (L-AmB or other lipid formulotions of AmB). Given the broad dose range used and the small number of patients treated with the two lipid formulations of AmB, a formal recommendation for the dose of each agent cannot be made. For VCZ, we strongly recommend the standard dose intravenous treatment, with step-down to oral VCZ after disease control and the use of therapeutic drug monitoring (Allu), with a target trough level of...
1.5 mg/l – 6 mg/l, which has been shown to ensure efficacy and avoid toxicity in patients with invasive aspergillosis\textsuperscript{358,402} (Table 1). D-AmB should not be used for treatment of invasive fusariosis when other active antifungal agents are available. For other agents a marginal recommendation is given.

Combination therapy is frequently used in the primary treatment of invasive fusariosis because of the severity of the disease, difficulties to achieve VCZ trough levels within the targeted range, and because MICs for azoles and polyenes are often high. Primary combination therapy with a potential early step down to monotherapy later – once MICs come back - is an approach we strongly recommend.

**Endophthalmitis**

**Evidence** – Ocular involvement in disseminated fusariosis occurs occasionally and may be associated with loss of vision\textsuperscript{403}. Proposed treatment strategies have relied on the use of systemic and intravitreal antifungal agents, with or without vitrectomy. The literature on endophthalmitis in hematological patients is limited to case reports in which patients were treated with either systemic VCZ\textsuperscript{82,280}, AmB\textsuperscript{233,371,391}, or VCZ plus AmB\textsuperscript{71,171,244,256,313}, with or without intravitreal VCZ or AmB, with or without surgery.

Outside the setting of hematological patients, endophthalmitis caused by *Fusarium* spp. has been occasionally reported in other immunosuppressed patients such as SOT recipients\textsuperscript{164}, in immunocompetent patients following ocular surgery\textsuperscript{54,96,394-398}, patients with keratitis (which is usually treated with natamycin 5% ophthalmic formulation)\textsuperscript{69,105,399,401}, or after dissemination from a primary skin lesion\textsuperscript{393}. The majority of patients were treated with systemic VCZ plus intravitreal VCZ or AmB and surgery, with variable responses.

**Recommendations** – Considering that VCZ is an option for the treatment of invasive fusariosis and that it has good tissue distribution including the eyes, we favor the use of systemic VCZ (with or without AmB) with intravitreal VCZ or AmB (moderately recommended) over systemic AmB (marginally recommended). Surgical intervention (pars plana vitrectomy) should be discussed with an experienced ophthalmologist on a patient to patient basis.
Salvage therapy

Evidence – Because the outcome of invasive fusariosis is largely dependent on recovery of host defenses, poor response to primary therapy does not necessarily mean that the antifungal drug is not active. Nevertheless, patients who fail to respond to treatment should receive salvage therapy. A caveat that must be acknowledged is that severely ill patients may die before a second treatment is offered and therefore response rates with salvage therapy may be inflated because of this selection bias. Another consideration is that the drug chosen for salvage therapy depends on which agent was used for primary treatment. Considering these factors, since most patients with invasive fusariosis have received formulations of AmB in the past, the majority of data pertains to the use of a mold-active triazole as salvage therapy. This does not necessarily mean that a lipid formulation of AmB cannot be used as salvage therapy for a patient who received a triazole as primary therapy for invasive fusariosis.

The largest series of salvage therapy reported the outcome of 57 patients who received salvage therapy with VCZ. The most frequent prior therapies were AmB (any formulation, 21 patients), an echinocandin (10 patients) and another triazole (10 patients). The overall response rate was 47%. The second largest series reported 21 patients who were refractory (n=17) to or intolerant (n=4) of primary therapy with another drug (lipid formulation of AmB in 20 patients). The overall response rate was 48%. Another series reported 11 patients who received salvage VCZ, with a response rate of 45%. Salvage therapy for fusariosis with ISA was given to four patients, with one positive response (Table 4).

Table 4. Antifungal salvage treatment for Fusarium spp. infections

<table>
<thead>
<tr>
<th>Population</th>
<th>Intention</th>
<th>Intervention</th>
<th>SoR</th>
<th>QoE</th>
<th>Reference</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any</td>
<td>To cure</td>
<td>VCZ +/- other antifungal (CASPO, L-AmB, TRB, PCZ, or white blood cell transfusion)</td>
<td>B</td>
<td>IIu</td>
<td>Lortholary AAC 2010</td>
<td>N= 57, success in 27</td>
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<tr>
<td></td>
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<td></td>
<td></td>
<td>Baden Transplantation 2003</td>
<td>N=3, success in 3</td>
</tr>
<tr>
<td>Any</td>
<td>To cure</td>
<td>PCZ tablet or iv formulation preferred</td>
<td>B</td>
<td>IIu</td>
<td>Raad CID 2006</td>
<td>N=21, success in 10</td>
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<td></td>
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<td></td>
<td></td>
<td>Campo J Infect 2010</td>
<td>N=2 hematolgy</td>
</tr>
<tr>
<td>Any</td>
<td>To cure</td>
<td>VCZ iv for ≥3 d, switch to po or VCZ</td>
<td>B</td>
<td>IIu</td>
<td>Perfect CID 2003</td>
<td>N=11, success in 5</td>
</tr>
<tr>
<td>Any</td>
<td>To cure</td>
<td>ISA</td>
<td>C</td>
<td>III</td>
<td>Cornely Mycoses 2018</td>
<td>N=4, success in 1</td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td>Marty Mycoses 2018</td>
<td>N=3, success in 3</td>
</tr>
<tr>
<td>Any with disseminated fusariosis</td>
<td>To cure</td>
<td>TRB 500-750mg qd + VCZ iv or L-AmB</td>
<td>B</td>
<td>III</td>
<td>nano JIC 2013</td>
<td>N=3, success in 3</td>
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<td></td>
<td></td>
<td>Rothe AnnHematol 2004</td>
<td>N=3, success in 3</td>
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<td></td>
<td></td>
<td>Neuberger TID 2008</td>
<td>N=3, success in 3</td>
</tr>
</tbody>
</table>
Hematological malignancy with skin infection and endophthalmitis

To cure VCZ + AmB iv, intravitreal + vitrectomy C III Malavade IDCP 2013 N=1, outcome not reported

Exogenous endophthalmitis

To cure VCZ +/- VCZ intraocular 1% +/- VCZ intravitreal 2.5 μg/0.1 ml +/- AmB intravitreal 5 μg/0.1 ml +/- vitrectomy C II Troke Infection 2012 N=16, response in 11 Alves da Costa Pertuset CROM 2016 N=1, success Comer Clinophthalmol 2012 N=3, success

Exogenous endophthalmitis

To cure PCZ C III Tu AOJ 2007 N=2, response

Standard dose unless stated otherwise; AmB, amphotericin B; bid, twice a day; d, days; ISA, isavuconazole; iv, intravenous; L-AmB, liposomal amphotericin B; PCZ, posaconazole; po, orally; qd, once a day; QoE, quality of evidence; SoR, strength of recommendation; tid, three times a day; TRB, terbinafine; VCZ, voriconazole.

Recommendations – We moderately recommend VCZ as salvage therapy for patients with progressive disease who fail treatment with a lipid formulation of AmB. PCZ is a moderately recommended alternative, especially if the intravenous formulation and/or the modified release tablet formulation are available, which provide more reliable serum levels than the oral solution. Other moderately recommended options for salvage therapy include the combinations of TRB with VCZ or L-AmB, and combinations of VCZ with other antifungals. ISA as salvage therapy is a marginally recommended alternative, with stronger recommendations pending more data becoming available. Likewise, a lipid formulation of AmB is a reasonable alternative for a patient who fails primary treatment with a triazole, but only marginally recommended as strong supporting data are lacking.

Ancillary therapies

Evidence – Ancillary therapies for invasive fusariosis include surgical debridement of infected tissue, also following trauma18,411,412, the use of colony-stimulating factors such as granulocyte colony-stimulating factor (G-CSF) and granulocyte-monocyte colony-stimulating factor (GM-CSF)167,403, and the use of granulocyte transfusions167,403.

In one study, surgical debridement for localized Fusarium infection in bone and joint resulted in control of infection in all six patients411. Similar results were observed in a cohort of immunocompetent patients with fusariosis confined to the skin18.
The use of G-CSF or GM-CSF was evaluated in 17 patients with invasive fusariosis with hematological malignancies, with a response rate of 41%. The contribution of colony-stimulating factors on the favourable outcome is difficult to evaluate.

The best evidence for the use of granulocyte transfusions in patients with invasive fusariosis comes from a study that analyzed 11 patients, with 10 showing unequivocal signs of clinical response. It must be acknowledged that the use of colony-stimulating factors or granulocyte transfusions are measures undertaken to allow time for neutrophil recovery. If the patient remains neutropenic, the outcome is very poor (Table 5).

Table 5. Other treatment options for Fusarium spp. infections

<table>
<thead>
<tr>
<th>Population</th>
<th>Intention</th>
<th>Intervention</th>
<th>SoR</th>
<th>QoE</th>
<th>Reference</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any</td>
<td>To cure</td>
<td>Resection of pulmonary infiltration/lobectomy and AmB</td>
<td>C</td>
<td>III</td>
<td>Lupinetti ATS 1990</td>
<td>N=1, success</td>
</tr>
<tr>
<td>Hematological malignancies</td>
<td>To cure</td>
<td>Granulocyte transfusion</td>
<td>C</td>
<td>III</td>
<td>Boutati Blood 1997</td>
<td>N=7, response 3/7</td>
</tr>
<tr>
<td>Neutropenic</td>
<td>To cure</td>
<td>G-CSF or GM-CSF</td>
<td>B</td>
<td>IIu</td>
<td>Kadri Transfusion 2015</td>
<td>N=11, granulocyte transfusion, response in 10; 90 d survival 73%</td>
</tr>
<tr>
<td>Any with fungemia</td>
<td>To cure</td>
<td>Removal of indwelling central venous catheters</td>
<td>B</td>
<td>IIu</td>
<td>Janum CDSR 2016</td>
<td>N=84</td>
</tr>
<tr>
<td>Any with skin fusariosis</td>
<td>To cure</td>
<td>Surgical debridement</td>
<td>A</td>
<td>IIu</td>
<td>Muhammed Medicine 2013</td>
<td>N=11</td>
</tr>
<tr>
<td>Bone and joint infections</td>
<td>To cure</td>
<td>Surgical debridement and antifungal treatment</td>
<td>A</td>
<td>IIr</td>
<td>Koehler CRM 2016</td>
<td>N=6, response 6/6</td>
</tr>
</tbody>
</table>

AmB, amphotericin B; d: day(s); G-CSF, granulocyte-colony stimulating factor; GM-CSF, granulocyte-macrophage colony-stimulating factor; QoE, quality of evidence; SoR, strength of recommendation

Recommendations – We strongly recommend surgical debridement of infected tissue in cases of localized fusariosis of, for example, the skin following trauma, joints and bone. The use of G-CSF or GM-CSF should be considered if there is an expectancy of timely bone marrow recovery (moderately recommended).

Duration of treatment

Evidence – In the largest series of treatment for invasive fusariosis in severely immunocompromised patients, treatment was usually given until bone marrow recovery in neutropenic patients, or resolution of immunosuppression in non-neutropenic patients (Table 6).
### Table 6. Treatment duration for *Fusarium* spp. infections

<table>
<thead>
<tr>
<th>Population</th>
<th>Intention</th>
<th>Intervention</th>
<th>Sor</th>
<th>QoE</th>
<th>Reference</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematological malignancies or HSCT</td>
<td>To cure</td>
<td>VCZ or AmB until resolution of neutropenia and of clinical manifestations of infection</td>
<td>A</td>
<td>III</td>
<td>Nucci CMI 2014&lt;sup&gt;28&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Exogenous endophthalmitis</td>
<td>To cure</td>
<td>VCZ for 4 wk to 4 mo</td>
<td>C</td>
<td>III</td>
<td>Buchta Mycopathol 2013&lt;sup&gt;355&lt;/sup&gt;</td>
<td>N=20</td>
</tr>
<tr>
<td>Exogenous endophthalmitis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Comer ClinOphthalmol 2013&lt;sup&gt;300&lt;/sup&gt;</td>
<td>N=2, success</td>
</tr>
<tr>
<td>Hematological malignancy with disseminated fusariosis</td>
<td>To cure</td>
<td>L-AmB +/- VCZ +/- TRB for &gt; 2 mo</td>
<td>B</td>
<td>III</td>
<td>Neuburger TID 2008&lt;sup&gt;499&lt;/sup&gt;</td>
<td>N=1, success</td>
</tr>
<tr>
<td>Endogenous endophthalmitis</td>
<td>To cure</td>
<td>VCZ iv for 5 d, then 4 mo VCZ po</td>
<td>C</td>
<td>III</td>
<td>Milligan AJOCR 2016&lt;sup&gt;616&lt;/sup&gt;</td>
<td>N=1, retinal detachment</td>
</tr>
<tr>
<td>Eye infections</td>
<td>To cure</td>
<td>VCZ for 6 wk to 7 mo</td>
<td>C</td>
<td>III</td>
<td>Troke Infection 2012&lt;sup&gt;597&lt;/sup&gt;</td>
<td>N=24</td>
</tr>
</tbody>
</table>

AmB, amphotericin B; d, days; drug application as standard dose unless stated otherwise; HSCT, hematopoietic stem cell transplantation; iv, intravenous; L-AmB, liposomal amphotericin B; mo, month(s); po, orally; QoE, quality of evidence; SoR, strength of recommendation, TRB, terbinafine; VCZ, voriconazole; wk, week(s).

### Recommendations

We strongly recommend continuing treatment for invasive fusariosis until recovery of host defences, and moderately recommend for disseminated disease a minimum treatment duration of 2 months.

Treatment pathways for adults in different settings (Figure 5, and Figure 6).
Figure 5. Optimal treatment pathway for fusariosis in adults when all treatment modalities and antifungal drugs are available

Suspected and confirmed invasive infections due to Fusarium spp. are emergencies and require rapid action

Immediate treatment initiation

Surgical debridement of infected tissue in localized infections

Amphotericin B lipid complex
1 x 3-5 mg/kg/d
or
Liposomal Amphotericin B
1 x 3-10 mg/kg/d

Voriconazole iv
2 x 6 mg/kg/d (d1);
2 x 4 mg/kg/d from d2;
use TDM

Endophthalmitis

Amphotericin B deoxycholate if alternatives for treatment are available

Progressive disease*

Response assessment (e.g. weekly imaging)

Voriconazole iv
2 x 6 mg/kg/d (d1);
2 x 4 mg/kg/d from d2;
use TDM

Amphotericin B lipid complex
1 x 3-5 mg/kg/d
or
Liposomal Amphotericin B
1 x 3-10 mg/kg/d

Caspofungin
1 x 70 mg d1; 1 x 50 mg from d2
or
Micafungin
1 x 100 mg/d
or
Posaconazole iv/tab
2 x 300 mg d1; 1 x 300 mg from d2
or
Terbinafine
500-1000 mg/d

± combination with

Voriconazole iv
2 x 6 mg/kg/d (d1);
2 x 4 mg/kg/d from d2;
use TDM

Amphotericin B lipid complex
1 x 3-5 mg/kg/d
or
Liposomal Amphotericin B
1 x 3-10 mg/kg/d

Caspofungin
1 x 70 mg d1; 1 x 50 mg from d2
or
Micafungin
1 x 100 mg/d
or
Posaconazole iv/tab
2 x 300 mg d1; 1 x 300 mg from d2
or
Terbinafine
500-1000 mg/d

Amphotericin B lipid complex
1 x 3-5 mg/kg/d
or
Liposomal Amphotericin B
1 x 3-10 mg/kg/d

Posaconazole iv/tab
2 x 300 mg d1;
1 x 300 mg from d2
or
Voriconazole iv
2 x 6 mg/kg/d (d1);
2 x 4 mg/kg/d from d2;
use TDM

Isavuconazole
3 x 200 mg/d (d1-3);
1 x 200 mg from d3

Legend:

- strongly recommended
- moderately recommended
- marginally recommended
- recommended against

TDM, therapeutic drug monitoring

* Choice of salvage treatment always depends by the treatment that the patient failed to respond to
Figure 6. Optimal treatment pathway for fusariosis in adults when triazoles are not available

Suspected and confirmed invasive infections due to *Fusarium* spp. are emergencies and require rapid action.

**Immediate treatment initiation**

Surgical debridement of infected tissue in localized infections

- **Amphotericin B lipid complex**
  - 1 x 3-5 mg/kg/d
  - or
- **Liposomal Amphotericin B**
  - 1 x 3-10 mg/kg/d

**Response assessment** (e.g. weekly imaging)

- **Caspofungin**
  - 1 x 70 mg/d d1; 1 x 50 mg/d from d2
  - or
- **Micafungin**
  - 1 x 100 mg/d
  - or
- **Terbinafine**
  - 500-1000 mg/d

**Progressive disease**

- **Terbinafine**
  - 500-1000 mg/d
  - +
- **Liposomal Amphotericin B**
  - 1 x 3-10 mg/kg/d

- **Amphotericin B deoxycholate**
  - if alternatives for treatment are available

Legend:
- strongly recommended
- moderately recommended
- marginally recommended
- recommended against

* Choice of salvage treatment always depends by the treatment that the patient failed to respond to.
**Specific considerations on treatment of fusariosis in children**

**Evidence** – As in adults, *Fusarium* spp. can cause severe disseminated disease in children, which are associated with high mortality. To date, data in the pediatric setting are very limited and based on single cases or small case series, including in patients with burns. Most immunocompromised children received either VCZ monotherapy or as part of combination therapy, which included any AmB formulation or an echinocandin. The limited data suggest that children receiving VCZ have better outcomes than those not receiving VCZ (cure rate 40/55 vs. 9/26). Similarly, in the seven case reports on salvage therapy, children receiving VCZ seemed to have a benefit (Table 7). Surgical debridement can be an essential adjunctive treatment for localized infections.

**Table 7. Therapy in children for *Fusarium* spp. infections**

<table>
<thead>
<tr>
<th>Population</th>
<th>Intention</th>
<th>Intervention</th>
<th>SoR</th>
<th>QoE</th>
<th>Reference</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematological malignancy</td>
<td>To cure</td>
<td>AmB + 5-FC</td>
<td>C</td>
<td>III</td>
<td>Richardson RID 1988&lt;sup&gt;44&lt;/sup&gt;</td>
<td>N=1, 7 yrs, failure</td>
</tr>
<tr>
<td>Hematological malignancy</td>
<td>To cure</td>
<td>1- AmB 1.5 mg/kg qd + ICZ 2.5 mg/kg qd po</td>
<td>C</td>
<td>III</td>
<td>Hsu PIDJ 1994&lt;sup&gt;40&lt;/sup&gt;</td>
<td>N=1, 3 mo, failure</td>
</tr>
<tr>
<td>Hematological malignancy</td>
<td>To cure</td>
<td>D-AmB</td>
<td>D</td>
<td>III</td>
<td>Schwartz JPIDS 2015&lt;sup&gt;21&lt;/sup&gt;</td>
<td>N=2, 9 yrs, 8 yrs, failure</td>
</tr>
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<td></td>
<td>Litvinov CMI 2015&lt;sup&gt;17&lt;/sup&gt;</td>
<td>N=2, 6 yrs, 9 yrs, failure</td>
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<td></td>
<td>Abisetti Infection 2004&lt;sup&gt;22&lt;/sup&gt;</td>
<td>N=1, 2 yrs, success</td>
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<td></td>
<td>Alvarez-Franco PedDermatol 1992&lt;sup&gt;22&lt;/sup&gt;</td>
<td>N=1, 18 yrs, failure</td>
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<td>Amnari CID 1993&lt;sup&gt;21&lt;/sup&gt;</td>
<td>N=1, 13 yrs, success</td>
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<td>Repiso PedDermatol 1996&lt;sup&gt;24&lt;/sup&gt;</td>
<td>N=1, 7 yrs, success</td>
</tr>
<tr>
<td>Hematological malignancy</td>
<td>To cure</td>
<td>VCZ 4 mg/kg bid or 200 mg bid + D-AmB 1 mg/kg qd</td>
<td>C</td>
<td>III</td>
<td>Litvinov CMI 2015&lt;sup&gt;17&lt;/sup&gt;</td>
<td>N=3, 10 mo-16 yrs, response 1/3</td>
</tr>
<tr>
<td>Hematological malignancy</td>
<td>To cure</td>
<td>VCZ + AmB lipid formulation</td>
<td>A</td>
<td>III</td>
<td>Hassler PIDJ 2017&lt;sup&gt;19&lt;/sup&gt;</td>
<td>N=5, 0-13 yrs, success, granulocyte transfusions +/- G-CSF in 3/5</td>
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<td></td>
<td>Seban CNM 2017&lt;sup&gt;25&lt;/sup&gt;</td>
<td>N=1, 12 yrs, localized infection, success</td>
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<td></td>
<td>Litvinov CMI 2015&lt;sup&gt;17&lt;/sup&gt;</td>
<td>N=4, 8-16 yrs, response 1/4</td>
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<td>Arnoni Mycopathol 2018&lt;sup&gt;90&lt;/sup&gt;</td>
<td>N=3, 6-11 yrs, response 2/3</td>
</tr>
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<td></td>
<td>Jemura PIDJ 2018&lt;sup&gt;24&lt;/sup&gt;</td>
<td>N=1, 10 yrs, failure, L-AmB 6 mg/kg</td>
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<td></td>
<td>Silva Mycopathal 2013&lt;sup&gt;20&lt;/sup&gt;</td>
<td>N=1, 15 yrs, failure</td>
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<td></td>
<td></td>
<td></td>
<td>Schwartz JPIDS 2013&lt;sup&gt;21&lt;/sup&gt;</td>
<td>N=1, 3 yrs, success</td>
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<td></td>
<td></td>
<td></td>
<td>Schwartz JPIDS 2013&lt;sup&gt;21&lt;/sup&gt;</td>
<td>N=1, 15 yrs, failure</td>
</tr>
<tr>
<td>Hematological malignancy</td>
<td>To cure</td>
<td>VCZ + echinocandin</td>
<td>C</td>
<td>III</td>
<td>Hassler PIDJ 2017&lt;sup&gt;19&lt;/sup&gt;</td>
<td>N=3, 8-10 yrs, response 1/3</td>
</tr>
<tr>
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<td></td>
<td>Litvinov CMI 2015&lt;sup&gt;27&lt;/sup&gt;</td>
<td>N=1, 17 yrs, success</td>
</tr>
<tr>
<td>Hematological malignancy</td>
<td>To cure</td>
<td>VCZ</td>
<td>A</td>
<td>III</td>
<td>Carllesse AMRIC 2017&lt;sup&gt;23&lt;/sup&gt;</td>
<td>N=6, 1-8 yrs, success 6/6</td>
</tr>
<tr>
<td></td>
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<td></td>
<td>Hassler PIDJ 2017&lt;sup&gt;19&lt;/sup&gt;</td>
<td>N=2, 3 yrs, 7 yrs, failure 2/2</td>
</tr>
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<td></td>
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<td></td>
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<td></td>
<td>Vallernini J Infect 2017&lt;sup&gt;11&lt;/sup&gt;</td>
<td>N=1, 12 yrs, success</td>
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<td></td>
<td></td>
<td></td>
<td>Arnoni Mycopathol 2018&lt;sup&gt;80&lt;/sup&gt;</td>
<td>N=1, 9 yrs, success</td>
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<td></td>
<td></td>
<td></td>
<td>Siddhu IJPM 2013&lt;sup&gt;27&lt;/sup&gt;</td>
<td>N=1, 12 yrs, survived</td>
</tr>
<tr>
<td>Hematological malignancy</td>
<td>To cure</td>
<td>L-AmB</td>
<td>C</td>
<td>III</td>
<td>Carllesse AMRIC 2017&lt;sup&gt;23&lt;/sup&gt;</td>
<td>N=1, 9 mo, success</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>Vaghe Bmc ID 2007&lt;sup&gt;93&lt;/sup&gt;</td>
<td>N=1, 11 yrs, failure</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Tracz JCM 2009&lt;sup&gt;28&lt;/sup&gt;</td>
<td>N=1, 12 yrs, failure</td>
</tr>
<tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Cesaro Mycoses 2010&lt;sup&gt;42&lt;/sup&gt;</td>
<td>N=1, 8 yrs, failure</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Hol BMT 2014&lt;sup&gt;21&lt;/sup&gt;</td>
<td>N=1, 1 yr, success</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>Morel PedDermatol 2013&lt;sup&gt;42&lt;/sup&gt;</td>
<td>N=1, 13 yrs, failure</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td>Rodriguez BMT 2003&lt;sup&gt;44&lt;/sup&gt;</td>
<td>N=1, 3 yrs, success</td>
</tr>
<tr>
<td>Hematological malignancy with endophthalmitis</td>
<td>To cure</td>
<td>ABCD 5 mg/kg tid + VCZ intravitreal 100 μg/0.1 ml</td>
<td>C III</td>
<td>Kivivouri EJP 2004435</td>
<td>N=2, 5 yrs, 8 yrs, failure 2/2</td>
<td></td>
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<td></td>
<td></td>
<td>Guzman-Cottrill PID 2004435</td>
<td>N=1, 3 mo, failure</td>
<td></td>
</tr>
<tr>
<td>Chronic granulomatous disease</td>
<td>To cure</td>
<td>D-AmB + ketoconazole 150 mg qd</td>
<td>C III</td>
<td>Bassiri-Jahromi MedMycol 2012439</td>
<td>N=1, 15 yrs, success</td>
<td></td>
</tr>
<tr>
<td>Burn</td>
<td>To cure</td>
<td>Voriconazole + amphotericin B deoxycholate + surgical intervention</td>
<td>C III</td>
<td>Rosanova BJID 2016439</td>
<td>N=15 (mean age: 2 yrs; range 1-9 yrs) success 14, failure 1</td>
<td></td>
</tr>
<tr>
<td>Burn</td>
<td>To cure</td>
<td>AmB</td>
<td>C III</td>
<td>Schaal Burns 2015439</td>
<td>N=1, 2 yrs, success</td>
<td></td>
</tr>
<tr>
<td>Burn</td>
<td>To cure</td>
<td>VCZ</td>
<td>C III</td>
<td>Muhammed Medicine 2013439</td>
<td>N=3, 4-17 yrs, success 3/3</td>
<td></td>
</tr>
<tr>
<td>Burn</td>
<td>To cure</td>
<td>L-AmB, VCZ</td>
<td>C III</td>
<td>Muhammed Medicine 2013439</td>
<td>N=1, 8 yrs, success</td>
<td></td>
</tr>
<tr>
<td>Burn</td>
<td>To cure</td>
<td>L-AmB, MICA</td>
<td>C III</td>
<td>Muhammed Medicine 2013439</td>
<td>N=1, 4 yrs, failure</td>
<td></td>
</tr>
<tr>
<td>Burn</td>
<td>To cure</td>
<td>L-AmB</td>
<td>C III</td>
<td>Muhammed Medicine 2013439</td>
<td>N=1, 15 yrs, success</td>
<td></td>
</tr>
<tr>
<td><strong>Antifungal salvage treatment</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hematological malignancy</td>
<td>To cure</td>
<td>L-AmB 5-9 mg/kg qd + CASPO 70 mg/m² qd loading on d1, 50 mg/m² qd from d2</td>
<td>C III</td>
<td>Jemura PIDJ 2018439</td>
<td>N=1, 10 yrs, ALL, L-AmB (9 mg/kg qd) + CASPO (70 mg/m² qd as loading dose followed by 50 mg/m² qd), F. keratoctyiscum cultured, success</td>
<td></td>
</tr>
<tr>
<td>Hematological malignancy</td>
<td>To cure</td>
<td>VCZ + CASPO</td>
<td>C III</td>
<td>Leszaro Mycoses 2010439</td>
<td>N=1, 8 yrs, ALL, success</td>
<td></td>
</tr>
<tr>
<td>Hematological malignancy</td>
<td>To cure</td>
<td>VCZ</td>
<td>C III</td>
<td>Tezcan JCM 2009439</td>
<td>N=1, 12 yrs, HSCT, success</td>
<td></td>
</tr>
<tr>
<td>Hematological malignancy</td>
<td>To cure</td>
<td>L-AmB 10 mg/kg qd + VCZ start 4 d after L-AmB</td>
<td>C III</td>
<td>Rodriguez BMT 2003439</td>
<td>N=1, 3 yrs, aplastic anemia, success</td>
<td></td>
</tr>
<tr>
<td>Hematological malignancy</td>
<td>To cure</td>
<td>AmB + 5-FC</td>
<td>C III</td>
<td>Richardson RID1988439</td>
<td>N=1, 7 yrs, ALL, failure</td>
<td></td>
</tr>
</tbody>
</table>

**Standard pediatric dose unless stated otherwise:** 5-FC, 5-fluorocytosine; ABCD, amphotericin B colloidal dispersion; ALL, acute lymphocytic leukemia; AmB, amphotericin B; AML, acute myeloid leukemia; bid, twice a day; CASPO, caspofungin; D-AmB, amphotericin B deoxycholate; d, days; FCZ, fluconazole; G-CSF, granulocyte colony-stimulating factor; HLH, hemophagocytic lymphohistiocytosis; HSCT, hematopoietic stem cell transplantation; JMML, Juvenile myelomonocytic leukemia; L-AmB, liposomal amphotericin B; MICA, micafungin; mo, month(s); po, orally; qd, once a day; QoE, quality of evidence; SoR, strength of recommendation; tid, three times a day; TRB, terbinafine; VCZ, voriconazole; yrs, years.

**Recommendations** – First-line treatment with VCZ monotherapy or combination therapy with VCZ and a lipid formulation of AmB is strongly recommended. Monotherapy with L-AmB is marginally supported; monotherapy with D-AmB is discouraged. Combination therapy with VCZ plus high-dose L-AmB or an echinocandin is recommended as salvage therapy with marginal strength. In line with recommendations in adults, surgical debridement is strongly recommended for localized infections.
2. Lomentosporiosis

Epidemiology of lomentosporiosis

Based on phylogenetic profiling, *Lomentospora prolificans* is now distinguished from *Scedosporium* spp.439. *L. prolificans* is ubiquitously found as a soil saprophyte predominately in arid climates of Australia, south-western US and Spain, reflected by the proportionally higher number of reported cases from these regions9,440,441. Prevalence and incidence data for lomentosporiosis are largely unknown. In a US study, *L. prolificans* accounted for 2% of mold infections and 6% of non-Aspergillus infections identified in liver and heart transplant recipients442. In France, four cases in hematological patients have been reported within 6 years443. Another study in the US reported 0.2 lomentosporiosis cases per 100,000 inpatient days in hematological patients (4 patients between 1989 and 2006)444. Immunocompromised patients treated for hematological malignancy and those undergoing HSCT or SOT are at highest risk for lomentosporiosis11,445.

In more than 80% of hematological patients, *L. prolificans* causes disseminated disease, mostly with fungemia, which is associated with a particularly dire outcome11,446. Endocarditis and brain infections are commonly seen in disseminated disease. The risk of dissemination in HSCT and SOT patients depends on the type of transplantation and immunosuppressive regimen447. In one review, only 34 of 162 patients (21%) were noted to have no underlying disease441. Infections after direct inoculation via surgical wounds or after traumatic injuries may also disseminate to non-contiguous organs11,440,444,445,448,456 (Figure 7).
Figure 7. Worldwide distribution of lomentosporiosis (reported cases between 2000 and 2019 per million population)

Cases of *Lomentospora*-related infections reported in the medical literature were identified in a PubMed search on November 15, 2019 using the search string “Scedospori* OR Pseudallescheri* OR Lomentospori*” that yielded 1,628 publications. In total, 233 cases were identified from 18 countries. The vast majority of cases were reported from Australia (n=108), the United States (n=53), followed by Spain (n=20), Germany (n=15), and Japan (n=12). Australia reported ~8-times more lomentosporiosis cases per million population than the average number of all countries. The number of cases reported between 2000 and 2019 is presented as cases per million population per country. The resident population per country was obtained from www.worldometers.info.

Diagnosis of lomentosporiosis

Evidence – The definitive diagnosis of *L. prolificans* infection relies on isolation of the fungus from biopsies, sterile body fluids and blood cultures. For respiratory tract samples of patients with cystic fibrosis (CF), a special selective medium (SceSel+) has shown improved rates of isolation as it inhibits
the overgrowth by aspergilli. Other selective fungal culture media that have been successfully used are the inhibitory mold agar (IMA), and brain heart infusion (BHI) agar. If all three are not available, specimens can be cultured on sabouraud dextrose agar (SDA), or horse blood agar at 30°C or 37°C.

In contrast to Scedosporium, L. prolificans is not capable to grow in the presence of cycloheximide. Species identification is achieved by identification by macroscopic and microscopic examination of the colonies. L. prolificans is usually characterized by the black color of its colonies, and its characteristic flask-shaped and annellated conidiogenous cells (Table 8), but identification should be confirmed by subsequent ITS gene sequencing. In direct microscopy L. prolificans may form pigmented hyphae in infected tissue sections, the organism is therefore classified as a cause of phaeohyphomycosis.

Recommendations – The guideline group strongly recommends obtaining infected tissue and body fluids for histological evaluation and culture. For respiratory tract samples from CF patients, the guideline group strongly supports the usage of SceScl+, IMA or BHI media.

Diagnosis – Microbiology – Serology

Evidence – Standardized commercial serological tests for the detection of L. prolificans are lacking. Heat shock protein 70 and 90, enolase and immunomes (conidial and hyphal proteins/enzymes) reacting with human IgA have been identified in sera as candidate antigens for serodiagnostic tests (Table 8).

Recommendations – There is currently no commercial serological test, and in-house tests are only marginally recommended.

Diagnosis – Microbiology – Molecular-based

Evidence – Standardized commercial PCR assays are lacking for the diagnosis of L. prolificans infection. Various assay formats (oligoarray, multiplex PCR, PCR+reverse line blot hybridization, multiplex+microarray, pan-fungal PCR + ITS sequencing, and multiplex tandem PCR) have been published from different groups in the field mainly based on the ITS region (Table 8).
**Recommendations** – Based on case reports, the use of broad-range PCR with subsequent hybridization or microarray ID is marginally supported as no standardized commercial assay is available.

**Diagnosis – Microbiology – Species identification**

**Evidence** – Based on positive cultures, accurate species identification is mainly achieved by morphological identification or ITS sequencing\(^{440,484,495,555-557}\). On autopsy material broad-range PCR and subsequent hybridization or microarray identification is used\(^{531,558}\). MALDI-TOF MS also may identify *L. prolificans* from culture extract\(^{327}\) (Table 8).

**Recommendations** – The guideline group strongly supports obtaining pure cultures for species identification via morphological characteristics, MALDI-TOF MS or ITS sequencing. Also, establishing a diagnosis based on autopsy samples by culture and histopathology/ITS sequencing is strongly recommended.

**Microbiology – susceptibility testing**

**Evidence** – *L. prolificans* is a highly drug resistant fungus, sometimes even showing high MIC values for all antifungal agents tested [AmB, itraconazole (ICZ), VCZ, PCZ, TRB, caspofungin (CASPO ), micafungin (MICA ), and anidulafungin (ANID )], although occasionally lower MICs are observed against VCZ, sometimes PCZ and rarely for more antifungal classes\(^{4,151,469,559,560}\). Similar results were found using CLSI\(^{561}\), EUCAST\(^{559}\) and Sensititre® YeastOne® YO10 panel (Trek Diagnostic Systems Ltd.) methods\(^{151,560}\) (Table 8).

**Recommendations** – The guideline group strongly recommends susceptibility testing of *L. prolificans* to inform susceptibility patterns for epidemiological purposes and moderately for clinical decision making, despite the fact that clinical breakpoints are not available.

**Diagnosis - Pathology**

**Evidence** – Histological findings include mostly hyaline hyphae, although the cultures can be dark and hyphae may appear melanized in direct microscopy after KOH treatment, which may be in contrast to *Scedosporium* spp., *Aspergillus* spp., and *Fusarium* spp., which have hyaline hyphae\(^ {445}\). Calcufluor white
staining can provide better sensitivity than KOH. In general, however, Lomentospora hyphae may not differ markedly from those of Scedosporium spp. Other typical features of L. prolificans include irregular branching patterns and adventitious conidiation in tissue. In contrast, other common hyalohyphomycotic molds usually present with regular hyphal septation, and dichotomous branching (Table 8).

**Recommendations** – The guideline group strongly recommends histopathological examination of biopsy tissue in cases of suspected infection.

**Diagnosis – Imaging**

**Evidence** – *L. prolificans* may cause CNS disease, usually during disseminated infection. Case reports have outlined imaging procedures for brain, sinuses, lung, abdomen, heart, bones, and disseminated infections. As with other invasive fungal infections, imaging is important to detect and localize *L. prolificans* infection and guide microbiological sampling of infected tissue and/or body fluids (Table 8).

<table>
<thead>
<tr>
<th>Table 8. Microbiological, histopathological and imaging diagnostics of Lomentospora spp. infections</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Population</strong></td>
</tr>
<tr>
<td>Microscopy, culture, MIC testing</td>
</tr>
<tr>
<td>Any</td>
</tr>
<tr>
<td>Any</td>
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<tr>
<td>CF</td>
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<td>Hematology</td>
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<td>Test / Technique</td>
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<td>Any</td>
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<td>Any</td>
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<tr>
<td>Any</td>
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<tr>
<td>Serology assays</td>
</tr>
<tr>
<td>Oncology</td>
</tr>
<tr>
<td>Any</td>
</tr>
<tr>
<td>All</td>
</tr>
<tr>
<td>Nucleic-acid based assays</td>
</tr>
<tr>
<td>Any</td>
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<tr>
<td>Neutropenic patients</td>
</tr>
<tr>
<td>Any</td>
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<tr>
<td>CF</td>
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<td>CF</td>
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<tr>
<td>CF</td>
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<tr>
<td>Any with meningitis</td>
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<tr>
<td>Any</td>
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<tr>
<td>Any</td>
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<tr>
<td>CF</td>
</tr>
<tr>
<td>Tissue-based diagnosis</td>
</tr>
<tr>
<td>Imaging studies</td>
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<tr>
<td>Any with brain lesions/ abscesses</td>
</tr>
<tr>
<td>Any with sinusitis</td>
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<tr>
<td>Any with pneumonia</td>
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</tbody>
</table>
### Recommendations

For the detection and localization of lomentosporiosis and imaging-guided sampling of biopsies and body fluids, the guideline group strongly recommends magnetic resonance imaging (MRI) and CT scan for bones, MRI scan for the brain, transesophageal echocardiogram for the heart, and CT scan of the sinuses, lungs, and abdomen, based on suspected site of infection. The guideline group moderately supports the usage of positron emission tomography (PET) scan for disseminated lomentosporiosis and CT of the brain. Conventional radiography of the bones and the chest is marginally supported (Figure 8).

<table>
<thead>
<tr>
<th>Any with pneumonia</th>
<th>Recommendations</th>
<th>Imaging characteristics</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>To assess clinical manifestations and imaging characteristics</td>
<td>CT scan of the lungs</td>
<td>A III</td>
<td>Berenguer Medicine 1997⁵⁵², Maertens AnnHematol 2000⁵⁴⁰, Uno JIC 2014⁵³⁶, Ochi IHJ 2015⁵¹⁰, Bouza CID 1996⁵⁶⁵</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Any with abdominal / lymph node infection</th>
<th>Recommendations</th>
<th>Imaging characteristics</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>To assess clinical manifestations and imaging characteristics</td>
<td>CT scan of the abdomen</td>
<td>A III</td>
<td>Ochi IHJ 2015⁵¹⁰</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Any with bone infection</th>
<th>Recommendations</th>
<th>Imaging characteristics</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone radiography</td>
<td>MRI scan for bones</td>
<td>A III</td>
<td>Gosbell Mycoses 2003⁵⁷⁵, Taj-Aldeen Medicine 2015⁵³⁸, Pickles JInfect 1996⁵³⁷, Ochi IHJ 2015⁵¹⁰</td>
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</table>

<table>
<thead>
<tr>
<th>Any with bone infection</th>
<th>Recommendations</th>
<th>Imaging characteristics</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRI of spine / bones</td>
<td>PET/CT</td>
<td>B III</td>
<td>Kelly BMCID 2016⁵⁶⁵</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Any with dissemination</th>
<th>Recommendations</th>
<th>Imaging characteristics</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>PET/CT</td>
<td>MRI of spine / bones</td>
<td>A III</td>
<td>Kelly BMCID 2016⁵⁶⁵</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Any with endocarditis</th>
<th>Recommendations</th>
<th>Imaging characteristics</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Echocardiogram (preferably transesophageal)</td>
<td>PET/CT</td>
<td>B III</td>
<td>Kelly BMCID 2016⁵⁶⁵, Wakabayashi IntMed 2016⁵³⁸</td>
</tr>
</tbody>
</table>

AmB, amphotericin B; CF, cystic fibrosis; CLSI, Clinical and Laboratory Standards Institute; CT, computed tomography; DNA, deoxyribonucleic acid; EUCAST, European Committee for Antimicrobial Susceptibility Testing; FCZ, fluconazole; FFPE, formalin-fixed paraffin-embedded; HSCT, hematopoietic stem cell transplantation; Hsp, heat shock proteins; ICZ, itraconazole; IgA, immunoglobin A; ITS, internal transcribed spacer; KOH, potassium hydroxide; MALDI-TOF MS, matrix assisted laser desorption ionization-time of flight mass spectrometry; MIC, minimal inhibitory concentration; MRI, magnetic resonance imaging; PET, positron emission tomography; PCR, polymerase chain reaction; PCZ, posaconazole; QoE, quality of evidence; SceSel+, Scedosporium-selective medium; SDA, Sabouraud dextrose agar; SoR, strength of recommendation; VCZ, voriconazole.
**Figure 8.** Optimal diagnostic pathway for lomentosporiosis, when all imaging and assay techniques are available

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**Legend:**
- **strongly recommended**
- **moderately recommended**
- **marginally recommended**
- **recommended against**

BH1, brain heart infusion agar; CT, computed tomography; IMA, inhibitory mold agar; ITS, internal transcribed spacer; MALDI-TOF MS, matrix-assisted laser desorption/ionization time-of-flight mass spectrometry; MRI, magnetic resonance imaging
Treatment approaches to lomentosporiosis

Treatment in adults

First-line antifungal monotherapy

Evidence – *L. prolificans* appears to be intrinsically resistant to most antifungals, with VCZ showing the best *in vitro* activity against this fungus. In several case series, the use of VCZ monotherapy led to the successful treatment of invasive lomentosporiosis in patients with various organ involvement patterns, with successful outcomes varying by case series between 25% to 66%. In two case series, outcome with AmB monotherapy was inferior to VCZ monotherapy, with survival in 2/13 patients receiving AmB monotherapy in one case series and 0/4 patients successfully treated in another case series.

ISA monotherapy was effective in one case report in a patient with interstitial pulmonary disease and miltefosine was effective in a patient with disseminated lomentosporiosis and anazole drug-drug interaction (Table 9).

<table>
<thead>
<tr>
<th>Population</th>
<th>Intention</th>
<th>Intervention</th>
<th>SoR</th>
<th>QoE</th>
<th>Reference</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any</td>
<td>To cure</td>
<td>VCZ iv + TRB +/- other antifungals</td>
<td>A</td>
<td>Iilu</td>
<td>Jenks CMI 2020</td>
<td>N=40, VCZ + TRB combination (+/- other antifungals) 10/16 (63%) success, other treatments 7/24 (29%) success</td>
</tr>
<tr>
<td></td>
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<td></td>
<td>Seidel CRM 2019</td>
<td>N=56, mortality with VCZ 52.6% vs. therapy w/o VCZ 68.8%, mortality with VCZ mono 50% or in combination 55.3%</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>Jenks IJAA 2018</td>
<td>N=6, VCZ + TRB 3/3 survived vs. VCZ or L-AmB 0/3 survived</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Wangchinda MMCR 2018</td>
<td>N=1</td>
</tr>
<tr>
<td>Any</td>
<td>To cure</td>
<td>VCZ + either L-AmB OR MICA</td>
<td>B</td>
<td>III</td>
<td>Jenks IJAA 2018</td>
<td>N=2, 1/2 survived</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Jenks CID 2020</td>
<td>N=8, response 2/8 (25%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Seidel CRM 2019</td>
<td>N=17 7/17 [41%] survived</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Tamaki TID 2016</td>
<td>N=1, failure</td>
</tr>
<tr>
<td>Any</td>
<td>To cure</td>
<td>VCZ iv bid</td>
<td>B</td>
<td>Iilu</td>
<td>Cobo MedMycol 2017</td>
<td>N=5, success 2/4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Troke AAC 2008</td>
<td>N=36, success 16/36 (44%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Hussain CID 2005</td>
<td>N=18, VCZ 2/3 survived vs. AmB 2/13 survived</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Jenks CID 2020</td>
<td>N=7, success 3/7; breakthrough lomentosporiosis in N=6 with VCZ prophylaxis</td>
</tr>
<tr>
<td>Intersitial</td>
<td>To cure</td>
<td>ISA</td>
<td>C</td>
<td>III</td>
<td>Marty Mycoses 2018</td>
<td>N=1, success</td>
</tr>
<tr>
<td>pulmonary</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hematological malignancy patients</td>
<td>To cure</td>
<td>VCZ + TRB</td>
<td>A</td>
<td>III</td>
<td>Cooley EID 2007</td>
<td>N=7, VCZ plus TRB 2/4 survived vs. ICZ plus TRB or AmB 0/3 survived</td>
</tr>
<tr>
<td>CF with lung infection</td>
<td>To cure</td>
<td>VCZ + either MICA iv, TRB po OR AmB inhaled</td>
<td>C</td>
<td>III</td>
<td>Schwarz JCF 2018</td>
<td>N=3, achieved improvement but no eradication</td>
</tr>
</tbody>
</table>

Table 9. First-line antifungal therapy for Lomentospora spp. infections
Recommendations – While combination antifungal therapy is the preferred option (see next paragraph), the guideline group moderately supports first-line treatment with VCZ monotherapy specifically in those who are more immunocompetent and have localized infection. Given superior outcomes seen with other antifungal treatment strategies, monotherapy with L-AmB is not recommended. Although treatment success was reported in one case report with miltefosine monotherapy, more data are needed before recommending this option. There is no evidence supporting other first-line monotherapy regimens.

First-line antifungal combination therapy

Evidence – In the largest case series of lomentosporiosis infections published to date combination antifungal therapy was associated with increased 28-day survival (15/24 survived vs. 4/16 receiving monotherapy)\(^367\). In vitro synergism has been demonstrated with combinations of AmB plus MICA\(^576\), AmB plus pentamidine\(^577\), colistin plus VCZ\(^578\) and particularly VCZ plus TRB\(^572,579,580\). In several case reports and case series, combination antifungal therapy successfully treated lomentosporiosis with various organ involvement patterns and mixed underlying disease, particularly with VCZ (intravenous 6 mg twice daily loading dose followed by 4 mg twice daily) plus TRB (500 mg daily), plus or minus other antifungals\(^486\). In one case report, VCZ plus TRB and surgical debridement resulted in suppression of \textit{L. prolificans} osteomyelitis in an immunocompetent woman\(^556\) and in a small case series, 3/3 patients treated with VCZ plus TRB combination therapy survived\(^162\). In two larger case series, 8/18 (45%) individuals treated with VCZ plus TRB combination therapy were alive at Day 42\(^51\) and 10/16 (63%) who were treated with VCZ plus TRB combination therapy plus or minus other antifungals were alive at Day 28 in another case series\(^367\); in the latter case series, survival at 84 and 360 days was significantly higher in those who received VCZ plus TRB combination therapy plus or minus other antifungals compared to those receiving other antifungal therapies\(^367\).

Combination therapy with VCZ plus either AmB or MICA has resulted in treatment response and survival in patients with mixed underlying disease in several case series\(^11,162,367\), although outcomes did not differ.
compared to those treated with VCZ plus TRB combination therapy plus or minus other antifungals. In patients with hematological malignancy in one case series, 2/4 (50%) who were treated with VCZ plus TRB combination therapy survived, while 0/3 survived who received ICZ plus TRB or AmB. In a case series of three patients with CF, combination therapy with VCZ plus MICA, TRB, or inhaled AmB resulted in clinical improvement but not in eradication of the fungus. Surgery as adjunct treatment has been shown to be significantly associated with survival. Resection of surgically amenable lesions is an important adjunct to management of infections caused by \textit{L. prolificans}. Correction of underlying immune deficiencies is also an important adjunct to antifungal therapy.

**Recommendations** – The guideline group strongly supports first-line VCZ-based combination antifungal therapy for treatment of infections caused by \textit{L. prolificans}, particularly VCZ plus TRB plus or minus other antifungal agents. Combination therapy with VCZ plus either L-AmB or MICA is moderately supported. In patients with hematological malignancy, combination therapy with VCZ plus TRB plus or minus other antifungal agents is also strongly recommended. In patients with CF, combination therapy with VCZ plus MICA, TRB, or inhaled AmB is marginally supported, as available data are too limited to give stronger support to this strategy. There is little evidence supporting other first-line combination therapy regimens.

**Other treatment options**

**Evidence** – Surgery in general and surgical debridement has been associated with improved treatment response. (Table 10).

**Table 10. Other treatment options for \textit{Lomentospora} spp. infections**

<table>
<thead>
<tr>
<th>Population</th>
<th>Intention</th>
<th>Intervention</th>
<th>SoR</th>
<th>QoE</th>
<th>Reference</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematopoietic stem cell transplant patients</td>
<td>To cure</td>
<td>VCZ as secondary prophylaxis</td>
<td>C</td>
<td>III</td>
<td>Penteado TID 2018</td>
<td>N=1, failure</td>
</tr>
<tr>
<td>Immunocompetent with localized infection</td>
<td>To cure</td>
<td>Surgical debridement</td>
<td>A</td>
<td>III</td>
<td>Wangchinda MMCR 2018</td>
<td>N=1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Masukane IntMed 2017</td>
<td>N=1, success</td>
</tr>
<tr>
<td>Hematological malignancy</td>
<td>To cure in context azole drug-drug interactions</td>
<td>Miltefosine</td>
<td>C</td>
<td>III</td>
<td>Trubiano Mycoses 2014</td>
<td>N=1, success</td>
</tr>
<tr>
<td>All</td>
<td>To cure</td>
<td>Surgery (debridement, enucleation, vitrectomy)</td>
<td>A</td>
<td>II</td>
<td>Rodriguez-Tudela MedMycol 2009</td>
<td>N=169, survival associated with surgery</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Jenks CMI 2020</td>
<td>N=7, survival associated with surgery</td>
</tr>
</tbody>
</table>

QoE, quality of evidence; SoR, strength of recommendation; VCZ, voriconazole.
Recommendations – The guideline group strongly recommends the use of surgical debridement where applicable.

Antifungal salvage treatment

Evidence – VCZ monotherapy with TDM was effective in one large case series of 36 patients when VCZ was used for compassionate use or salvage therapy. In a small case series of two patients, both VCZ plus AmB plus PCZ, and TRB plus AmB plus PCZ combinations led to treatment response in both patients.

Miltefosine was effective in one case report in a patient with disseminated *L. prolificans* infection and an azole drug-drug interaction (Table 11).

Table 11. Antifungal salvage treatment for *Lomentospora spp.* infections

<table>
<thead>
<tr>
<th>Population</th>
<th>Intention</th>
<th>Intervention</th>
<th>SoR</th>
<th>QoE</th>
<th>Reference</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any</td>
<td>To cure</td>
<td>VCZ + TDM</td>
<td>B</td>
<td>Ilu</td>
<td>Troke AAC 2008</td>
<td>N=36, 44% success</td>
</tr>
<tr>
<td>Any</td>
<td>To cure</td>
<td>PCZ + L-AmB + either VCZ OR TRB</td>
<td>C</td>
<td>III</td>
<td>Jenks CID 2020</td>
<td>N=2, response 2/2</td>
</tr>
</tbody>
</table>

*Standard dose unless stated otherwise; L-AmB, liposomal amphotericin B; PCZ, posaconazole; QoE, quality of evidence; SoR, strength of recommendation; TDM, therapeutic drug monitoring; TRB, terbinafine; VCZ, voriconazole.*

Recommendations – Although there is limited evidence to support a specific regimen to be used as salvage therapy for invasive lomentosporiosis, the guideline group recommends the use of combination antifungal therapy that should be tailored based on prior antifungal treatment and to the individual patient. VCZ is moderately recommended.

Treatment duration of lomentosporosis

Evidence – Extended duration of antifungal treatment has been associated with treatment success and/or survival in multiple case reports and case series. In two case series of patients with various underlying diseases and organ involvement patterns, patients who survived received VCZ plus TRB for at least 180 days and antifungal treatment for three to six months in another case series. In one case report of an immunocompetent patient with vertebral osteomyelitis, surgical debridement plus VCZ plus TRB for 180 days resulted in clinical improvement and this patient was maintained on suppressive therapy. In
a literature review of immunocompromised adults and children with osteomyelitis, patients were treated for a mean duration of 115 days with a treatment response in 86% of patients. In a multi-center study of CF patients and lomentosporiosis, mean duration of combination therapy was 3.9 months (Table 12).

Table 12. Treatment duration for Lomentospora spp. infections

<table>
<thead>
<tr>
<th>Population</th>
<th>Intention</th>
<th>Intervention</th>
<th>SoR</th>
<th>QoE</th>
<th>Reference</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any</td>
<td>To cure</td>
<td>181 d of therapy with VCZ + TRB</td>
<td>B</td>
<td>III</td>
<td>Jenks CID 2020</td>
<td>IQR 69-332 d</td>
</tr>
<tr>
<td>Adults and pediatric immunocompromised patients with osteomyelitis</td>
<td>To cure</td>
<td>Mean duration of 115 d (5 d-730 d) of combined treatment</td>
<td>B</td>
<td>Iir</td>
<td>Taj-Aldeen Medicine 2015</td>
<td>Systematic literature review</td>
</tr>
<tr>
<td>Immunocompetent with osteomyelitis</td>
<td>To cure</td>
<td>&gt;180 d of therapy with VCZ and TRB</td>
<td>C</td>
<td>II</td>
<td>Wangchinda MMCR 2018</td>
<td>Case report and literature review</td>
</tr>
<tr>
<td>CF patients</td>
<td>To cure</td>
<td>1-14 mo of therapy, mean duration 3.9 months</td>
<td>B</td>
<td>II</td>
<td>Schwarz JCF 2019</td>
<td>N=31, AmB 25 mg qd by inhalation + iv + VCZ 40 mg qd by inhalation + iv</td>
</tr>
<tr>
<td>Any</td>
<td>To cure</td>
<td>3-6 mo of therapy</td>
<td>B</td>
<td>II</td>
<td>Jenks IJAA 2018</td>
<td>N=7</td>
</tr>
</tbody>
</table>

*Standard dose unless stated otherwise; bid, twice a day; CF, cystic fibrosis; d, days; IQR, interquartile range; iv, intravenous; mo, month(s); qd, once a day; QoE, quality of evidence; SoR, strength of recommendation; TRB, terbinafine; VCZ, voriconazole.*

Recommendations – Extended durations of antifungal therapy have been associated with improved outcomes and survival, although no evidence exists to support a pre-specified duration of therapy. It is reasonable to tailor the duration of therapy to the individual patient and consider continuing antifungal therapy until immunological recovery and resolution of all clinical evidence of disease, if possible. A duration of at least 4 to 6 months of combination therapy has been most associated with positive outcomes and thus is moderately recommended (Figure 9).
Figure 9. Optimal treatment pathway for lomentosporiosis in adults when all treatment modalities and antifungal drugs are available.

Suspected and confirmed invasive infections due to *Lomentospora* spp. are emergencies and require rapid action.

Immediate treatment initiation

Surgery (debridement, enucleation, vitrectomy)

- Voriconazole iv
  - 2 x 6 mg/kg/d d1;
  - 2 x 4 mg/kg/d from d2; use TDM
  + Terbinafine
  - 500-1000 mg/d
  - Other antifungals

- Voriconazole iv
  - 2 x 6 mg/kg/d d1;
  - 2 x 4 mg/kg/d from d2; use TDM

- Liposomal Amphotericin B

Response assessment (e.g., weekly imaging)

Progressive disease*

- Voriconazole iv
  - 2 x 6 mg/kg/d d1;
  - 2 x 4 mg/kg/d from d2; use TDM

- Posaconazole iv/tab
  - 2 x 300 mg/d d1;
  - 1 x 300 mg/d from d2
  + Liposomal Amphotericin B
  - 1 x 3-10 mg/kg/d
  + Voriconazole iv
  - 2 x 6 mg/kg/d d1;
  - 2 x 4 mg/kg/d from d2; use TDM
  + or
  - Terbinafine
  - 500-1000 mg/d

Legend:
- strongly recommended
- moderately recommended
- marginally recommended
- recommended against

TDM, therapeutic drug monitoring

* Choice of salvage treatment always depends by the treatment that the patient failed to respond to.
Specific considerations on treatment of lomentosporiosis in children

Evidence – Published case reports and case series show poor outcomes from pneumonia and fungemia caused by *L. prolificans* in immunocompromised children. A larger case series of osteoarticular infections caused by non-*Aspergillus* molds showed a higher incidence of *L. prolificans* bone and joint infections in children compared to adults (35% vs 10%). In addition, direct inoculation was the main mechanism of infection in 73.5% in children compared to 43.5% in adults. In a recent review of invasive *Lomentospora* (*n*=22) and *Scedosporium* (*n*=33) infections in children, surgery and VCZ treatment were associated with improved clinical outcome (Table 13).

### Table 13. First-line antifungal therapy for *Lomentospora* spp. infections in children

<table>
<thead>
<tr>
<th>Population</th>
<th>Intention</th>
<th>Intervention</th>
<th>SoR</th>
<th>QoE</th>
<th>Reference</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any</td>
<td>To cure</td>
<td>VCZ + other antifungals + surgery for localized infections</td>
<td>A</td>
<td>III</td>
<td>Seidel IJID 2019</td>
<td>N=22</td>
</tr>
<tr>
<td>Neuroblastoma</td>
<td>To cure</td>
<td>AmB lipid-based formulations</td>
<td>C</td>
<td>III</td>
<td>Sparrow PHO 1992</td>
<td>N=1, 2.6 yrs, died</td>
</tr>
<tr>
<td>Hematological malignancy</td>
<td>To cure</td>
<td>L-AmB 12 mg/kg qd</td>
<td>C</td>
<td>III</td>
<td>Ponteado TID 2018</td>
<td>N=1, 14 yrs, failure</td>
</tr>
<tr>
<td>Any with osteoarticular infections</td>
<td>To cure</td>
<td>Surgery</td>
<td>B</td>
<td>II</td>
<td>Taj-Aldeen Medicine 2015</td>
<td>N=12, mostly trauma/puncture wounds; 9/12 (75%) complete response</td>
</tr>
</tbody>
</table>

*Standard pediatric dose unless stated otherwise; AmB, amphotericin B; ICZ, itraconazole; L-AmB, liposomal amphotericin B; qd, once a day; QoE, quality of evidence; SoR, strength of recommendation; VCZ, voriconazole; yrs, years.*

Recommendation - Treatment recommendations follow those given for adults, with VCZ (+ TDM) being the backbone of therapy, with improved outcomes reported when combined with TRB, L-AmB or MICA (strong recommendation). Surgery plays a major role and is strongly recommended in the treatment of localized infections.

3. Scedosporiosis

Epidemiology of scedosporiosis

*Scedosporium* spp. are ubiquitous saprophytes mostly found in temperate areas, with regional differences in species distribution. In the clinical setting, the most commonly isolated species are *Scedosporium boydii* and *Scedosporium apiospermum*. *Scedosporium aurantiacum* is isolated to a lesser extent mainly...
in Australia and Europe\textsuperscript{440,445,451,588-590}. Only few cases of infections caused by \textit{Scedosporium dehoogii} have been reported\textsuperscript{591-594}.

\textit{Scedosporium} spp. initiates two distinct diseases: mycetoma and scedosporiosis. \textit{Scedosporium} spp. are an important cause of eumycotic mycetoma and the most common cause of this infection in the United States\textsuperscript{595}. \textit{Scedosporium} mycetoma usually develops in immunocompetent patients. SOT and treatment for hematological disease are major risk factors for scedosporiosis. Patients predominantly present with pulmonary, cutaneous or cerebral infections\textsuperscript{11,445}. Secondary CNS infections may appear without an evident dissemination. Infection may also affect the paranasal sinuses or bones\textsuperscript{11,445}.

\textit{Scedosporium} spp. have been recovered from respiratory secretions of patients with chronic pulmonary conditions such as CF, ranking as the second most frequently isolated fungal pathogen after \textit{Aspergillus} spp.\textsuperscript{440,456,596}. The significance of \textit{Scedosporium} in this setting is uncertain but may be the first step towards invasive disease\textsuperscript{543,590}. Colonization has also been described in cancer patients\textsuperscript{444}. Surgery, intravenous drug injection, and repeated corticosteroid injections have also been associated with localized infections. The main route of entry of the pathogen in immunocompetent patients is traumatic inoculation or aspiration of contaminated water. Near drowning-, tsunami-, and earthquake-victims represent a high risk group for developing scedosporiosis\textsuperscript{597-600}. Near drowning has been associated with cerebral infection caused by \textit{S. apiospermum} that results from hematogenous spread from the lungs as the primary site of infection\textsuperscript{448,455}. CNS infection related to near drowning events caused by \textit{Scedosporium} spp. may also arise from penetration through the cribiform plate with direct invasion of the CNS. Eye infections after traumatic injuries are also common\textsuperscript{66,601-605}. Other affected body sides include the spine\textsuperscript{448,451,454}.

In a US study, \textit{S. apiospermum} accounted for 6\% of mold infections and 19\% of non-\textit{Aspergillus} infections identified in liver and heart transplant recipients\textsuperscript{442}. The incidence of scedosporiosis was 0.93 per 100,000 patient-inpatient days, with a noted increase from 1993 to 2005 in a US cancer center\textsuperscript{444}. In Australia, among 137 patients who were monitored for a median of 4 years post-lung transplantation, 13 had fungal infection and 3 of these were caused by \textit{S. apiospermum}\textsuperscript{596}. One percent of patients with lung transplantation developed infections caused by \textit{S. apiospermum}\textsuperscript{606}. (Figure 10).
Cases of severe *Scedosporium*-related infections reported in the medical literature were identified in a PubMed search on November 15, 2019 using the search string “Scedosporium* OR Pseudallescheria* OR Lomentospora*” that yielded 1,628 publications. In total, 541 cases were identified from 43 countries. Most cases were reported from the United States (n=146), Australia (n=73), Germany (n=60), India (n=58), Spain (n=41), and Japan (n=28). Australia and Austria (n=10) reported most of the cases per million population. Number of cases reported between 2000 and 2019 are presented as cases per million population per country. The resident population per country was obtained from www.worldometers.info.

**Diagnosis of Scedosporiosis**

**Diagnosis – Microbiology – Conventional Methods**

**Evidence** – Definitive diagnosis of scedosporiosis is based on culture of the pathogen from infected tissue samples and body fluids from sterile body regions or from blood. Direct microscopy and histopathology of clinical specimens is important for the diagnosis of a hyalohyphomycosis, while further discrimination based on microscopy is rarely possible. Branching patterns of...
Scedosporium spp. often resemble Aspergillus spp., with sometimes dichotomously branching septate hyphae seen in tissue, although branching off to the side at a 60° to 70° angle, which is different than the 45° angle seen with Aspergillus spp. In addition, distinctive coremia or an ascocarp as well the presence of pyriform adventitious conidia may indicate Scedosporium spp. as the mold. After a few days, the mold colony takes on a tan color and has sporulating structures that differ from Aspergillus spp. See also Figure 11 for microbiological characteristics.

**Figure 11. Microbiological characteristics of Pseudallescheria state of S. boydii (owned by co-author V. Arsic-Arsenjevic)**

*A. Pseudallescheria state of S. boydii growth on blood agar, B fully developed and ruptured cleistothecium, the hallmark of the sexual stage (teleomorph) of this fungus.*

Based on >11,600 respiratory tract samples from CF patients, the selective medium Scedosporium Selective agar (SceSel+) showed higher isolation rates than the standard medium\(^{543}\). Blyth *et al.* found a 90.6% isolation rate for SceSel+ compared with 50% Mycosel and 46.9% for Sabouraud dextrose agar\(^{544}\). Other selective fungal culture media that have been successfully used are the inhibitory mold agar (IMA), and brain heart infusion (BHI) agar\(^{546}\). Species identification of cultures is achieved by subsequent ITS sequencing\(^{13,495,541,542,599,671,760,846,879}\) or by macroscopic and microscopic examination of the colonies (Table 14).
Recommendations – The guideline group strongly recommends obtaining infected tissue and body fluids for histological evaluation, direct microscopy, and culture. For respiratory tract samples from CF patients, the guideline group strongly supports the use of selective fungal culture media like SceSceI+, IMA or BHI agar. Based on pure cultures, members of the genus Scedosporium can rarely be identified by morphology alone.

Diagnosis – Microbiology – Serology

Evidence – Standardized commercial serological tests for the detection of Scedosporium spp. infection are lacking. For CF patients, an ELISA test is under development that is based on the detection of mycelial catalase A1 of the S. apiospermum complex (Table 14).

Recommendations – There is currently no commercial serological test available.

Diagnosis – Microbiology – Molecular-based

Evidence – Standardized commercial PCR assays are lacking for the diagnosis of scedosporiosis. Various assay formats (oligoarray, multiplex PCR, PCR + reverse line blot hybridization, multiplex + microarray, pan-fungal PCR + ITS sequencing) have been published from different groups in the field mainly based on the ITS region. The assays from Harun et al. and Lu et al. aim to discriminate all Scedosporium spp. plus L. prolificans, while the assays from Bouchara et al. and Nagano et al. focus on the identification of the S. apiospermum complex. All assays have been evaluated on respiratory tract samples of CF patients. Highest sensitivity (100%) and specificity (99.2%) were found for the oligonucleotide array published by Bouchara et al. (Table 14).

Recommendations – The guideline group moderately supports the use of the oligonucleotide array published by Bouchara et al. for the detection of S. apiospermum complex in the sputum of CF patients, and marginally recommends other methods. Future studies are needed to evaluate these tests outside the CF setting.

Diagnosis – Microbiology – Species identification
Evidence – Based on positive cultures, species complex identification is mainly achieved by morphological identification or ITS sequencing. For the identification to the species level, sequencing of both ITS and β-tubulin is required\textsuperscript{555,902}. Alternative approaches are: loop-mediated isothermal amplification (LAMP), quantitative real time PCR (qPCR), PCR-based reverse line blot hybridization (PCR-RLB), rolling circle amplification (RCA), repetitive sequence PCR and PCR-ESI-TOF MS, multiplexed PCR and liquid-phase array that allow identification\textsuperscript{553,903,904}. Identification and genotyping can be done by repetitive sequence-based PCR\textsuperscript{905}. MALDI-TOF MS has been shown to be a reliable method for the identification to the genus level\textsuperscript{570} (Table 14).

Recommendations – The guideline group strongly recommends species identification of pure cultures using ITS1-ITS2 and β-tubulin sequencing, and marginally supports identification via alternative molecular methods.

Microbiology – Susceptibility testing

Evidence – Scedosporium spp. exhibit high MIC values for AmB, ISAV, ICZ, and fluconazole\textsuperscript{906}. Lowest MIC values are found for VCZ, followed by PCZ and the echinocandins (ANID, CASPO, MICA)\textsuperscript{151,559,907-909}. Similar results were found using CLSI\textsuperscript{151}, EUCAST testing\textsuperscript{559} and Sensititre\textsuperscript{®} YeastOne\textsuperscript{®} YO10 panels (Trek Diagnostic Systems Ltd.) \textsuperscript{151}. All studies found that VCZ was the most effective drug \textit{in vitro} (Table 14).

Recommendations – The guideline group strongly recommends susceptibility testing of Scedosporium spp. using Sensititre\textsuperscript{®} YeastOne\textsuperscript{®} YO10 panels (Trek Diagnostic Systems Ltd.), EUCAST or CLSI methodology to inform susceptibility patterns and moderately for clinical decision making, given the fact that clinical breakpoints are not available.

Diagnosis - Pathology

Evidence – Fresh tissue microscopy with KOH treatment in the microbiology laboratory shows hyaline hyphae similar to the hyphae of Aspergillus spp., Fusarium spp. and other hyalohyphomycetes. Discrimination from other hyalohyphomycetes is therefore difficult, even though Scedosporium spp. may show
some morphological features in histological findings with H&E or GMS stains such as irregular branching patterns, vascular invasion, and/or intra-tissue conidiation (Table 14).

**Recommendations** – The guideline group strongly recommends histopathology in the diagnosis of disease, and moderately recommends direct microscopy of biopsies using KOH treatment.

**Diagnosis – Imaging**

**Evidence** – Best imaging modality depends on the site of infection\(^411,910\). In case of suspected bone, spine, and joint infections MRI represents the method of choice for diagnosis of scedosporiosis, with fluorodeoxyglucose (PET)-CT being a suitable alternative imaging modality\(^411,454,910\). For detection of brain involvement (e.g. CNS abscess formations), MRI and, if MRI was not available, CT have been used successfully\(^448,451,452,597-599\). In CF patients, near drowning victims, and victims of natural disasters, who are at risk for developing pulmonary manifestations of scedosporiosis, chest CT is the imaging modality of choice, while for differentiating colonization from infection in CF patient thorax CT or chest radiograph have been used to detect the abundance of pulmonary infiltrates\(^445,452\) (Table 14).

<table>
<thead>
<tr>
<th>Population</th>
<th>Intention</th>
<th>Approach</th>
<th>SoR</th>
<th>QoE</th>
<th>Reference</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any with CF</td>
<td>To diagnose</td>
<td>Culture and histopathology</td>
<td>A III</td>
<td></td>
<td>Balandin MMCR 2016(^462)</td>
<td></td>
</tr>
<tr>
<td>Any</td>
<td>To diagnose</td>
<td>Culture and histopathology</td>
<td>A III</td>
<td></td>
<td>Balandin MMCR 2016(^462)</td>
<td></td>
</tr>
<tr>
<td>Any</td>
<td>To diagnose</td>
<td>Culture (species identification by ITS sequencing)</td>
<td>A III</td>
<td></td>
<td>Tortorano CMI 2014(^14)</td>
<td></td>
</tr>
<tr>
<td>Any</td>
<td>To diagnose</td>
<td>Direct microscopy</td>
<td>A III</td>
<td></td>
<td>Torres-Sánchez TransProceed 2018(^55)</td>
<td></td>
</tr>
<tr>
<td>Any</td>
<td>To diagnose</td>
<td>Culture of respiratory tracts samples on selective media (SceSel+, inhibitory mold agar or brain heart infusion agar)</td>
<td>A III</td>
<td></td>
<td>Sedlacek JCF 2015(^14)</td>
<td></td>
</tr>
<tr>
<td>Any</td>
<td>To diagnose</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(^455\) 452 (Table 14).
**Any** | To determine susceptibility | Susceptibility testing with microdilution EUCAST method | A | III | Alastruey-Izquierdo AAC 2018<sup>115</sup> | Most active compound VCZ with MIC50=1 mg/L, followed by echinocandins
---|---|---|---|---|---|---
**Any** | To determine susceptibility | Susceptibility testing with CLSI M38-A2 method | A | III | Espinel-Ingroff AJCM 2005<sup>105</sup> | No clinical breakpoints available
**Any** | To determine susceptibility of *S. apiospermum* | Susceptibility testing with Sensititre® YO10 test (TREK Diagnostic Systems Ltd) | A | IU | Halliday IJAA 2016<sup>111</sup> | N=14 isolates, VCZ most active antifungal
**Any** | To inform antifungal treatment | Susceptibility testing with microdilution EUCAST or CLSI method | B | III | Alastruey-Izquierdo AAC 2018<sup>115</sup> | No clinical breakpoints available

### Serology assays

**Any with CF** | To diagnose | Detection by ELISA of antibodies to mycelial catalase | C | III | Mina CVI 2015<sup>902</sup> | Catalase A1 might be a good candidate for the development of an immunoassay for serodiagnosis of infections caused by the *S. apiospermum* complex in patients with CF. Test not commercially available

### Nucleic-acid based assays

**Any with CF** | To detect *S. boydii* / *S. apiospermum* | Digoarray, with ITS region amplicons hybridized to the array for species identification | B | III | Bouchara JCM 2009<sup>111</sup> | N=57, sputum samples from 39 cases; *S. apiospermum* detected in 16/57 samples vs. 12/57 by culture
**Any with CF** | To detect *Scedosporium* species and *L. prolificans* | Reverse line blot (RLB) hybridization after group-specific PCR | C | III | Lu Mycoses 2011<sup>114</sup> | N=59, sputum samples from 52 cases; 62.7% of samples were positive by RLB vs. 8.5% by culture
**Any with CF** | To detect fungal species including *S. apiospermum* | PCR targeting the 18S-ITS1-5.8S-ITS2-28S rRNA gene plus nested PCR | C | III | Nagano MedMycol 2010<sup>802</sup> | N=77, sputum samples from 77 cases; *S. apiospermum* detected in 37/77 samples vs. 2/77 by selective culture
**Any with CF** | To detect and identify *Scedosporium* spp. and *L. prolificans* | Multiplex PCR, followed by RFLP analysis of ITS region | C | III | Harun JCM 2011<sup>102</sup> | 208 sputum samples from 69 cases; Sens. 62%, spec. 97%
**Any** | To identify ITS1-ITS2 + beta-tubulin sequencing | A | III | Hedayati MicPath 2019<sup>902</sup> | *S. boydii* in 2/90 and *Scedosporium ellipsoideum* in 1/90 CF patients
**Any** | To identify Culture + ITS1-ITS2/beta-tubulin sequencing | A | III | Ziesing MedMycol 2016<sup>855</sup> | *S. apiospermum/ Scedosporium boydii* in 2-3% CF patients, *S. aurantiacum, S. minutissimum* sporadically (N=3,186, over 5-yr period)
**Any** | To identify MALDI-TOF MS | B | III | Sitterie CMI 2014<sup>120</sup> | *S. boydii* in 2/90 and *Scedosporium ellipsoideum* in 1/90 CF patients
**Any with CF** | To identify ITS sequencing / microarray | C | III | Schwarz PIOSONe 2017<sup>704</sup> | *S. boydii, S. apiospermum, S. aurantiacum*
**Any with CF** | To identify and genotypen | Repetitive sequence-based PCR | C | III | Matray MedMycol 2016<sup>805</sup> | *S. boydii, S. apiospermum, S. minutissimum, S. aurantiacum, S. ellipsoideum*

### Tissue based diagnosis

**Any** | Species identification | Direct microscopy of biopsies using KOH treatment | B | III | Ramirez-Garcia MedMycol 2018<sup>445</sup> Kimura PatholInt 2010<sup>177</sup> | Difficult to distinguish *Scedosporium*-infected tissues from those infected by Aspergillus or Fusarium, as all of them present hyaline hyphae, regular hyphal septation, and sometimes dichotomous branching. Unique features such as irregular branching patterns or intravascular invasion and intratissue conidiation may help pathologists to diagnose *Scedosporium* mycoses.
**Any** | To diagnose mold infection | Histopathology of biopsies | A | III | Walts DiagnCyto 2002<sup>911</sup> | 

### Imaging studies

**Any** | To diagnose bone/joint infections | MRI | A | III | Koehler CRM 2014<sup>411</sup> Zimmerli NEJM 2010<sup>120</sup> | 
**Any** | FDG-PET/CT | A | III | Koehler CRM 2014<sup>411</sup> | If MRI is not possible
To diagnose bone/joint infections

Any with brain lesions / abscesses
To assess clinical manifestations and imaging characteristics
CT scan of the brain

Berenguer Medicine 1997
Uno JIC 2014
McKelvie CEO 2001

To assess clinical manifestations and imaging characteristics
MRI of the brain

Kelly BMCID 2016
Ochi IJH 2015

Any
To diagnose pulmonary infection
CT Thorax

Nakamura JMCR 2011
Ramirez-Garcia MedMycol 2018

Any
To diagnose pulmonary infection
Chest X-ray

Nakamura JMCR 2011
Ramirez-Garcia MedMycol 2018

Any with CF
To differentiate colonization from infection
CT Thorax

Ramirez-Garcia MedMycol 2018

Recommendations – For all patients, the guideline group strongly recommends the use of MRI for the
detection of brain abscesses and moderately recommends the use of contrast enhanced CT of the brain, when MRI is not available. For the detection of pulmonary infection, chest CT is strongly supported. For the detection and localization of scedosporiosis and the guided sampling of biopsies and body fluids, the guideline group strongly recommends MRI for the localization of scedosporiosis in bones and/or joints, or FDG-PET CT if MRI is not available. For suspected pulmonary infections the guideline group strongly recommends chest CT, and moderately recommends chest X-ray if chest CT is not available. Diagnostic pathways are displayed in Figure 12.
Figure 12. Optimal diagnostic pathway for scedosporiosis, when all imaging and assay techniques are available

Invasive infection due to *Scedosporium* spp.

Any population

Consider rule out dissemination

Cystic fibrosis

**Imaging procedures** (CT scan, MRI, X-ray) on suspected sites of infection

**Direct microscopy**
irregular septate hyphae

**Culture from any site**
Respiratory tract
BHI, IMA or SceSel+

**Antifungal susceptibility testing**
to inform antifungal treatment

**Histology**
irregular septate hyphae

For further species identification
**ITS 1, ITS 2 and β tubulin sequencing**

For further species identification
**MALDI-TOF MS**

**Legend:**
strongly recommended
moderately recommended
marginally recommended
recommended against

BHI, brain heart infusion agar; CT, computed tomography; IMA, inhibitory mold agar; ITS, internal transcribed spacer; MALDI-TOF MS, matrix-assisted laser desorption/ionization time-of-flight mass spectrometry
Treatment approaches to scedosporiosis

Treatment in Adults

Diagnosis-driven treatment

Evidence – Studies have reported success of diagnosis-driven treatment in lung transplant recipients with *Scedosporium* spp. colonization \(^{493,912}\), while results were more mixed for empiric treatment in patients after near-drowning accidents \(^{644,728}\).

Recommendations – In lung transplant recipients with colonization, pre-emptive treatment is moderately recommended. Every attempt to obtain a diagnosis should be made at the time of initiation of therapy, but should not delay therapy. Empiric treatment after near drowning accidents is marginally recommended.

First-line antifungal monotherapy

Evidence – In several studies, outcomes with VCZ based therapy were superior to any formulation of AmB\(^{11,447}\). Daily doses administered are started with 6 mg loading IV, followed by 4 mg IV twice daily. *In vitro* clinical resistance to AmB formulations, as well as breakthrough infections, have been reported repeatedly. Use of AmB formulations should be restricted to settings in which there is no other antifungal therapy available. For the use of ISA, ICZ or PCZ only limited evidence exists\(^{381,440,444,469}\).

Recommendations – First-line treatment with VCZ is strongly supported across all patterns of organ involvement. Use of AmB formulations is discouraged whenever VCZ is available. The guideline group marginally supports the use of ISA, ICZ or PCZ for first line-treatment.

First-line antifungal combination therapy

Evidence – In multiple studies antifungal combination therapy showed increased efficacy and improved survival compared to monotherapy with AmB\(^{11,444,456,468}\). There is a paucity of data evaluating combination therapy vs. VCZ monotherapy (Table 15).
### Table 15. First line treatment of *Scedosporium* spp. infections

<table>
<thead>
<tr>
<th>Population</th>
<th>Intention</th>
<th>Intervention</th>
<th>SoR</th>
<th>QoE</th>
<th>Reference</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any with hematological malignancy</td>
<td>To cure S. apioespernum infection</td>
<td>VCZ</td>
<td>C</td>
<td>III</td>
<td>Sirmenia JCM 1998&lt;sup&gt;111&lt;/sup&gt;</td>
<td>N=1, died</td>
</tr>
<tr>
<td>Any with exogenous disease</td>
<td>Any with chronic lung infection</td>
<td>Hematological Immunocompetent Immunocompromised</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any with apiospermum infection</td>
<td>To cure</td>
<td>Pre-emptive treatment</td>
<td>B</td>
<td>Ilu</td>
<td>Johnson TID 2014&lt;sup&gt;113&lt;/sup&gt;</td>
<td>N=27; 17/20 VCZ and/or others, 9/17 cleared</td>
</tr>
<tr>
<td>Any with chronic lung infection</td>
<td>To cure</td>
<td>Empiric treatment</td>
<td>C</td>
<td>III</td>
<td>Katragkou Mycoses 2007&lt;sup&gt;78&lt;/sup&gt;</td>
<td>N=12, mostly AmB</td>
</tr>
<tr>
<td>Near-drowning accidents</td>
<td>To cure</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First-line treatment</td>
<td>To cure</td>
<td>VCZ iv, step down to oral possible</td>
<td>A</td>
<td>Ilu</td>
<td>Seidel CRM 2019&lt;sup&gt;111&lt;/sup&gt;</td>
<td>N=137, VCZ N=63, AmB</td>
</tr>
<tr>
<td>Any with S. apioespernum</td>
<td>To cure</td>
<td>ISA</td>
<td>C</td>
<td>III</td>
<td>Cornely Mycoses 2018&lt;sup&gt;79&lt;/sup&gt;</td>
<td>N=2, clinical response 1/2</td>
</tr>
<tr>
<td>Any with S. aurantiacum infection</td>
<td>To cure</td>
<td>VCZ OR PCZ</td>
<td>C</td>
<td>III</td>
<td>Heath CMI 2009&lt;sup&gt;80&lt;/sup&gt;</td>
<td>N=29, low MICs against VCZ and PCZ</td>
</tr>
<tr>
<td>Immunocompromised</td>
<td>To cure</td>
<td>AmB lipid formulations</td>
<td>D</td>
<td>Ilu</td>
<td>Seidel CRM 2019&lt;sup&gt;111&lt;/sup&gt;</td>
<td>N=118, N=50 with AmB, N=30 AmB monotherapy, VCZ 642 mortality 11.3% vs. AmB 58.8% in immunocompromised, higher mortality with AmB mono vs. combination</td>
</tr>
<tr>
<td>Immunocompetent</td>
<td>To cure</td>
<td>AmB lipid formulations alone OR in combination</td>
<td>C</td>
<td>Ilu</td>
<td>Seidel CRM 2019&lt;sup&gt;111&lt;/sup&gt;</td>
<td>N=90, VCZ 42 mortality 14% vs. AmB 23.1%</td>
</tr>
<tr>
<td>Hematological malignancy</td>
<td>To cure</td>
<td>PCZ +/- AmB lipid formulation</td>
<td>C</td>
<td>III</td>
<td>Lamaris CID 2006&lt;sup&gt;84&lt;/sup&gt;</td>
<td>N=4, 3/4 survived (including 2 with PCZ monotherapy)</td>
</tr>
<tr>
<td>Hematological malignancy</td>
<td>To cure</td>
<td>AmB lipid formulation + CASPO +/- VCZ</td>
<td>C</td>
<td>III</td>
<td>Lamaris CID 2006&lt;sup&gt;84&lt;/sup&gt;</td>
<td>N=7, AmB + CASPO +/- VCZ 2/2 survived vs. AmB + ICZ 0/5 survived</td>
</tr>
<tr>
<td>Any with CF and lung infection</td>
<td>To cure</td>
<td>VCZ + either CASPO/MICA iv or inhaled AmB or both</td>
<td>B</td>
<td>III</td>
<td>Schwarz JCF 2018&lt;sup&gt;85&lt;/sup&gt;</td>
<td>N=24, 2-drug combi 8/10 response, 3-drug combi 14/14 response, VCZ mono 1/6 response</td>
</tr>
<tr>
<td>Any with chronic lung disease</td>
<td>To cure</td>
<td>ICZ</td>
<td>D</td>
<td></td>
<td>Cooley EID 2007&lt;sup&gt;86&lt;/sup&gt;</td>
<td>N=4, 3/4 died</td>
</tr>
<tr>
<td>Any with exogenous endophthalmitis</td>
<td>To cure</td>
<td>VCZ (po/iv, intravitreal), vitrectomy</td>
<td>C</td>
<td>III</td>
<td>Bui JOPT 2016&lt;sup&gt;87&lt;/sup&gt;</td>
<td>N=2, success 2/2</td>
</tr>
<tr>
<td>Any with exogenous endophthalmitis</td>
<td>To cure</td>
<td>AmB iv + intravitreal</td>
<td>D</td>
<td></td>
<td>Royle OII 2018&lt;sup&gt;88&lt;/sup&gt;</td>
<td>N=2, failure 2/2</td>
</tr>
<tr>
<td>Any with endogenous endophthalmitis</td>
<td>To cure</td>
<td>VCZ iv, oral, intravitreal +/- TRB +/- vitrectomy</td>
<td>B</td>
<td>III</td>
<td>Moloney Retina 2014&lt;sup&gt;89&lt;/sup&gt;</td>
<td>N=4, success 4/4</td>
</tr>
<tr>
<td>Any with endogenous endophthalmitis</td>
<td>To cure</td>
<td></td>
<td></td>
<td></td>
<td>Jain ArchOphthalm 2007&lt;sup&gt;91&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Chen CEO 2007&lt;sup&gt;90&lt;/sup&gt;</td>
<td>N=2, lack of response due to delayed therapy 2/2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Sarvat JOI 2007&lt;sup&gt;91&lt;/sup&gt;</td>
<td>N=1, success</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Musk JHLT 2006&lt;sup&gt;92&lt;/sup&gt;</td>
<td>N=2, success 2/2</td>
</tr>
</tbody>
</table>
Hematological malignancy with endogenous endophthalmitis + other disseminated infections

To cure AmB iv / intravitreal, VCZ po (delayed treatment) D III McKelvie CEO 2001[363] N=2, failure 2/2

Table 16. Antifungal salvage treatment for Scedosporium spp. infections

<table>
<thead>
<tr>
<th>Population</th>
<th>Intention</th>
<th>Intervention</th>
<th>SoR</th>
<th>QoE</th>
<th>Reference</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any</td>
<td>To cure</td>
<td>VCZ</td>
<td>B</td>
<td>Ilu</td>
<td>Perfect CID 2003[376]</td>
<td>N=10, response 3/10</td>
</tr>
<tr>
<td>Any</td>
<td>To cure</td>
<td>VCZ + echinocandin + GM-CSF</td>
<td>C</td>
<td>III</td>
<td>Goldman MMCR 2016[379]</td>
<td>N=1 cured after deteriorating on VCZ alone</td>
</tr>
<tr>
<td>Any</td>
<td>To cure</td>
<td>ISA</td>
<td>D</td>
<td>III</td>
<td>Cornely Mycoses 2018[381]</td>
<td>N=2, failure 2/2</td>
</tr>
<tr>
<td>Hematological malignancy with brain abscess</td>
<td>To cure</td>
<td>PCZ</td>
<td>C</td>
<td>III</td>
<td>Mellinghoff CID 2002[387]</td>
<td>N=1, success</td>
</tr>
</tbody>
</table>

| Standard dose unless stated otherwise; | GM-CSF, granulocyte-macrophage colony-stimulating factor; ISA, isavuconazole; PCZ, posaconazole; QoE, quality of evidence; SoR, strength of recommendation; VCZ, voriconazole. |

1038

Recommendations – There are limited data reporting successful outcomes with antifungal combination therapy with VCZ plus lipid formulation of AmB, VCZ plus TRB, and VCZ plus echinocandins[11,444,456,785]. The guideline group does moderately support VCZ-based antifungal combination therapy for infections caused by Scedosporium spp.

1042

**Antifungal salvage treatment**

Evidence – In general, there are two drug-related reasons for treatment failures, refractory scedosporiosis or toxicity or intolerance to first-line regimens. For the triazole class, hepatic toxicity has the highest prevalence and with AmB formulations renal toxicity may be a limiting factor. Toxicity may be caused by antifungals, or expected due to pre-existing organ damage. Only two drug classes show acceptable efficacy in scedosporiosis, thus salvage treatment mostly means switching to the other class. Successful outcomes have been reported with VCZ after primary treatment failure with lipid formulations of AmB[376], PCZ[917], and after adding an echinocandin[699] to pre-existing VCZ therapy (Table 16).

1051

<table>
<thead>
<tr>
<th>Population</th>
<th>Intention</th>
<th>Intervention</th>
<th>SoR</th>
<th>QoE</th>
<th>Reference</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any</td>
<td>To cure</td>
<td>VCZ</td>
<td>B</td>
<td>Ilu</td>
<td>Perfect CID 2003[376]</td>
<td>N=10, response 3/10</td>
</tr>
<tr>
<td>Any</td>
<td>To cure</td>
<td>VCZ + echinocandin + GM-CSF</td>
<td>C</td>
<td>III</td>
<td>Goldman MMCR 2016[379]</td>
<td>N=1 cured after deteriorating on VCZ alone</td>
</tr>
<tr>
<td>Any</td>
<td>To cure</td>
<td>ISA</td>
<td>D</td>
<td>III</td>
<td>Cornely Mycoses 2018[381]</td>
<td>N=2, failure 2/2</td>
</tr>
<tr>
<td>Hematological malignancy with brain abscess</td>
<td>To cure</td>
<td>PCZ</td>
<td>C</td>
<td>III</td>
<td>Mellinghoff CID 2002[387]</td>
<td>N=1, success</td>
</tr>
</tbody>
</table>

1053

Recommendations – The guideline group moderately recommends VCZ, and marginally PCZ or adding an echinocandin to VCZ monotherapy for salvage treatment.

1056
Other treatment options

Evidence – Other treatment options include surgery and discontinuation/reduction of immunosuppressive drugs (Table 17).

Table 17. Other treatment options for Scedosporium spp. infections

<table>
<thead>
<tr>
<th>Population</th>
<th>Intention</th>
<th>Intervention</th>
<th>SoR</th>
<th>QoE</th>
<th>Reference</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immunocompromised patients with subcutaneous</td>
<td>To cure</td>
<td>Discontinuation of cyclosporine and prednisone</td>
<td>C</td>
<td>III</td>
<td>Ji Mycopathol 2017[59]</td>
<td>N=1, success</td>
</tr>
<tr>
<td>scedosporiosis</td>
<td></td>
<td>followed by 2 wk levofloxacin iv without</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>antifungal treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Iv, intravenous; QoE, quality of evidence; SoR, strength of recommendation; wk, week(s)

Treatment duration for scedosporiosis

Evidence – The duration of therapy necessary to treat scedosporiosis is unknown. In general, weeks to months of therapy are given. If the underlying immunodeficiency resolves (e.g., diabetes is controlled, neutropenia definitively resolved, or immunosuppression can be tapered or stopped), therapy can be continued until resolution of signs and symptoms (Table 18).

Table 18. Treatment duration for Scedosporium spp. infections

<table>
<thead>
<tr>
<th>Population</th>
<th>Intention</th>
<th>Intervention</th>
<th>SoR</th>
<th>QoE</th>
<th>Reference</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>CNS infections</td>
<td>To cure</td>
<td>VCZ for &gt;3 mo</td>
<td>B</td>
<td>III</td>
<td>Schwartz Infection 2011</td>
<td>Aspergillus spp. 63%, Scedosporium spp. 18%,</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Duration (mean) 93 d (1-1.128)</td>
</tr>
<tr>
<td>Any with fungal osteoarticular infections</td>
<td>To cure</td>
<td>VCZ for &gt; 3 mo</td>
<td>B</td>
<td>III</td>
<td>Kumashi CMI 2006[72]</td>
<td>Aspergillus fumigatus N=2, non-fumigatus Aspergil</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>lus spp. N=8, non-specified Aspergillus spp.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>N=3, Fusarium spp. N=6, Zygomyces N=5, S.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>apiospermum N=2, Exserohilum spp. N=1,</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Duration: 5 mo (median 3 mo; range 11 d to 18</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>mo)</td>
</tr>
</tbody>
</table>

Standard dose unless stated otherwise; CNS, central nervous system; d, day(s); mo, month(s); QoE, quality of evidence; SoR, strength of recommendation; VCZ, voriconazole.

Treatment pathways for adults are displayed in Figure 13.
Figure 13. Optimal treatment pathway for scedosporiosis in adults when all treatment modalities and antifungal drugs are available

Suspected and confirmed invasive infections due to *Scedosporium* spp. are emergencies and require rapid action

Suspected and confirmed invasive infections due to *Scedosporium* spp. are emergencies and require rapid action

Suspected and confirmed invasive infections due to *Scedosporium* spp. are emergencies and require rapid action

Immediate treatment initiation

Voriconazole iv
2 x 6 mg/kg/d d1;
2 x 4 mg/kg/d from d2;
use TDM

± Amphotericin B lipid complex
1 x 2-10 mg/kg/d or
Liposomal Amphotericin B
1 x 3-10 mg/kg/d
± Echinocandins
± Terbinafine
500-1000 mg/d

Itraconazole
1 x 400 mg/d
or Isavuconazole
3 x 200 mg/d d1-2;
1 x 200 mg/d from d3
or Posaconazole iv/tab
2 x 300 mg/d d1;
1 x 300 mg/d from d2

Eye infections

Surgery

± Echinocandins

Amphotericin B lipid complex or Liposomal Amphotericin B monotherapy

Response assessment (e.g. weekly imaging)

Progressive disease*

Voriconazole iv
2 x 6 mg/kg/d d1;
2 x 4 mg/kg/d from d2;
use TDM

Posaconazole iv/tab
2 x 300 mg/d d1;
1 x 300 mg/d from d2

Legend:

- strongly recommended
- moderately recommended
- marginally recommended
- recommended against

TDM, therapeutic drug monitoring

* Choice of salvage treatment always depends by the treatment that the patient failed to respond to
Specific considerations on treatment of scedosporiosis in children

Evidence – The clinical presentation of scedosporiosis in immunocompromised children is comparable to that observed in adult patients, with a high rate of disseminated disease. Pulmonary and CNS scedosporiosis in near-drowning patients is an important characteristic of Scedosporium spp., and the association of invasive fungal disease and near drowning seems to be unique to scedosporiosis. Reported outcomes for disseminated diseases are dramatically poor, both in immunocompromised and immunocompetent patients. In a recent review of invasive Lomentospora (n=22) and Scedosporium (n=33) infections in children VCZ use and surgery were associated with improved clinical outcome. Favourable outcome for localized infections in immunocompetent children treated with VCZ have been reported also in other studies (Table 19).

Table 19. Therapy in children for Scedosporium spp. infections

<table>
<thead>
<tr>
<th>Population</th>
<th>Intention</th>
<th>Intervention</th>
<th>SoR</th>
<th>QoE</th>
<th>Reference</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any</td>
<td>To cure</td>
<td>VCZ +/- other antifungals + surgery for localized infections</td>
<td>A</td>
<td>III</td>
<td>Seidel IIJD 2019</td>
<td>N=22</td>
</tr>
<tr>
<td>Immunocompetent</td>
<td>To cure</td>
<td>VCZ 8-9 mg/kg qd iv, use of TDM</td>
<td>A</td>
<td>III</td>
<td>Stripelis Med-Mycol 2009</td>
<td>N=1, 10 yrs, success</td>
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<td></td>
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<td></td>
<td>Cruysmans PID 2015</td>
<td>N=1, 7 yrs, success</td>
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<td></td>
<td>Salamat IPO 2015</td>
<td>N=1, 6 yrs, success</td>
</tr>
<tr>
<td>Any</td>
<td>To cure</td>
<td>VCZ iv + TRB 25 mg qd po</td>
<td>C</td>
<td>III</td>
<td>Whyte PID 2010</td>
<td>N=1, 8 yrs, survived</td>
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<td></td>
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<td></td>
<td></td>
<td>Tintelnot Med-Mycol 2009</td>
<td>N=1, 9 yrs</td>
</tr>
<tr>
<td>Hematological malignancy</td>
<td>To cure</td>
<td>L-AmB (N=11, 9 died)</td>
<td>C</td>
<td>IIlt</td>
<td>Caira Haematol 2008</td>
<td>Literature review, N=52, median age 47 (3-79): S. apiospermum N=15, 7/15 died (1 adult, died): L. prolificans N=37, 33/37 died</td>
</tr>
<tr>
<td></td>
<td></td>
<td>D-AmB (N=24, 21 died)</td>
<td>C</td>
<td>IIlt</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>D-AmB + SFC (N=2, 2 died)</td>
<td>C</td>
<td>IIlt</td>
<td></td>
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</tr>
<tr>
<td></td>
<td></td>
<td>D-AmB + azoles (N=9, 6 died)</td>
<td>C</td>
<td>IIlt</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Azoles (N=6, 4 died)</td>
<td>C</td>
<td>IIlt</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hematological malignancy</td>
<td>To cure</td>
<td>Surgery + azole</td>
<td>C</td>
<td>IIlt</td>
<td>Jasakainen MedMycol 2010</td>
<td>N=1, 14 yrs, success</td>
</tr>
<tr>
<td>Hematological malignancy with endogenous endophthalmitis + disseminated</td>
<td>To cure</td>
<td>VCZ 8 mg/kg qd iv, 100 µg intravitreal, TRB 125 mg qd, CASPO 50 mg qd, vitrectomy, surgical debridement</td>
<td>C</td>
<td>III</td>
<td>Chiam JAAPPOS 2013</td>
<td>N=1, success</td>
</tr>
<tr>
<td>Any with exogenous endophthalmitis</td>
<td>To cure</td>
<td>VCZ po, intravitreal 2x 200 µg, vitrectomy</td>
<td>C</td>
<td>III</td>
<td>Zarkovic In-Ophthalmol 2007</td>
<td>N=1, success</td>
</tr>
<tr>
<td>Any with chronic granulomatous disease</td>
<td>To cure</td>
<td>VCZ (OR ICZ)</td>
<td>C</td>
<td>III</td>
<td>Jabado CID 1998</td>
<td>N=2, + surgery, 2/2 survived</td>
</tr>
<tr>
<td>Hematological malignancy</td>
<td>To cure</td>
<td>L-AmB (N=2, 2 died)</td>
<td>D</td>
<td>III</td>
<td>Caira Haematol 2008</td>
<td>Literature review, N=52, median age 47 (3-79): S. apiospermum N=15, 7/15 died (1 adult, died): L. prolificans N=37, 33/37 died</td>
</tr>
<tr>
<td></td>
<td></td>
<td>L-AmB + VCZ (N=1, died)</td>
<td>C</td>
<td>IIlt</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>L-AmB + ICZ (N=1, survived)</td>
<td>C</td>
<td>IIlt</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>ICZ (N=4, 3 died)</td>
<td>C</td>
<td>IIlt</td>
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<tr>
<td></td>
<td></td>
<td>VCZ (N=1, died)</td>
<td>D</td>
<td>IIlt</td>
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<tr>
<td></td>
<td></td>
<td>PCZ (N=1, survived)</td>
<td>C</td>
<td>IIlt</td>
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<tr>
<td></td>
<td></td>
<td>VCZ + TRB (N=1, survived)</td>
<td>C</td>
<td>IIlt</td>
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</tbody>
</table>
Standard pediatric dose unless stated otherwise; 5-FC, 5-fluorocytosine; bid, twice a day; CASPO, caspofungin; d, day(s); D-AmB, amphotericin B deoxycholate; CASPO, caspofungin; ICZ, itraconazole; iv, intravenous; L-AmB, liposomal amphotericin B; PCZ, posaconazole; po, orally; qd, once a day; QoE, quality of evidence; SoR, strength of recommendation; TDM, therapeutic drug monitoring; TRB, terbinafine; VCZ, voriconazole; yrs, years.

1084

Recommendations – Treatment recommendations follow those given for adults. VCZ (+ TDM) is the first-line treatment of infections due to members of the genus *Scedosporium*. Surgery for localized disease is strongly recommended. Additional measures to reduce the immunosuppression should be considered.

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4. Phaeohyphomycosis

Epidemiology of phaeohyphomycosis

Phaeohyphomycosis (Greek: phaeo = dark) is caused by a heterogeneous group of melanized dematiaceous fungi that have a worldwide distribution and are found in soil, wood and decaying matter. Clinically important species causing systemic infections belong to the genera *Alternaria*, *Aureobasidium*, *Bipolaris*, *Chaetomium*, *Cladophialophora*, *Cladosporium*, *Curvularia*, *Exophiala*, *Exserohilum*, *Fonsecaea*, *Helminthosporium*, *Lomentospora* (see lomentosporiosis), and *Ochroconis*. The term phaeohyphomycosis has been introduced to separate these infections from the clinically and pathologically distinct chromoblastomycosis or mycetoma that are also caused by melanized fungi. Phaeohyphomycosis occurs more frequently in male than female individuals and, unlike other mold infections, commonly occurs in immunocompetent patients, presenting as keratitis, subcutaneous, rhinosinusitis, allergic bronchopulmonary, but sometimes also as invasive pulmonary or severe cerebral infections with fungemia, with recent research indicating that previously unrecognized CARD9 immunodeficiency is present in many patients developing severe infections who were previously thought to be immunocompetent. Eye and subcutaneous phaeohyphomycosis usually follow a traumatic injury or surgery, without apparent underlying immune deficiency, in contrast, a history of previous trauma is rarely found in immunocompromised patients. If left untreated subcutaneous lesions slowly increase in size to form abscesses. Eye infections are frequently caused by *Alternaria*, *Curvularia*, *Exserohilum*, or *Helminthosporium* spp.. In skin infections,
commonly associated genera are *Alternaria, Bipolaris, Exophiala,* and *Phialophora*\(^{248,922,927-929}\). Brain infections are comparably common, may present as brain abscess, meningitis, or encephalitis\(^{925}\), and are mainly caused by *Cladophialophora bantiana*, a neurotropic fungus that caused severe infections also in immunocompetent patients, with a considerable number of cases described in India\(^{924,928,930}\). However, other fungi, such as *Rhinocladiella mackenziei, Chaetomium strumarium, Verruconis gallopava* and *Exophiala dermatitidis* in immunocompromised hosts and *Exserohilum rostratum* in a recent outbreak in the United States are also well described as causing CNS phaeohyphomycosis\(^{925,931-933}\). *Bipolaris* and *Curvularia* are associated with fungal sinusitis with brain invasion, a clinical form that is becoming more common\(^{922}\). Melanized molds can cause endocarditis after valve replacement, mediastinitis following surgery, and peritonitis in patients on continuous peritoneal dialysis\(^{934-938}\). Disseminated phaeohyphomycosis is mostly associated with immunocompromising or debilitating disease and is thought to originate in the lung after inhalation of the fungal agent\(^{923,929,939}\).

The prevalence of phaeohyphomycosis varies between regions, patient population and etiological agent.

Cerebral phaeohyphomycosis occurs worldwide, but most cases have been reported from the United States, mostly in immunocompromised patients. Iatrogenic meningitis and other infections related to epidural injections of corticosteroids have been reported in two recent US outbreaks traced to environmental contamination at compounding pharmacies. During 2012, 754 cases of infection and 64 deaths were confirmed among the 13,534 people potentially exposed to contaminated lots of methylprednisolone\(^{932}\). Cerebral phaeohyphomycosis has also been frequently reported from India, particularly affecting immunocompetent individuals\(^{940}\). In India, *Alternaria* and *Curvularia* accounted for 7% of mold-related keratitis in a 10-year study\(^{248}\). In a multicentre study, 9.4% of fungal infections in liver and heart transplant recipients were related to phaeohyphomycosis, affecting sinuses, lung and CNS\(^{442}\) (Figure 14).
Figure 14. Worldwide distribution of phaeohyphomycosis (reported cases between 2009 and 2019 per million population)

Cases of phaeohyphomycosis reported in the medical literature were identified in a PubMed search on October 31, 2019 using the search string (Phaeohyphomycosis OR Acrophialophora OR Alternaria OR Anthothopsis OR Arnium OR Arthrinium OR Aureobasidium OR Bipolaris OR Botryodiplodia OR Botryomyces OR Chaetomium OR Chrysonilia OR Cladophialophora OR Cladosporium OR Cladorrhinum OR Coniothyrium OR Corynespora OR Curvularia OR Cyphellophora OR Dichomomphthora OR Dichomomphthoropsis OR Dissitimurus OR Drechslera OR Exophiala OR Wangiella OR Exserohilum OR Fonsecaea OR Hormonema OR Hortaea OR Lecytophora OR Leptosphaeria OR Medicopsis OR Microsphaeropsis OR Myceliophthora OR Mycocentrospora OR Mycoleptodiscus OR Nattrassia OR Neoscytalidium OR Neurospora OR Nigrograna OR Nodulisporium OR Ochroconis OR Oidiodendron OR Onychochola OR Papulaspora OR Periconia OR Phaeoacremonium OR Phaeosclera OR Phaeotheca OR Phaeotrichoconis OR Phialemonium OR Phialophora OR Phillostica OR Phoma OR Didymella OR Phomopsis OR Phyllostictina OR Pleurophoma OR Pleurophomopsis OR Pleurostoma OR Polycyella OR Pseudomicrodochium OR Pyrenochaeta OR Ramichloridium OR Rhinocladiella OR Rhizidhysteron OR Sarcinomyces OR Scytalidium OR Taeniolella OR Tetraploa OR Thermomyces OR Trematosphaeria OR Trichomaris OR Ulocladium OR Veronaea OR Verruconis) AND (case [Title/Abstract] OR patient [All Fields] OR report [Title/Abstract] OR infections OR invasive OR fungemia OR blood OR disseminat*) NOT Chromoblastomycosis[Title/Abstract] NOT mycetoma [Title/Abstract]) that
yielded 3,325 publications. In total, 935 cases were identified from 55 countries. Most cases were reported from India (n>200), China (n=188), United States (n=162), Spain (n=44), and Japan (n=41). Most infections were related to species of the genera *Alternaria* (>300), *Curvularia*, *Exophiala* (~100 each), *Exserohilum* (~70), *Cladosiphialophora*, *Bipolaris* (~50 each), *Phaeoacremonium*, *Cladosporium*, *Fonsecaea*, *Aureobasidium* (~20 each). Number of cases reported between 2009 and 2019 are presented as cases per million population per country. The resident population per country was obtained from www.worldometers.info. *One case each was reported from French Guiana, Martinique and New Caledonia (>2 cases per million population between 2009 and 2019)357,1092,1272.

**Diagnosis of phaeohyphomycosis**

**Diagnosis – Microbiology – Conventional Methods**

**Evidence** – Diagnosis relies on histopathology and careful gross and microscopic examination of cultured strains, which show dark colonies with usually darkly pigmented septate hyphae with widely variable conidia and conidiophores, respectively14,1131,1354. Pleomorphism that is seen in dematiaceous organisms on histopathology is the most specific finding in microscopy. The Fontana-Masson stain helps to make melanin visible in dematiaceous molds that may appear pale in H&E and other stains, and helps to differentiate melanized elements of phaeohyphomycetes from other mold structures in tissue samples14 (Table 20).

**Recommendations** – The guideline group strongly recommends histological evaluation and culture from clinical samples.

**Diagnosis – Microbiology – Serology**

**Evidence** – There are no simple serological or antigen diagnostic tests for infections caused by phaeohyphomycetes, mainly due to the huge diversity of these pathogens. BDG and GM tests may cross-react with some melanized fungi, though neither has been proven useful for diagnosis of phaeohyphomycosis in general518 (Table 20).
Recommendations – While the guideline group marginally supports serology on a case by case basis, there is currently no serological test that can be recommended.

Diagnosis – Microbiology – Molecular-based

Evidence – ITS1/ITS2 targeting oligonucleotide probes or PCR followed by sequencing on DNA extracted directly from sputum, tissue samples or sinus aspirates were occasionally applied successfully, showing a higher sensitivity than culture. However, much more data is needed for routine use of this approach. Possible contamination should be carefully considered due to the ubiquitous nature of dematiaceous fungi (Table 20).

Recommendations – Based on case reports, direct analysis of clinical samples using oligonucleotide arrays or universal PCR followed by sequencing can only marginally be supported.

Diagnosis – Microbiology – Species identification

Evidence – Morphological identification may be complicated by limited sporulation of causative pathogens. Identification to species level is performed by ITS1/ITS2 or D1/D2 sequencing and/or MALDI-TOF MS analysis of strains cultured from tissue or blood samples. The usefulness of MALDI-TOF MS is highly dependent on the use of enriched databases (Table 20).

Recommendations – The guideline group strongly recommends identification to species level by ITS1/ITS2 or D1/D2 sequencing and moderately by MALDI-TOF MS analysis of cultured strains.

Microbiology – Susceptibility testing

Evidence – The relevance of susceptibility testing is not yet fully defined, as breakpoints have not been established by CLSI or EUCAST, and there is a limited correlation between in vitro MICs and clinical outcomes. VCZ or PCZ are the most active drugs when tested by broth microdilution. A number of genera showed good in vitro susceptibility to ICZ, PCZ, VCZ, and AmB using Sensititre® YeastOne® YO10 panel (Table 20).
**Recommendations** – Susceptibility testing is strongly recommended for identifying susceptibility patterns, and moderately for guiding treatment.

**Diagnosis - Pathology**

**Evidence** – Histopathological examination of tissue samples may lead to diagnosis or provides important diagnostic information (Table 20).

**Recommendations** – The guideline group strongly recommends histopathological examination of tissue samples.

**Diagnosis – Imaging**

**Evidence** – Chest CT scan was the most common abnormal radiographic study in transplant recipients suffering from phaeohyphomycosis. Cranial CT/MRI is indicated for evaluation of possible CNS infection (Table 20).

**Table 20. Microbiological, histopathological and imaging diagnostics for phaeohyphomycetes/dematiaceous fungi/black fungi infections**

<table>
<thead>
<tr>
<th>Population</th>
<th>Intention</th>
<th>Intervention</th>
<th>SoR</th>
<th>QoE</th>
<th>Reference</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Microscopy, culture, MIC testing</td>
<td>Any</td>
<td>To diagnose</td>
<td>Direct microscopy</td>
<td>A</td>
<td>III</td>
<td>Chowdhary CMI 2014</td>
</tr>
<tr>
<td></td>
<td>Any</td>
<td>To diagnose</td>
<td>Culture, species identification by morphological characteristics or ITS sequencing</td>
<td>A</td>
<td>III</td>
<td>Chowdhary CMI 2014</td>
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<tr>
<td></td>
<td>Any</td>
<td>To diagnose</td>
<td>Histopathology and culture</td>
<td>A</td>
<td>III</td>
<td>To ADV 2017</td>
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<td>Shi Dermatopathol 2017</td>
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<td>Taj-Aldeen MedMycol 2010</td>
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<td>Koo MedMycol 2010</td>
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<td>Osteomyelitis and septic arthritis</td>
<td>To diagnose</td>
<td>Biopsy culture + histopathology</td>
<td>A</td>
<td>III</td>
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<td>Any</td>
<td>To identify susceptibility pattern</td>
<td>Sensititre® YeastOne® YO10 panels</td>
<td>A</td>
<td>III</td>
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<td>Any</td>
<td>To identify susceptibility patterns</td>
<td>CSLI testing of isolates</td>
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<td>III</td>
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<td>Any</td>
<td>To guide treatment of Alternaria malarum infection</td>
<td>Culture and molecular identification</td>
<td>B</td>
<td>III</td>
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<td>Any</td>
<td>To guide treatment of E. dermatitidis infection</td>
<td>Culture and molecular identification</td>
<td>B</td>
<td>III</td>
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<td>Immunosuppressed patients</td>
<td>To guide treatment of Exophiala oligosperma infection</td>
<td>Culture and molecular identification</td>
<td>B</td>
<td>III</td>
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<tr>
<td>Serology assays</td>
<td>Transplant patients</td>
<td>To diagnose</td>
<td>Serum GM or BDG</td>
<td>C</td>
<td>III</td>
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<td></td>
<td>Allergic bronchopulmonary aspergillosis</td>
<td>To detect fungus in sinus aspirates</td>
<td>Serum IgE level</td>
<td>C</td>
<td>III</td>
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<tr>
<td>Nucleic-acid based assays/MALDI-TOF MS</td>
<td>Transplant patients</td>
<td>To diagnose</td>
<td>DNA sequencing from tissue</td>
<td>C</td>
<td>III</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Any with CF</td>
<td>To detect in sputum</td>
<td>PCR + ITS1-ITS2 sequencing</td>
<td>C</td>
<td>III</td>
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<tr>
<td></td>
<td>Any with CF</td>
<td>To detect in sputum</td>
<td>Oligoarray, developed with probes designed according to ITS1/ITS2 sequence data</td>
<td>C</td>
<td>III</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Any with allergic fungal rhinosinusitis</td>
<td>To detect fungus in sinus aspirates</td>
<td>PCR assays using universal fungal primers (ITS 1-ITS4), followed by Bipolaris primers (Bipol A73 + B572)</td>
<td>C</td>
<td>III</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Any with fungal meningitis or other infections linked to contaminated</td>
<td>To detect E. rostratum and other in CSF</td>
<td>PCR using broad-range primers targeting ITS2 region vs. E. rostratum - specific primers</td>
<td>C</td>
<td>II</td>
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</tr>
</tbody>
</table>
methylprednisolone acetate

| Any | Species identification from culture | Species identification by ITS or D sequencing | A | III | Revankar OFID 2017 | N=99, Diagnosis confirmed by culture in 97/99 (98%). Using ITS sequencing, the CDC further identified 5 isolates to the species level, 2 unknown isolates were identified, and 1 isolate initially identified as *P. verucosa* was determined to be *P. richardsiae*. Histopathology showed granulomatous inflammation and/or fungal elements in 49 of 99 (49%) cases.

Any | Species identification from culture | Species identification by MALDI-TOF MS | B | III | Fraser JCM 2017 | MALDI-TOF MS for species identification from strains cultured from tissue

**Tissue-based diagnosis**

| SOT recipients | To diagnose | Histology | A | Ilu | Schieffelin TID 2014 | N=27, 4 diagnosed by histological appearance alone

| SOT or HSCT transplant recipients | To diagnose | Histopathology | A | Ilu | McCarthy MedMycol 2015 | N=56, histopathology added to the diagnostic information in 15 patients with 13 (86.7%) of those being skin specimens

| Any with allergic rhinosinusitis | To diagnose | Histopathology | A | III | Montone HNP 2016 | Microscopic examination in allergic fungal rhinosinusitis reveals eosinophilic mucin

**Imaging studies**

| SOT or HSCT transplant recipients | To diagnose | Chest CT, chest X-ray, cranial CT, cranial MRI | A | Ilu | McCarty MedMycol 2015 | N=56, Chest CT most common abnormal radiographic study, assisting in the diagnosis of 24 patients

ANID, anidulafungin; BAL, bronchoalveolar lavage; CASPO, caspofungin; CDC, Centers for Disease Control; CF, cystic fibrosis; CLSI, Clinical and Laboratory Standards Institute; CNS, central nervous system; CSF, cerebrospinal fluid; CT, computed tomography; d, day(s); DNA, deoxyribonucleic acid; FCZ, fluconazole; HSCT, hematopoietic stem cell transplantation; ICZ, itraconazole; ISA, isavuconazole; ITS, internal transcribed spacer; MALDI-TOF MS, matrix assisted laser desorption ionization-time of flight mass spectrometry; MEC, minimum effective concentration; MICA, micafungin; MIC, minimal inhibitory concentration; MRI, magnetic resonance imaging; PCR, polymerase chain reaction; PCZ, posaconazole; QoE, quality of evidence; SoR, strength of recommendation; SOT, Solid organ transplantation; TRB, terbinafine; VCZ, voriconazole.

**Recommendations** – The guideline group strongly recommends chest CT scan and cranial CT/MRI in the case of suspected lower respiratory tract and CNS infection, respectively (Figure 15).
**Figure 15. Optimal diagnostic pathway for phaeohyphomycosis, when all imaging and assay techniques are available**

**Invasive infection due to phaeohyphomycetes / dematiaceous fungi / black fungi**

- **Any population**
- **Cystic fibrosis**
- **HSCT / SOT recipients**

**Imaging procedures** (CT scan, MRI, X-ray) on suspected sites of infection

**Direct microscopy**
- darkly pigmented dichotomously branching, septate hyphae

**Culture from any site**

**Antifungal susceptibility testing**
- to guide treatment

**Antibody and biomarker**

**Histology**
- darkly pigmented dichotomously branching, septate hyphae

**For further species identification**
- **ITS 1, ITS 2 and β tubulin sequencing**
- **MALDI-TOF MS**

**Legend:**
- strongly recommended
- moderately recommended
- marginally recommended
- recommended against

CT, computed tomography; HSCT, hematopoietic stem cell transplantation; ITS, internal transcribed spacer; MALDI-TOF MS, matrix-assisted laser desorption/ionization time-of-flight mass spectrometry; MRI, magnetic resonance imaging; SOT, solid organ transplantation
Treatment approaches to phaeohyphomycosis

Targeted first-line antifungal therapy

Evidence – The use of either VCZ or lipid formulations of AmB (including combinations particularly for disseminated infections) has successfully treated phaeohyphomycosis cases with various organ involvement patterns\(^{378,518,932,1322,1477,1485-1487}\). There are reports of successful treatment with CASPO or PCZ mono- or combination therapy\(^{518,1477,1486,1487}\).

In several case series of CNS phaeohyphomycosis, D-AmB or lipid formulations of AmB as well as - more recently - VCZ (alone or in combination with lipid formulations of AmB) were the most commonly successfully used agents\(^{518,923,924,940}\). VCZ alone (n=301) or in combination with L-AmB (n=143) has been successfully used in the outbreak associated with *E. rostratum* contaminated methylprednisolone injections\(^{932}\).

Large case series report the successful use of either ICZ or VCZ (both sometimes in combination with surgery) for cutaneous or subcutaneous phaeohyphomycosis, with smaller case-series reporting similar success rates for PCZ, and case reporting of successful use of TRB\(^{518,926,1119,1476,1488-1491}\). ICZ has also been most frequently used to successfully treat chromoblastomycosis\(^{1492}\).

ISA has been used successfully in first-line treatment for *Exserohilum* or *Curvularia* infections but not for infections due to *Cladophialophora* spp. or *Cladosporium* spp.\(^{381}\).

Intravenous or intravitreal AmB (with or without VCZ, 5-fluorocytosine (5-FC) or vitrectomy) has been the mainstay of the treatment for patients with endogenous or exogenous endophthalmitis with inconsistencies in treatment outcomes reported\(^{518,952,1030,1082,1390,1453,1493-1499}\) (Table 21).

**Table 21. First-line antifungal therapy for phaeohyphomycetes/dematiaceous fungi/black fungi infections**

<table>
<thead>
<tr>
<th>Population</th>
<th>Intention</th>
<th>Intervention</th>
<th>SoR</th>
<th>QoE</th>
<th>Reference</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any</td>
<td>To cure</td>
<td>AmB lipid formulations</td>
<td>B</td>
<td>Ilu</td>
<td>Perfect CID 2005(^{378})</td>
<td>N=4 with <em>Curvularia</em>, response/cure 3/4 (75%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Ben-Ami CID 2009(^{1460})</td>
<td>N=9, response 6/9</td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td>Bagga MMCR 2019(^{1390})</td>
<td>N=1, success</td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td>McCarty MedMycol 2015(^{1477})</td>
<td>N=56, L-AmB N=20, combination therapy N=15, overall death N=14</td>
</tr>
<tr>
<td>Any with Cladophialophora or Cladosporium infection</td>
<td>To cure</td>
<td>ISA</td>
<td>D</td>
<td>Ilu</td>
<td>Cornely Mycoses 2018(^{381})</td>
<td>N=2, <em>C. bantiana + Cladosporium</em> spp., response 0/2</td>
</tr>
<tr>
<td>Any with Exserohilum or Curvularia infection</td>
<td>To cure</td>
<td>ISA</td>
<td>C</td>
<td>Ilu</td>
<td>Cornely Mycoses 2018(^{381})</td>
<td>N=2, <em>E. rostratum and Curvularia lunata</em>, response 2/2</td>
</tr>
<tr>
<td>Status</td>
<td>Treatment</td>
<td>outcome</td>
<td>References</td>
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</tr>
<tr>
<td>Any with disseminated infection</td>
<td>To cure</td>
<td></td>
<td>AmB lipid formulation + VCZ / PCZ / ICZ OR echinocandin OR all three +/- TRB +/- 5-FC</td>
<td>B</td>
<td>III</td>
<td>Ben-Ami CID 20091486 N=27, AmB lipid formulation + VCZ/PCZ N=10 OR + echinocandin N=14 OR all three N=3; combination therapy 22/27 response, monotherapy 13/19 response</td>
</tr>
<tr>
<td>Any with disseminated infection</td>
<td>To cure</td>
<td>N=3, response 2/3</td>
<td>Ben-Ami CID 20091486</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any with disseminated infection</td>
<td>To cure</td>
<td>N=4, response 3/4</td>
<td>Pundhir JISTJAD 20161504 N=1, Sceletosporidium spp., response</td>
<td></td>
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</tr>
<tr>
<td>Any with disseminated infection</td>
<td>To cure</td>
<td>N=6, CASPO N=7, combination 15, 14/56 died</td>
<td>McCarty MedMycol 20151477</td>
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</tr>
<tr>
<td>Any with disseminated infection</td>
<td>To cure</td>
<td>N=26, response d30 31%, mortality d30 38%. Combination 5/16 response vs. monotherapy 3/10 response. 18/26 died, 11/16 combination vs. 7/10 monotherapy.</td>
<td>Revanker OFID 20171318</td>
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<tr>
<td>Any with disseminated infection</td>
<td>To cure</td>
<td>N=2, 2/2 failed</td>
<td>Thomas MM 20181445 N=1, + surgery, failed</td>
<td></td>
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<tr>
<td>Any with disseminated infection</td>
<td>To cure</td>
<td>N=26, 16/26 combination, 2/4 endocarditis patients survived</td>
<td>Revanker OFID 20171318</td>
<td></td>
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<tr>
<td>Any with disseminated infection</td>
<td>To cure</td>
<td>N=1, response</td>
<td>Ben-Ami CID 20091486</td>
<td></td>
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</tr>
<tr>
<td>Any with disseminated infection</td>
<td>To cure</td>
<td>N=1, V. gallopava, success</td>
<td>Moran CID 20131359 N=1, V. gallopava, success</td>
<td></td>
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<tr>
<td>Any with disseminated infection</td>
<td>To cure</td>
<td>N=1, Alternaria alternata, + surgery, success</td>
<td>Sribenjalux MIDI 20131363 N=1, Alternaria alternata, + surgery, success</td>
<td></td>
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<tr>
<td>Any with disseminated infection</td>
<td>To cure</td>
<td>N=1, Phaeoacremonium parasiticum, success</td>
<td>Shah MIDI 20191365 N=1, Phaeoacremonium parasiticum, success</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Phaeohyphomycosis of the CNS</td>
<td>To cure</td>
<td>N=109, AmB N=59, L-AmB N=8, 5-FC + AmB N=24, ICZ +/- AmB N=18, +/- surgery, overall death N=66</td>
<td>Revanker CID 20041254</td>
<td></td>
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</tr>
<tr>
<td>Phaeohyphomycosis of the CNS</td>
<td>To cure</td>
<td>N=1, fatal outcome</td>
<td>Thomas MM 20181470 N=1, fatal outcome</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phaeohyphomycosis of the CNS</td>
<td>To cure</td>
<td>N=1, C. bantiana, failure</td>
<td>Howlett MM 20191151 N=1, C. bantiana, failure</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Phaeohyphomycosis of the CNS</td>
<td>To cure</td>
<td>N=1, + surgery, success</td>
<td>Dobias FMicrobiol 20181282 N=1, F. monophora, success</td>
<td></td>
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</tr>
<tr>
<td>Phaeohyphomycosis of the CNS</td>
<td>To cure</td>
<td>N=1, Bipolaris spicifera, success</td>
<td>Gopalakrishnan JMM 20171329 N=2, C. bantiana, success 2/2</td>
<td></td>
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</tr>
<tr>
<td>Phaeohyphomycosis of the CNS</td>
<td>To cure</td>
<td>N=1, success</td>
<td>Rosow MIDI 20111341 N=1, Bipolaris spicifera, success</td>
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<tr>
<td>Phaeohyphomycosis of the CNS</td>
<td>To cure</td>
<td>N=1, success</td>
<td>Santos CMI 20171317</td>
<td></td>
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<tr>
<td>Phaeohyphomycosis of the CNS</td>
<td>To cure</td>
<td>N=1, + surgery, success</td>
<td>Jung JNS 20141320</td>
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<tr>
<td>Phaeohyphomycosis of the CNS</td>
<td>To cure</td>
<td>N=1, Curvularia spp., + surgery, success</td>
<td>Gadgil JCN 20131308</td>
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<tr>
<td>Any with cutaneous / subcutaneous phaeohyphomycosis</td>
<td>PCZ +/- surgical debridement</td>
<td>B</td>
<td>III</td>
<td>Los-Arcos TID 2019[1158]</td>
<td>N=1, Medicopsis romeroi, success</td>
<td></td>
</tr>
<tr>
<td>Any with cutaneous / subcutaneous phaeohyphomycosis</td>
<td>ICZ +/- surgery</td>
<td>A</td>
<td>Illu</td>
<td>Schieffelin TID 2014[1476]</td>
<td>N=24, excision N=22, ICZ N=19, VCZ N=2, no antifungal therapy N=3</td>
<td></td>
</tr>
<tr>
<td>To cure</td>
<td>ICZ +/- surgery</td>
<td>A</td>
<td>Illu</td>
<td>Chan SMI 2014[1510]</td>
<td>N=1, M. romeroi, success</td>
<td></td>
</tr>
<tr>
<td>To cure</td>
<td>TID</td>
<td>A</td>
<td>Illu</td>
<td>Santos CMI 2017[1488]</td>
<td>N=51, surgical excision w/o antifungals N=21, ICZ N=30, success 51/51</td>
<td></td>
</tr>
<tr>
<td>Any with cutaneous / subcutaneous phaeohyphomycosis</td>
<td>L-AmB + PCZ / ICZ +/- surgery</td>
<td>C</td>
<td>III</td>
<td>Ogawa Mycopathol 2016[1489]</td>
<td>N=6, 2 Exophiala and 3 Fonseccoa; ICZ N=4, ICZ + surgery N=2, success</td>
<td></td>
</tr>
<tr>
<td>Any with cutaneous / subcutaneous phaeohyphomycosis</td>
<td>PCZ +/- surgical debridement</td>
<td>B</td>
<td>III</td>
<td>Ferrándiz-Pulido Mycoses 2018[1326]</td>
<td>N=6, response 3/6, failure 3/6</td>
<td></td>
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<tr>
<td>Any with cutaneous / subcutaneous phaeohyphomycosis</td>
<td>TID</td>
<td>A</td>
<td>Illu</td>
<td>Chan SMI 2014[1510]</td>
<td>N=1, M. romeroi, success</td>
<td></td>
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<tr>
<td>Any with cutaneous / subcutaneous phaeohyphomycosis</td>
<td>ICZ +/- surgery</td>
<td>A</td>
<td>Illu</td>
<td>Santos CMI 2017[1488]</td>
<td>N=51, surgical excision w/o antifungals N=21, ICZ N=30, success 51/51</td>
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<tr>
<td>Any with cutaneous / subcutaneous phaeohyphomycosis</td>
<td>L-AmB + PCZ / ICZ +/- surgery</td>
<td>C</td>
<td>III</td>
<td>Ogawa Mycopathol 2016[1489]</td>
<td>N=6, 2 Exophiala and 3 Fonseccoa; ICZ N=4, ICZ + surgery N=2, success</td>
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<tr>
<td>Any with cutaneous / subcutaneous phaeohyphomycosis</td>
<td>PCZ +/- surgical debridement</td>
<td>B</td>
<td>III</td>
<td>Ferrándiz-Pulido Mycoses 2018[1326]</td>
<td>N=6, response 3/6, failure 3/6</td>
<td></td>
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<tr>
<td>Any with cutaneous / subcutaneous phaeohyphomycosis</td>
<td>TID</td>
<td>A</td>
<td>Illu</td>
<td>Chan SMI 2014[1510]</td>
<td>N=1, M. romeroi, success</td>
<td></td>
</tr>
<tr>
<td>Any with cutaneous / subcutaneous phaeohyphomycosis</td>
<td>ICZ +/- surgery</td>
<td>A</td>
<td>Illu</td>
<td>Santos CMI 2017[1488]</td>
<td>N=51, surgical excision w/o antifungals N=21, ICZ N=30, success 51/51</td>
<td></td>
</tr>
<tr>
<td>Any with cutaneous / subcutaneous phaeohyphomycosis</td>
<td>L-AmB + PCZ / ICZ +/- surgery</td>
<td>C</td>
<td>III</td>
<td>Ogawa Mycopathol 2016[1489]</td>
<td>N=6, 2 Exophiala and 3 Fonseccoa; ICZ N=4, ICZ + surgery N=2, success</td>
<td></td>
</tr>
<tr>
<td>Any with cutaneous / subcutaneous phaeohyphomycosis</td>
<td>PCZ +/- surgical debridement</td>
<td>B</td>
<td>III</td>
<td>Ferrándiz-Pulido Mycoses 2018[1326]</td>
<td>N=6, response 3/6, failure 3/6</td>
<td></td>
</tr>
<tr>
<td>Any with cutaneous / subcutaneous phaeohyphomycosis</td>
<td>TID</td>
<td>A</td>
<td>Illu</td>
<td>Chan SMI 2014[1510]</td>
<td>N=1, M. romeroi, success</td>
<td></td>
</tr>
<tr>
<td>Any with cutaneous / subcutaneous phaeohyphomycosis</td>
<td>ICZ +/- surgery</td>
<td>A</td>
<td>Illu</td>
<td>Santos CMI 2017[1488]</td>
<td>N=51, surgical excision w/o antifungals N=21, ICZ N=30, success 51/51</td>
<td></td>
</tr>
<tr>
<td>Any with cutaneous / subcutaneous phaeohyphomycosis</td>
<td>L-AmB + PCZ / ICZ +/- surgery</td>
<td>C</td>
<td>III</td>
<td>Ogawa Mycopathol 2016[1489]</td>
<td>N=6, 2 Exophiala and 3 Fonseccoa; ICZ N=4, ICZ + surgery N=2, success</td>
<td></td>
</tr>
<tr>
<td>Any with cutaneous / subcutaneous phaeohyphomycosis</td>
<td>PCZ +/- surgical debridement</td>
<td>B</td>
<td>III</td>
<td>Ferrándiz-Pulido Mycoses 2018[1326]</td>
<td>N=6, response 3/6, failure 3/6</td>
<td></td>
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<tr>
<td>Any with cutaneous / subcutaneous phaeohyphomycosis</td>
<td>TID</td>
<td>A</td>
<td>Illu</td>
<td>Chan SMI 2014[1510]</td>
<td>N=1, M. romeroi, success</td>
<td></td>
</tr>
<tr>
<td>Any with cutaneous / subcutaneous phaeohyphomycosis</td>
<td>ICZ +/- surgery</td>
<td>A</td>
<td>Illu</td>
<td>Santos CMI 2017[1488]</td>
<td>N=51, surgical excision w/o antifungals N=21, ICZ N=30, success 51/51</td>
<td></td>
</tr>
<tr>
<td>Condition</td>
<td>Treatment</td>
<td>Notes</td>
<td></td>
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<tr>
<td>Any with subcutaneous chromoblastomycosis</td>
<td>To cure</td>
<td>TRB +/- VCZ / ICZ C III Mohammed AIM 2019, N=9, E. jeanselmei, success Thomas MMI 2018, N=2, success 1/2 Ogawa Mycopathol 2016, N=1, success Katoconazole + surgery D III Radhakrishnan UMM 2010, N=1, E. spinifera, failure</td>
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<tr>
<td>Any with cutaneous endophthalmitis</td>
<td>To cure</td>
<td>TRB + local thermotherapy</td>
<td>C III Shi MMCRR 2016, N=1, F. monophora, success C III Dupont TID 2010, N=1, C. carrioni, success</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intravenous drug user with endophthalmitis</td>
<td>To cure</td>
<td>AmB intravitreal, iv, VCZ iv + vitrectomy D III Fox JOII 2016, N=1, Pleurostoma richardiae, failure</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Post-op patients with exogenous endophthalmitis</td>
<td>To cure</td>
<td>AmB intracocular, VCZ intracocular, po + vitrectomy D III Alex MMCRR 2013, N=1, C. lunata, failure</td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Post-op patients with exogenous endophthalmitis</td>
<td>To cure</td>
<td>5-FC, AmB intravitreal, topical</td>
<td>C III Kaushik AJO 2001, N=1, C. lunata cultured, success</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Post-op patients with exogenous endophthalmitis</td>
<td>To cure</td>
<td>VCZ topical, intravitreal, FCZ po + vitrectomy C III Homa Mycopathol 2018, N=1, E. dermatitidis, success</td>
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<tr>
<td>Any with endogenous endophthalmitis</td>
<td>To cure</td>
<td>AmB intravitreal, iv, FCZ po +/- intravitreal +/- topical +/- vitrectomy</td>
<td>C III Rao Retina 2004, N=1, Alternaria spp, outcome was VA hand movements</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any with endogenous endophthalmitis</td>
<td>To cure</td>
<td>AmB intravitreal, topical, iv, FCZ intravitreal, topical, systemic, VCZ intravitreal, systemic + vitrectomy</td>
<td>C III Wu RCRR 2011, N=1, Cladosporium spp., success</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any with endogenous endophthalmitis</td>
<td>To cure</td>
<td>VCZ</td>
<td>C III Dogra IJO 2018, N=1, Lecythophora spp., success</td>
<td></td>
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</tr>
</tbody>
</table>

**Standard dose unless stated otherwise:** 5-FC, 5-fluorocytosine; AmB, amphotericin B; CASPO, caspofungin; CNS, central nervous system; CSF, cerebrospinal fluid; d, day(s); D-AmB, amphotericin B deoxycholate; FCZ, Fluconazole; ICZ, Itraconazole; ISA, isavuconazole; KCZ, ketoconazole; L-AmB, liposomal amphotericin B; PCZ, posaconazole; qd, once a day; QoE, quality of evidence; SoR, strength of recommendation; SOT, solid organ transplantation; TRB, terbinafine; VA, visual acuity; VCZ, voriconazole.
**Recommendation** – Lipid formulations of AmB alone or in combination with a triazole and/or echinocandin and VCZ monotherapy are all moderately supported as first-line treatment across all patterns of organ involvement, including the CNS. For CNS infection due to *C. bantiana*, the addition of 5-FC is marginally supported. Specifically for disseminated infections combination therapy with VCZ or PCZ plus an echinocandin or TRB is a moderately supported alternative. The use of D-AmB is discouraged whenever better tolerated lipid formulations of AmB are available.

For *E. rostratum* infections, first-line treatment with VCZ (with or without L-AmB) is moderately supported, while the guideline group marginally supports the use of combination therapy with L-AmB and another azole (with or without surgery). ISA is marginally supported as first-line treatment for *Exserohilum* or *Curvularia* infections, but the group recommends against the use of ISA for infections due to *Cladosiphialophora* spp. or *Cladosporium* spp. In patients with cutaneous or subcutaneous phaeohyphomycoses the guideline group strongly supports the use of VCZ or ICZ as first line treatment, with a moderate recommendation for PCZ and marginal recommendations for ISA or TRB.

**Salvage antifungal therapy**

**Evidence** – ISA has been successfully used as salvage therapy in patients infected with *Alternaria* spp. (n=1) and *Curvularia* spp. (n=1)\(^1\). PCZ and VCZ have also been successfully used for salvage treatment (Table 22).

<table>
<thead>
<tr>
<th>Population</th>
<th>Intention</th>
<th>Intervention</th>
<th>SoR</th>
<th>QoE</th>
<th>Reference</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any</td>
<td>To cure</td>
<td>ISA</td>
<td>B</td>
<td>I</td>
<td>Cornell Mycoses 2018(^1)</td>
<td>N=1, <em>Alternaria</em> spp., response</td>
</tr>
<tr>
<td>Any</td>
<td>To cure</td>
<td>PCZ</td>
<td>B</td>
<td>III</td>
<td>Cornell Mycoses 2018(^2)</td>
<td>N=1, <em>Curvularia</em> spp., response</td>
</tr>
<tr>
<td>Any with cutaneous/subcutaneous</td>
<td>To cure</td>
<td>VCZ +/- TRB + surgical</td>
<td>B</td>
<td>III</td>
<td>Meriden MedMycol 2012(^3)</td>
<td>N=1, <em>V. gallopava</em>, success</td>
</tr>
<tr>
<td></td>
<td></td>
<td>debridement</td>
<td></td>
<td></td>
<td>Secniková DermaTeraphy 2014(^4)</td>
<td>N=1, <em>A. alternata</em>, success</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Crabol PLOSNTD 2014(^5)</td>
<td>N=2, success 2/2</td>
</tr>
<tr>
<td>Immunocompromised patients with</td>
<td>To cure</td>
<td></td>
<td>C</td>
<td>III</td>
<td>Kulkarni ECT 2017(^6)</td>
<td>N=1, <em>M. romeroi</em>, success</td>
</tr>
<tr>
<td>subcutaneous phaeohyphomycosis</td>
<td></td>
<td>Intralesional L-AmB</td>
<td></td>
<td></td>
<td>Garcia-Reyne TID 2011(^7)</td>
<td>N=1, <em>Diaparthe longicolla</em>, success</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Ferrándiz-Pulido Mycoses 2018(^8)</td>
<td>N=3, success 3/3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Mahajan IJD 2014(^9)</td>
<td>N=1, <em>Rhizophyton</em> spp., success</td>
</tr>
</tbody>
</table>
Immunocompromised patient with chromoblastomycosis
To cure L-AmB, ICZ, intralional L-AmB
ICZ + TRB + local heat therapy
C III Tawade Cutis 2018 N=1, Cladosporium carrioni, success

Immunocompetent patient with recurrent infection
To cure CZ
C III Geltner Infection 2015 N=1, V. gallopava, relaps after discontinuation

Any with chromoblastomycosis
To cure VCZ
C III Criado JDT 2011 N=3, F. pedrosoi, partial response

Recommendation – ISA, PCZ or VCZ are recommended with moderate strength (BIII) for salvage treatment of phaeohyphomycosis.

Other treatment

i) Surgical/medical interventions

Evidence – In several case reports or series, surgical interventions (i.e. surgery, cryosurgery, cryotherapy, laser therapy, heat therapy or potassium iodide) were performed to contain localized cutaneous infection or reduce infectious burden in advanced phaeohyphomycosis cases. The surgery involved either debridement of the skin and soft tissue, resection of subcutaneous or pulmonary nodules, or drainage of brain abscess. For phaeohyphomycosis cases with cerebral abscess, complete excision with administration of antifungal therapy was documented. Complete excision of lesions was shown to be critical for successful management of C. bantiana-related CNS infection. The use of surgical intervention in addition to systemic corticosteroids for patients with allergic fungal sinusitis to reduce symptoms has been noted as well. For patients with allergic bronchopulmonary mycosis, surgical intervention alone for reducing symptoms was reported (Table 23).

Table 23. Other treatment options for phaeohyphomycetes/dematiaceous fungi/black fungi infections

<table>
<thead>
<tr>
<th>Population</th>
<th>Intention</th>
<th>Intervention</th>
<th>SoR</th>
<th>QoE</th>
<th>Reference</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any with localized cutaneous infection or subcutaneous nodule</td>
<td>To cure</td>
<td>Surgery</td>
<td>A</td>
<td>Flu</td>
<td>Ferrandiz-Pulido Mycoses 2018 N=11, surgery N=6</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Haridasan TID 2017 N=7</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Schiffelin TID 2017 N=17</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Guarro JCM 2003 N=2</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Ben-Ami CID 2009 N=14, 11/14 survived</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Santos CMI 2017 N=51, complete excision w/o antifungals N=21, partial debridement 16/30 with antifungals (53.3%), 51/51 cured</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any with localized cutaneous infection or subcutaneous nodule</td>
<td>To cure</td>
<td></td>
<td>C III</td>
<td>Yang MedMycol 2012 N=1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
**Recommendation** – For localized cutaneous infections or subcutaneous nodules, the guideline group strongly supports a complete surgical removal whenever possible. The group strongly supports the use of surgery in addition to systemic antifungal therapy or corticosteroids for patients with cerebral abscess or allergic fungal sinusitis, respectively.

**ii) Augmentation of host response**

**Evidence** – G-CSF or GM-CSF has been added to antifungal treatment in a case series that involved 39 cases of proven or probable phaeohyphomycosis.\(^{1486}\)

**Recommendation** – The guideline group marginally supports G-CSF or GM-CSF to augment host response against phaeohyphomycosis.
Treatment duration

Evidence – There is no standard treatment duration for phaeohyphomycosis, with durations ranging from weeks to months. A median duration of treatment with a variety of antifungal agents (i.e. VCZ, PCZ, ICZ, AmB or TRB) was reported as 50 to 73 days in all patients while in patients with underlying malignancy and infection with *E. dermatitidis*, the duration of successful treatment with triazoles ranged between 7 and 64 days. Among SOT recipients, an average treatment duration of 10 months was noted, ranging from 3 to 18 months (Table 24).

Table 24. Treatment duration for phaeohyphomycetes/dematiaceous fungi/black fungi infections

<table>
<thead>
<tr>
<th>Population</th>
<th>Intention</th>
<th>Intervention</th>
<th>SoR</th>
<th>QoE</th>
<th>Reference</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>SOT recipients with cutaneous infection</td>
<td>To cure</td>
<td>ICZ for 3–18 mo</td>
<td>B</td>
<td>III</td>
<td>Schieffelin TID 2014&lt;sup&gt;1475&lt;/sup&gt;</td>
<td>N=24; Average treatment among 17 survivors 10 mo (range 6–27 mo)</td>
</tr>
<tr>
<td>SOT recipients with cutaneous infection</td>
<td>To cure</td>
<td>Long term treatment with VCZ, PCZ, ICZ, AmB, 5-FC</td>
<td>B</td>
<td>III</td>
<td>Santos CMI 2017&lt;sup&gt;1444&lt;/sup&gt;</td>
<td>N=30, ICZ for 3-18 mo</td>
</tr>
<tr>
<td>Any</td>
<td>To cure</td>
<td>ICZ for a median of 50–73 d for local infections, VCZ for more severe infections +/- TRB or AmB</td>
<td>C</td>
<td>III</td>
<td>Revanker OFID 2017&lt;sup&gt;1518&lt;/sup&gt;</td>
<td>N=99, median duration 50–73 d (range 2–915 d)</td>
</tr>
<tr>
<td>Any</td>
<td>To cure</td>
<td><em>E. dermatitidis</em>: VCZ for 7–64 d</td>
<td>C</td>
<td>III</td>
<td>Vasquez CID 2017&lt;sup&gt;1487&lt;/sup&gt;</td>
<td>Local superficial infection: median duration 73 d (range 1–915 d). Local deep infection: median duration 50 d (range 3–710 d). Disseminated infection: median duration treatment 61 d (range 2–720 d).</td>
</tr>
</tbody>
</table>

5-FC, 5-fluorocytosine; AmB, amphotericin B; d, day(s); ICZ, itraconazole; PCZ, posaconazole; mo, month(s); QoE, quality of evidence; SoR, strength of recommendation; SOT, Solid organ transplant; TRB, terbinafine; VCZ, voriconazole.

Recommendation – The guideline group moderately supports treatment until all signs and symptoms of infection have resolved. The treatment duration is determined by clinical response regardless of the type of antifungal agents administered (Figure 16).
Figure 16. Optimal treatment pathway for phaeohyphomycosis in adults when all treatment modalities and antifungal drugs are available

Specific considerations on treatment of phaeohyphomycosis in children

Evidence - There are minimal data in children on the treatment of phaeohyphomycosis. All reported pediatric cases had CNS involvement (Table 25).

Table 25. First-line antifungal therapy in children for phaeohyphomycetes/dematiaceous fungi/black fungi infections

<table>
<thead>
<tr>
<th>Population</th>
<th>Intention</th>
<th>Intervention</th>
<th>SoR</th>
<th>QoE</th>
<th>Reference</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immunocompetent</td>
<td>To cure</td>
<td>ABLE 3-6 mg/kg qd + 5-FC, then ABLE 6 mg/kg qd + ICZ 6 mg/kg qd</td>
<td>C</td>
<td>III</td>
<td>Chang JCN 2009\textsuperscript{1571}</td>
<td>N=1, 3 yrs, cerebral abscesses, E. dermatisidis, failure</td>
</tr>
<tr>
<td>Immunocompetent</td>
<td>To cure</td>
<td>AmB, VCZ 200 mg bid</td>
<td>C</td>
<td>III</td>
<td>Alabaz MedMycol 2009\textsuperscript{1571}</td>
<td>N=1, 8 yrs, systemic infection, E. dermatitidis, failure</td>
</tr>
<tr>
<td>Hematological patients</td>
<td>To cure</td>
<td>AmB + surgery</td>
<td>C</td>
<td>III</td>
<td>Bay RCI 2017\textsuperscript{1572}</td>
<td>N=1, 8 yrs, nasal vestibule infection, Curvularia spicifera, success</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Saint-Jean CJDMM 2007\textsuperscript{1573}</td>
</tr>
</tbody>
</table>
Recommendation - Consideration should be given to prescribe an antifungal with sufficient CNS penetration. Combination therapy containing lipid formulations of AmB is moderately recommended, as is surgery.

5. Rasamsonia

Epidemiology of infections caused by Rasamsonia spp.

Rasamsonia is a new genus introduced in 2011 comprising 11 thermotolerant species that were formerly classified in the genera Geosmithia, Penicillium, or Talaromyces. Rasamsonia has rarely been reported as the causative pathogen of fungal infections in humans, and most of these reports originate from northern countries and high-resource settings. Rasamsonia can colonize the respiratory tract of patients with CF with variable clinical significance. Infections caused by Rasamsonia argillacea (formerly known as Geosmithia argillacea), Rasamsonia piperina and Rasamsonia aegroticola have been reported mainly in severely ill patients with chronic granulomatous disease or underlying malignancy, and those undergoing hematopoietic stem cell transplantation or lung transplantation. Diagnosis can be misleading as R. argillacea is morphologically similar to Penicillium spp. and Paecilomyces spp. and misidentification has been frequently reported. Rasamsonia-related infections predominantly affect the lungs and may disseminate to adjacent organs or to the CNS.
Figure 17. Worldwide distribution of infections caused by *Rasamsonia* spp. (reported cases between 2000 and 2019 per million population)

Cases of severe *Rasamsonia*-related infections reported in the medical literature were identified in a PubMed search on November 15, 2019 using the search string “*Rasamsonia* OR *Geosmithia* OR *Penicillium argillaceum*” that yielded 126 publications. Twenty eight cases have been reported from six countries since 2000\(^{10,1034,1577-1585,1587-1590}\). Most cases were reported from Germany (n=8), Canada (n=7) and the United States (n=6). The number of cases reported between 2000 and 2019 is presented as cases per million population per country. The resident population per country was obtained from www.worldometers.info\(^{321}\).

**Diagnosis of Rasamsonia infections**

**Diagnosis – Microbiology – Conventional Methods**

**Evidence** - Cultures using yeast extract-peptone-dextrose agar, Sabouraud dextrose agar or potato flakes agar can achieve the highest diagnostic value for clinical samples obtained from sterile body sites. Incubation at 28–30°C for up to four weeks has been reported\(^{10}\). For superficial and respiratory tract samples, clinical signs and symptoms are important to differentiate between colonization/contamination and infection\(^{1579-1583,1586,1587,1591-1593}\). Mucous sputum samples should be pretreated with a mucolytic agent before culture, but these pretreatments may cause false negative GM antigen levels\(^{1594,1595}\) (Table 26).
Recommendation - The guideline group strongly recommends culture from clinical samples.

Diagnosis – Microbiology – Serology

Evidence – GM cross-reacts with Rasamsonia spp. and positive results have been described from BALF and serum\textsuperscript{1585} (Table 26).

Recommendations – The guideline group moderately supports GM testing from BALF and serum.

Diagnosis – Microbiology – Molecular-based

Evidence - Direct fungal detection by real-time PCR of respiratory samples has been reported in CF patients\textsuperscript{1596} (Table 26).

Recommendation - The guideline group moderately recommends specific real-time PCR for detection of Rasamsonia spp. in respiratory samples from CF patients.

Diagnosis – Microbiology – Species identification

Evidence - Identification to the genus level can be done by microscopic examination. Rasamsonia spp. overall resembles Paecilomyces spp. and Penicillium spp., but Rasamsonia spp. differs from Paecilomyces spp. in having more regular branched conidiophores with distinct rough-walled structures, and from Paecilomyces spp. and Penicillium spp. by the shape of the conidia which are cylindrical. See also Figure 18 with microscopic morphology from the Atlas of Clinical Fungi project\textsuperscript{19} (Table 26).
Figure 18. Microscopic morphology of Rasamsonia spp.  

Panel A-B, R. argillacea, phialides with conidia in chains; Panel C-D, Rasamsonia eburnea, with erect conidiophores and monoverticillate, later becoming biverticillate penicilli producing ellipsoidal or ovoidal, conidia; Panel E-F, R. piperina, phialides with conidia in chains. Scale bars = 10 µm.

Accurate identification to the species level requires ITS/β-tubulin sequencing. Genotyping can be achieved by repetitive sequence-based PCR and random amplification of polymorphic DNA (Table 26).
Recommendation - The guideline group strongly recommends to perform microscopy of cultures, followed by ITS/β-tubulin gene sequencing for species identification.

Diagnosis – Microbiology – Susceptibility testing

Evidence - Antifungal susceptibility testing according to EUCAST or CLSI guidelines may be useful to determine susceptibilities; however, the absence of interpretive breakpoints warrants caution when utilizing MICs to guide treatment (Table 26).

Recommendation - The guideline group strongly recommends that antifungal susceptibility testing should be performed for epidemiological purposes, while susceptibility testing to guide the choice of antifungal therapy is moderately recommended.

Diagnosis – Microbiology – Pathology

Evidence - Histological examination of PAS, H&E, GMS stained tissue biopsy sections is important for ascertaining fungal structures (Table 26).

Recommendation - The guideline group strongly recommends that histology should be performed whenever possible.

Diagnosis – Microbiology – Imaging studies

Evidence – Diagnostic imaging studies of the affected organ/systems (CT for thorax, CT or MRI for brain) can delineate the extent of involvement of the infection. Invasion of adjacent structures as shown by CT examination has been reported (Table 26).
**Table 26. Microbiological, histopathological and imaging diagnostics for *Rasamsonia* infections**

<table>
<thead>
<tr>
<th>Population</th>
<th>Intention</th>
<th>Intervention</th>
<th>SoR</th>
<th>QoE</th>
<th>Reference</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Microscopy, culture, MIC testing</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any</td>
<td>To diagnose</td>
<td>Histology (GMS &amp; HE)</td>
<td>A</td>
<td>IIIu</td>
<td>Machouart JCM 2011[1383]</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any</td>
<td>To diagnose</td>
<td>Culture, SDA 28-30°C, s4 wk</td>
<td>A</td>
<td>IIIu</td>
<td>Abdolrasouli Mycoses 2018[1576]</td>
<td></td>
</tr>
<tr>
<td>Any with CF / chronic granulomatous disease</td>
<td>To diagnose</td>
<td>Culture – selection of YPDA, SDA, PFA</td>
<td>A</td>
<td>III</td>
<td>Giraud JCM 2010[1591]</td>
<td></td>
</tr>
<tr>
<td>Any with CF</td>
<td>To diagnose</td>
<td>Culture, sputum with mucolytic, homogenate, serial dilution, SDA + 100mg/L chloramphenicol, 28-30°C, s4 wk</td>
<td>A</td>
<td>IIIu</td>
<td>Abdolrasouli Mycoses 2018[1576]</td>
<td></td>
</tr>
<tr>
<td>Any</td>
<td>To diagnose</td>
<td>Microscopy of cultures</td>
<td>A</td>
<td>III</td>
<td>Hong JCF 2017[1541]</td>
<td></td>
</tr>
<tr>
<td>Children/neonates</td>
<td>To diagnose</td>
<td>Culture, gastric aspiration of sputum</td>
<td>B</td>
<td>III</td>
<td>Fujita TJEM 2019[1588]</td>
<td>Acid resistant</td>
</tr>
<tr>
<td>Chronic pulmonary disease with colonization</td>
<td>To diagnose underlyng disease</td>
<td>Test for CF</td>
<td>C</td>
<td>III</td>
<td>Erenouillet Mycopathol 2018[1594]</td>
<td>Colonization indicative of CF</td>
</tr>
<tr>
<td>Any with CF</td>
<td>To identify susceptibility patterns</td>
<td>Antifungal susceptibility testing according to EUCAST or CLSI</td>
<td>B</td>
<td>III</td>
<td>Giraud JCM 2010[1591]</td>
<td></td>
</tr>
<tr>
<td>Any</td>
<td>To guide treatment</td>
<td>Antifungal susceptibility testing of <em>R. argillacea</em></td>
<td>B</td>
<td>III</td>
<td>De Ravin CID 2011[1582]</td>
<td></td>
</tr>
<tr>
<td><strong>Serology assays</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any</td>
<td>To diagnose</td>
<td>GM testing (Platelia, Bio-Rad) in BAL and serum</td>
<td>B</td>
<td>III</td>
<td>Valentin BMT 2012[1580]</td>
<td></td>
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<tr>
<td><strong>Nucleic-acid based assays/MALDI-TOF MS</strong></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any</td>
<td>To diagnose from any sample</td>
<td>Molecular sequencing (ITS1, ITS2, β-tubulin)</td>
<td>B</td>
<td>III</td>
<td>Hong JCF 2017[1541]</td>
<td></td>
</tr>
<tr>
<td>Any</td>
<td>To diagnose from autopsies</td>
<td>PCR/ESE-ToF-MS</td>
<td>B</td>
<td>III</td>
<td>Giraud FMB 2013[1592]</td>
<td></td>
</tr>
<tr>
<td>CF</td>
<td>To detect in respiratory secretions</td>
<td>Real-time PCR</td>
<td>B</td>
<td>II</td>
<td>Steinman NMMI 2014[1596]</td>
<td>Not <em>R. eburnea</em></td>
</tr>
<tr>
<td>CF</td>
<td>To diagnose from sputum</td>
<td>Oligoarray, ITS2</td>
<td>C</td>
<td>III</td>
<td>Bouchara JCM 2009[151]</td>
<td>N-20 fungal species, 100% and spec. 99.2%, <em>Rasamsonia emersonii</em> included</td>
</tr>
<tr>
<td>Any</td>
<td>To identify</td>
<td>MALDI-TOF MS</td>
<td>C</td>
<td>IIIu</td>
<td>Barker MedMycol 2014[1597]</td>
<td>Only <em>R. argillacea</em></td>
</tr>
<tr>
<td>Any</td>
<td>To identify</td>
<td>ITS1-ITS2/beta-tubulin sequencing</td>
<td>A</td>
<td>IIIu</td>
<td>Houbraken JCM 2013[1598]</td>
<td></td>
</tr>
<tr>
<td>CF</td>
<td>To identify</td>
<td>Culture + ITS1-ITS2/beta-tubulin sequencing</td>
<td>A</td>
<td>III</td>
<td>Dissing MedMycol 2016[1555]</td>
<td></td>
</tr>
<tr>
<td>Any</td>
<td>To identify</td>
<td>Morphology, molecular genetics (beta-tubulin and calmodulin genes, ITS analysis)</td>
<td>A</td>
<td>IIIu</td>
<td>Houbraken JCM 2013[1578]</td>
<td>Differs from Poeclomyces by more regular branching</td>
</tr>
<tr>
<td>Any with CF</td>
<td>To identify and genotype</td>
<td>Repetitive sequence-based PCR</td>
<td>C</td>
<td>Mouhajir JCM 2016^{103}</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any</td>
<td>To genotype</td>
<td>RAPD</td>
<td>C</td>
<td>Saevra-Suarez JCM 2016^{104}</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Tissue-based diagnosis**

| Any | To diagnose | Histology; PAS, HE, GMS stainings | A | Mouhajir JCM 2016^{101} |
| Any with CF | To establish definitive diagnosis | Autopsy | A | Mouhajir JCM 2016^{101} |

**Imaging studies**

| Any with CGD | To detect | Chest CT | A | De Ravin CID 2011^{1580} |
| Any | To detect contiguous spread & dissemination | Chest CT, cranial CT | A | De Ravin CID 2011^{1580} |

AmB, amphotericin B; BAL, bronchoalveolar lavage; CF, cystic fibrosis; CGD, chronic granulomatous disease; CLSI, Clinical and Laboratory Standards Institute; CT, computed tomography; ESI-TOF MS, Electrospray Ionization time of flight mass spectrometry; EUCAST, European Committee for Antimicrobial Susceptibility Testing; GM, Galactomannan; GMS, Grocott-Gomori’s methenamine silver; HE, hematoxylin-eosin; ICZ, Itraconazole; ITS, internal transcribed spacer; MALDI-TOF MS, matrix assisted laser desorption ionization-time of flight mass spectrometry; MIC, minimal inhibitory concentration; PAS, periodic acid-Schiff; PCR, polymerase chain reaction; PCZ, posaconazole; PFA, potato flakes agar; QoE, quality of evidence; SDA, Sabouraud Dextrose agar; SoR, strength of recommendation; TRB, terbinafine; VCZ, voriconazole; wk, week(s); YPDA, yeast extract-peptone-dextrose agar.

**Recommendation** - The guideline group strongly recommends performing radiological examinations to delineate the extent of involvement of the infection (Figure 19).
Figure 19. Optimal diagnostic pathway for *Rasamsonia* infections, when all imaging and assay techniques are available

Invasive infection due to *Rasamsonia* spp.

Any population

**Imaging procedures** (CT scan, MRI, X-ray) on suspected sites of infection

Galactomannan in BAL and serum

Culture from any site

Microscopy of cultures

Antifungal susceptibility testing to guide treatment

Histology

For further species identification

**ITS 1, ITS 2 and β tubulin sequencing**

For further species identification MALDI-TOF MS

Legend:

- strongly recommended
- moderately recommended
- marginally recommended
- recommended against

BAL, bronchioalveolar lavage; CT, computed tomography; ITS, internal transcribed spacer; MALDI-TOF MS, matrix-assisted laser desorption/ionization time-of-flight mass spectrometry; MRI, magnetic resonance imaging

Treatment approaches to *Rasamsonia* infections

Treatment in Adults

Evidence - Evidence for the treatment of invasive infections due to *Rasamsonia* spp. is sparse, with currently only 23 cases available in the literature. Colonization, specifically in CF patients, was reported much more frequently. However, mortality reaches upwards of 40% in invasive infections, so treatment
should not be delayed for this significant pathogen\textsuperscript{10}. Overall, high MICs have been reported for triazoles, while echinocandins show best \textit{in vitro} susceptibility\textsuperscript{1577,1579-1583,1585,1587,1590}. CASPO and MICA have been used successfully\textsuperscript{1579,1584,1587,1605}, successful use of combination therapy with an echinocandin plus PCZ or L-AmB has also been reported\textsuperscript{1579,1584,1605}. Surgery is another important cornerstone of treatment of localized infections\textsuperscript{1579,1580,1587}. Secondary prophylaxis with PCZ has been reported\textsuperscript{1577,1580,1583,1587} (Table 27).

### Table 27. Therapy for \textit{Rasamsonia} infections

<table>
<thead>
<tr>
<th>Population</th>
<th>Intention</th>
<th>Intervention</th>
<th>SoR</th>
<th>QoE</th>
<th>Reference</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>First-line antifungal therapy</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any, any with CGD</td>
<td>To cure and avoid treatment failure/death</td>
<td>Avoid azole monotherapy</td>
<td>A</td>
<td>Iu</td>
<td>De Ravin CID 2011\textsuperscript{1585}</td>
<td>Azoles lead mostly to failure, MICs VCZ and occasional ICZ &gt;8-16, PCZ usually &gt;4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Marguet MMCR 2012\textsuperscript{1577}</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Machouart JCM 2011\textsuperscript{1581}</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Valentin BMT 2012\textsuperscript{1585}</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Doyon JCM 2013\textsuperscript{1587}</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Shiwada Mycopathol 2016\textsuperscript{1582}</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Hong JCF 2017\textsuperscript{1581}</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Babiker MMCR 2019\textsuperscript{1579}</td>
<td>In vitro study in CF; Echinocandins with highest activity; resistance to azoles</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Steinmann AAC 2016\textsuperscript{1580}</td>
<td></td>
</tr>
<tr>
<td>Any</td>
<td>To cure</td>
<td>CASPO OR MICA +/- PCZ</td>
<td>B</td>
<td>III</td>
<td>Abdolrasouli Mycoses 2018\textsuperscript{1578}</td>
<td>N=1, CF, response to CASPO</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Doyon JCM 2013\textsuperscript{1587}</td>
<td>N=1, MICA + PCZ, response</td>
</tr>
<tr>
<td>HSCT with GVHD</td>
<td>To cure</td>
<td>CASPO + L-AmB +/- PCZ</td>
<td>B</td>
<td>III</td>
<td>Valentin BMT 2012\textsuperscript{1585}</td>
<td>N=1, initial response, then deterioration; died</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Ocak RCR 2019\textsuperscript{1584}</td>
<td>N=1, partial clinical response</td>
</tr>
<tr>
<td>HSCT</td>
<td>To cure</td>
<td>L-AmB</td>
<td>C</td>
<td>III</td>
<td>Corzo-Leon Mycoses 2015\textsuperscript{1594}</td>
<td>N=1, died</td>
</tr>
<tr>
<td><strong>Antifungal salvage treatment</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any with CF</td>
<td>To cure</td>
<td>Echinocandin</td>
<td>C</td>
<td>III</td>
<td>Abdolrasouli Mycoses 2018\textsuperscript{1578}</td>
<td>N=1, clinical stable</td>
</tr>
<tr>
<td>Any with CGD</td>
<td>To cure</td>
<td>Empirical treatment with PCZ, L-AmB and CASPO</td>
<td>C</td>
<td>III</td>
<td>Ocak RCR 2019\textsuperscript{1584}</td>
<td>Babiker MMCR 2019\textsuperscript{1579}</td>
</tr>
<tr>
<td><strong>Other treatment options</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any with CGD</td>
<td>To cure</td>
<td>Surgery</td>
<td>B</td>
<td>III</td>
<td>De Ravin CID 2011\textsuperscript{1580}</td>
<td>N=4, 1/4 died</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Babiker MMCR 2019\textsuperscript{1579}</td>
<td>N=1, success</td>
</tr>
<tr>
<td>Immunocompetent</td>
<td>To cure</td>
<td>Surgery / resection of infected (graft) material</td>
<td>B</td>
<td>III</td>
<td>Doyon JCM 2013\textsuperscript{1587}</td>
<td>N=1, success</td>
</tr>
<tr>
<td><strong>Treatment duration</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any with CGD</td>
<td>To cure</td>
<td>Prolonged treatment / Secondary prophylaxis</td>
<td>B</td>
<td>Iu</td>
<td>Machouart JCM 2011\textsuperscript{1581}</td>
<td>N=9, 5/9 survived, 4/9 prolonged treatment/secondary prophylaxis up to 6 yrs</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>De Ravin CID 2011\textsuperscript{1580}</td>
<td></td>
</tr>
<tr>
<td>Immunocompetent</td>
<td>To cure</td>
<td>Prolonged treatment / Secondary prophylaxis</td>
<td>B</td>
<td>III</td>
<td>Doyon JCM 2013\textsuperscript{1587}</td>
<td>N=1, 13 mo of PCZ, success</td>
</tr>
</tbody>
</table>

**Recommendations** - The guideline group strongly recommends to avoid azole monotherapy due to reports of clinical failure and high MICs. The guideline group moderately recommends primary treatment...
with an echinocandin, or a combination of an echinocandin with either L-AmB or PCZ. Surgery, whenever possible is moderately recommended for treatment of *Rasamsonia* infections. Treatment duration depends on the affected site, clinical response and underlying condition but can be up to several months. Secondary prophylaxis is moderately recommended (Figure 20).

**Figure 20. Optimal treatment pathway for *Rasamsonia* infections in adults when all treatment modalities and antifungal drugs are available**
Specific considerations on treatment of Rasamsonia infections in children

Evidence – Invasive infections caused by Rasamsonia spp. have been described as a complication occurring in children with CGD\(^\text{1580}\). Breakthrough infections while on mold-active azole prophylaxis have been reported, but treatment with MICA has been associated with favorable outcome \(^\text{1402,1580,1588}\) (Table 28).

Table 28. First-line antifungal therapy in children for Rasamsonia infections

<table>
<thead>
<tr>
<th>Population</th>
<th>Intention</th>
<th>Intervention</th>
<th>SoR</th>
<th>QoE</th>
<th>Reference</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any with CGD</td>
<td>To cure</td>
<td>MICA+VCZ</td>
<td>B</td>
<td>II</td>
<td>Ishiwada Mycopathol 2015(^\text{1582})</td>
<td>N=1, 16 yrs, mixed infection with Aspergillus nidulans</td>
</tr>
<tr>
<td>Any</td>
<td>To cure</td>
<td>MICA</td>
<td>B</td>
<td>II</td>
<td>De Ravin CID 2011(^\text{1586}) De Ravin CID 2011(^\text{1586})</td>
<td>N=3 CGD, 3/3 survived;</td>
</tr>
<tr>
<td>Any with CF</td>
<td>To cure and improve lung function</td>
<td>Secondary prophylaxis</td>
<td>B</td>
<td>III</td>
<td>Marguet MMCR 2012(^\text{1587})</td>
<td>N=1, long-term prophylaxis with PCZ + intermittent echinocandin improved FEV1</td>
</tr>
</tbody>
</table>

Standard pediatric dose unless stated otherwise; CF, cystic fibrosis; CGD, chronic granulomatous disease; d, day(s); FEV1, forced expiratory volume in one second; iv, intravenous; MICA, micafungin; po, orally; QoE, quality of evidence; SoR, strength of recommendation; VCZ, voriconazole; wk, week(s); yrs, years.

Recommendations – Echinocandins with or without another antifungal are moderately recommended as first-line treatment in children, in line with recommendations in adults. Triazole monotherapy should be avoided. Surgery is moderately recommended if feasible and infection is not disseminated.

6. Schizophyllum and other basidiomycetes

Epidemiology of infections caused by Schizophyllum spp. and other basidiomycetes

Basidiomycetes, such as Schizophyllum commune, Coprinopsis cinerea (formerly Hormographiella aspergillata) and Phanerochaete chrysosporium (formerly Sporotrichum pruinosum) are often found in decaying matter. Despite their worldwide distribution invasive infections due to these fungal agents are rare. In humans, S. commune accounts for the majority of infections caused by these organisms, the vast majority of which presents as pulmonary disease or sinusitis\(^\text{1606-1610}\). C. cinerea is the second most prevalent basidiomycete causing mainly infections of the lung\(^\text{1611,1612}\). Eye infections have also been identified\(^\text{1613-1615}\). There are only few reports of infections affecting other organs such as brain, spine or peritoneum\(^\text{1616-1618}\). Fungemia is uncommon\(^\text{1619,1620}\).
Co-infection with other molds has often been reported, possibly because affected patients are critically ill or severely immunocompromised and thus are susceptible to concomitant infections.

True prevalence of these infections is likely underestimated, as microbiological methods of species identification are rather difficult due to lack of asexual reproduction (Figure 21).

Figure 21. Worldwide distribution of infections caused by *Schizophyllum* spp. and other basidiomycetes (reported cases between 1971 and 2019 per million population)

Cases of infections caused by *Schizophyllum*, *Coprinopsis* and other basidiomycetes reported in the medical literature were identified in a PubMed search on October 15, 2019 using the search string “(Trametes OR Lenzites OR Lophotrichus OR Schizophyllum OR Ustilago OR Coprinus OR Coprinopsis OR Hormographella aspergillata OR C. cinereus) AND (infection OR case report OR report [title/abstract] OR case [title/abstract] OR abscess OR fungemia OR blood OR invasive)” excluding reports on plants and animals that yielded 748 publications. Reports of 103 cases of rare basidiomycetes-related infections have been identified from 27 countries, 88 since the year 2000. S. commune and C. cinerea accounted for 73% of the cases. Infections due to *P. chrysosporium*, *Schizophyllum radiatum*, *Ustilago* spp. and other basidiomycetes were found sporadically in the literature. Most cases were reported from the United States (n=11) and India (n=6). In Singapore and Hong Kong one case each has been reported since 1971. The number of cases reported between 1971 and 2019 is presented as cases per million population.
per country. The resident population per country was obtained from www.worldometers.info. Two cases of infections caused by *Trametes polyzona* were reported from La Réunion (2.3 cases per million population between 1971 and 2019).

**Diagnosis of infections caused by *Schizophyllum* and other basidiomycetes**

**Diagnosis – Microbiology – Conventional Methods**

**Evidence** – Culture is mandatory for species identification and antifungal susceptibility testing, but many basidiomycetes are sterile and do not sporulate in the laboratory. In microscopy the hyphal clamp connections with spicules suggest *S. commune*. See also Figure 22 and Figure 23 for microscopic morphology from the Atlas of Clinical Fungi project.

**Figure 22. Microbiological characteristics of *S. commune* (owned by co-author V. Arsic-Arsenjevic)**

Panel A, GMS stain; Panel B-C, Spicula (blue arrows) in lactophenol cotton blue stain, microscopy x 400 and x 1000.
Figure 2. Microscopic morphology of *Schizophyllum* spp.  


For non-sterile samples, such as respiratory tract specimens, distinguishing among genuine infection, colonization, and contamination is important (Table 29).

**Recommendation** - The guideline group strongly recommends that tissue microscopy and culture should be performed when possible.

**Diagnosis – Microbiology – Serology**

**Evidence** – In general, basidiomycetes lack GM and BDG in their cell walls, but cases with elevated BDG have been reported1646,1675-1677. A positive GM test may suggest co-infection with *Aspergillus* species1612,1644,1646,1665,1675,1676. *S. commune* infection may lead to false-positive cryptococcal antigen testing and may result in misdiagnosis1631 (Table 29).
Recommendation – Serological testing is not recommended as part of the diagnostic evaluation for infections caused by Schizophyllum and other basidiomycetes.

Diagnosis – Microbiology – Molecular-based

Evidence – PCR sequencing of cultured strains and of formalin-fixed paraffin-embedded tissue samples can be useful for detection of basidiomycetes such as H. aspergillata and Phellinus undulatus (Table 29).

Recommendation - The guideline group moderately recommends PCR from formalin-fixed paraffin-embedded tissue samples.

Diagnosis – Microbiology – Species identification

Evidence – Definite identification requires PCR of fungal isolates followed by ITS and/or D1/D2 sequencing for this heterogeneous group of fungi. MALDI-TOF MS has been reported to be useful for identification of S. commune (Table 29).

Recommendation – While species identification of basidiomycetes may be difficult due to incomplete public databases and rareness of reference strains the guideline group strongly recommends that ITS and/or D1/D2 sequencing should be performed on the culture isolate for species identification, and marginally recommends MALDI-TOF MS for the same purpose.

Diagnosis – Microbiology – Susceptibility testing

Evidence – Antifungal susceptibility testing is useful to determine susceptibilities, however, the absence of interpretive breakpoints warrants caution when utilizing MICs to guide treatment (Table 29).

Recommendation - The guideline group strongly recommends that antifungal susceptibility testing should be performed for identifying susceptibility patterns, while susceptibility testing to guide the choice of antifungal therapy is moderately suggested.
Diagnosis – Pathology

Evidence – Histological examination of PAS and/or GMS stained tissue biopsy sections are important for ascertaining fungal invasion, but are often inconclusive and may confound basidiomycetes with Aspergillus spp. (Table 29).

Recommendation – The guideline group moderately recommends that histopathology should be performed when possible.

Diagnosis – Microbiology – Imaging studies

Evidence – Most diagnostic imaging studies involve infections caused by Hormogaphiella spp.. CT scan is useful to detect pulmonary and sino-orbito-cerebral infections1641 and MRI has been used to detect CNS involvement1641,1677 (Table 29).
### Table 29. Microbiological, histopathological and imaging diagnostics of infections caused by Schizoplyllum spp. and other basidiomycetes

<table>
<thead>
<tr>
<th>Population</th>
<th>Intention</th>
<th>Intervention</th>
<th>SoR</th>
<th>QoE</th>
<th>Reference</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any</td>
<td>To diagnose</td>
<td>Microscopy of tissue biopsy</td>
<td>A</td>
<td>III</td>
<td>Chowdhary JCM 20131622, Hoenigl Mycoses 20131623, Saha Mycopathol 20131624, Toya UH 20131625, De Ravin JCM 20141626, Verma Mycopathol 20141627, Shigemura Infection 20151628, Lim AJD 20171629, Jain JMM 20191630</td>
<td>Observation of tissue invasion by fungi. No definite identification of species provided. Occasionally spicules on the hyphae may be seen in biopsy samples from lung and sinuses. Culture and identification are mandatory for species identification.</td>
</tr>
<tr>
<td>Any</td>
<td>To diagnose</td>
<td>Culture</td>
<td>A</td>
<td>III</td>
<td>Friman SJID 20061631, Chowdhary JCM 20131632, Saha Mycopathol 20131633, Toya UH 20131634, Chen JCM 20141635, De Ravin JCM 20141636, Verma Mycopathol 20141637, Shigemura Infection 20151638, Lim AJD 20171639, Heilig Mycoses 20151640, Surmont MedMycol 20021641</td>
<td>Always need to distinguish between genuine infection, colonization and contamination specifically in respiratory specimens. Other molds co-exist in respiratory specimens culture. Multiple cultures may be necessary. Complementary with tissue biopsy. Basidiomycetes colonies in culture are white cottony to fluffy, fast-growing, with yellow-brown reverse. Basidiomycetes are sensitive to cycloheximide, allowing them to be distinguished from Coccioidoides spp. Many basidiomycetes are sterile and will not sporulate in the laboratory, although some develop clamp connections or spicules on the hyphae, and some isolates may produce basidiospores (after exposure of the culture plate to alternating cycles of light and darkness). Definitive species identification requires ITS and or LSU sequencing.</td>
</tr>
<tr>
<td>Any</td>
<td>To diagnose S. commune</td>
<td>Morphology</td>
<td>C</td>
<td>Illu</td>
<td>Michel MedMycol 20161642</td>
<td>Fungus usually does not sporulate under classical culture conditions.</td>
</tr>
<tr>
<td>Any</td>
<td>To guide treatment and correlate MICs with outcome for basidiomycetes</td>
<td>Antifungal susceptibility testing with CLSI method</td>
<td>Bu</td>
<td>Illu</td>
<td>Singh JCM 20131630, Gonzalez AAC 20011643</td>
<td>MIC AmB &lt; 1 µg/ml, VCZ &lt; 0.25 µg/ml</td>
</tr>
<tr>
<td>Any</td>
<td>To determine MICs of S. commune, Bjerkandera adusta and Coprinus spp.</td>
<td>Antifungal susceptibility testing</td>
<td>A</td>
<td>Illu</td>
<td>Gené AVL 19961644, Verweij JCM 19971645, Nanno TID 20161646, Abual JCM 20091647</td>
<td>MIC90 AmB 0.5 µg/ml, ICZ 0.125 µg/ml, PCZ 0.5 µg/ml, VCZ 0.5 µg/ml for S. commune, Bjerkandera adusta and Coprinus spp., FCZ and 5-FC higher MIC90 but within achievable concentrations in serum.</td>
</tr>
<tr>
<td>Any</td>
<td>To determine MICs of C. cinerea (formerly H. aspergillata) and Coprinus domesticus (formerly Hormogoniphila verticillata).</td>
<td>Antifungal susceptibility testing</td>
<td>A</td>
<td>Illu</td>
<td>Gené AVL 19961644, Verweij JCM 19971645, Nanno TID 20161646, Abual JCM 20091647</td>
<td>MICs miconazole 0.6 to 5.0 µg/ml, ICZ 0.07 to 0.6 µg/ml, and KCZ 0.2 to 1.6 µg/ml. Resistant to FCZ 20 to 80 µg/ml and 5-FC 320 to 0.322 µg/ml, susceptibility to AmB variable 0.07 to 4.6 µg/ml. All strains of C. domesticus susceptible to AmB; 4/7 of C. cinerea resistant 2.3 to 4.6 µg/ml</td>
</tr>
<tr>
<td>Any</td>
<td>To determine MICs of S. commune</td>
<td>Antifungal susceptibility testing</td>
<td>A</td>
<td>Illu</td>
<td>Chowdhary AAC 20131644</td>
<td>Low geometric mean MICs of AmB 0.29 µg/ml, ISA 0.19 µg/ml, ICZ 0.2 µg/ml, VCZ 0.24 µg/ml. High geometric mean MICs of FCZ 19.39 µg/ml and 5-FC</td>
</tr>
</tbody>
</table>

*Note: SoR stands for Strength of Recommendation, QoE for Quality of Evidence.*
<table>
<thead>
<tr>
<th>Tissue</th>
<th>To determine MICs of <em>S. commone</em> + <em>S. radia- tum</em></th>
<th>Antifungal susceptibility testing</th>
<th>A</th>
<th>Ilu</th>
<th>Siqueira JCM 2016\textsuperscript{1662}</th>
<th>Geometric mean MICs AmB 0.29 (\mu)g/ml, CFG 0.58 (\mu)g/ml and TBF 0.79 (\mu)g/ml, ICZ 1.67 (\mu)g/ml and PCZ 2.93 (\mu)g/ml. <em>S. radiatum</em> showed higher GM MICs for all the antifungals than <em>S. commone</em>, especially for ICZ and PCZ.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any</td>
<td>To determine MICs of <em>monoto/s/Phellinus spp.</em></td>
<td>Antifungal susceptibility testing, E-test</td>
<td>A</td>
<td>III</td>
<td>Davis PIDI 2007\textsuperscript{1634}</td>
<td>Sutton JCM 2005\textsuperscript{1667}</td>
</tr>
</tbody>
</table>

**Serology assays**

<table>
<thead>
<tr>
<th>Tissue</th>
<th>To diagnose</th>
<th>GM</th>
<th>D</th>
<th>III</th>
<th>Suarez JCM 2011\textsuperscript{1660}</th>
<th>Lagrou IMM 2005\textsuperscript{1644}</th>
<th>Nanno TID 2016\textsuperscript{1644}</th>
<th>Godet Mycopathol 2017</th>
<th>Haidar Mycoses 2017\textsuperscript{1635}</th>
<th>Shimamura Infection 2015\textsuperscript{1676}</th>
<th>Koncan JMBT 2016\textsuperscript{1648}</th>
<th>N=3 with elevated BDG, but in general basidiomycetes lack GM and BDG in their cell walls.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any</td>
<td>To diagnose</td>
<td>BDG</td>
<td>D</td>
<td>III</td>
<td>Chauhan LabMed 2017\textsuperscript{1616}</td>
<td>Nanno TID 2016\textsuperscript{1644}</td>
<td>Haidar Mycoses 2017\textsuperscript{1635}</td>
<td>Shimamura Infection 2015\textsuperscript{1676}</td>
<td>Koncan JMBT 2016\textsuperscript{1648}</td>
<td>N=3 with elevated BDG, but in general basidiomycetes lack GM and BDG in their cell walls.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**S. commone empyema thoracis**

| Tissue | To diagnose Cryptococcal Ag latex agglutination | D | III | Chan JCM 2014\textsuperscript{1631} | Cross-reactivity with Cryptococcal antigen test leading to misdiagnosis |

**Nucleic-acid based assays/MALDI-TOF MS**

<table>
<thead>
<tr>
<th>Tissue</th>
<th>To diagnose <em>C. cinerea</em></th>
<th>PCR</th>
<th>B</th>
<th>III</th>
<th>Heiblig Mycoses 2015\textsuperscript{1641}</th>
<th>PCR from formalin-fixed paraffin-embedded tissue samples. Described for <em>C. cinerea</em>.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any</td>
<td>To identify <em>S. commone</em></td>
<td>MALDI-TOF MS</td>
<td>C</td>
<td>III</td>
<td>Michel MedMycol 2016\textsuperscript{1606}</td>
<td>Homemade reference spectra library must be used</td>
</tr>
<tr>
<td>Any</td>
<td>To identify <em>S. commone</em></td>
<td>ITS sequencing</td>
<td>A</td>
<td>Ilu</td>
<td>Michel MedMycol 2016\textsuperscript{1606}</td>
<td>Buzina JCM 2001\textsuperscript{1678}</td>
</tr>
</tbody>
</table>

| Tissue | To identify *Hormophiella spp.* | ITS sequencing | A | III | Verweij JCM 1997\textsuperscript{1672} | Lagrou JMM 2005\textsuperscript{1644} | Suarez JCM 2011\textsuperscript{1660} | Jain JMM 2019\textsuperscript{1615} | Nanno TID 2016\textsuperscript{1644} | Correa Martinez NMI 2017\textsuperscript{1680} | Heiblig Mycoses 2015\textsuperscript{1641} | Formont MedMycol 2002\textsuperscript{1666} | Chauhan LabMed 2019\textsuperscript{1615} |

<table>
<thead>
<tr>
<th>Tissue</th>
<th>To identify <em>Hormophiella spp.</em></th>
<th>D1/D2 sequencing</th>
<th>A</th>
<th>III</th>
<th>Nanno TID 2016\textsuperscript{1646}</th>
</tr>
</thead>
</table>

| Tissue | To identify *monoto/s/Phellinus spp.* | ITS, D1/D2 sequencing | B | III | De Ravin JCM 2014\textsuperscript{1679} | Haidar Mycoses 2017\textsuperscript{1635} | Shimamura Infection 2015\textsuperscript{1676} | Williamson JMM 2011\textsuperscript{1677} | Case reports, species identification difficult besides sequencing due to incomplete public database/small amount of reference strains |

**Tissue-based diagnosis**

| Tissue | To diagnose | Histopathology of biopsy tissue; PAS and GMS stainings | C | III | Bojj Mycoses 2013\textsuperscript{1627} | Jain JMM 2019\textsuperscript{1615} | Nanno TID 2016\textsuperscript{1644} | Verweij JCM 1997\textsuperscript{1672} | Correa Martinez NMI 2017\textsuperscript{1680} | Heiblig Mycoses 2015\textsuperscript{1641} | Formont MedMycol 2002\textsuperscript{1666} | *Hormophiella* spp.: microscopic examination often inconclusive, only suggestive, may confound with *Aspergillus* spp. |
Any
To diagnose
Microscopy of tissue biopsy
A
III
Chowdhary JCM 20131632
Observation of tissue invasion by fungi. No definite identification of species provided. Occasionally spicules on the hyphae may be seen in biopsy samples from lung and sinuses. Culture and identification are mandatory for species identification.

Hematological/allogeneic SCT patients with respiratory symptoms or persistent neutropenic fever
To diagnose
Lung biopsy with histopathology (bronchoscopic or transthoracic)
A
III
Nanno TID 20161646
Surmont MedMycol 20021666

Any with CGD
To diagnose
Biopsy of inflamed tissue with histopathology and stainings
C
III
Davis PIDJ 20071624
De Ravin JCM 20141673
Haidar Mycoses 20161675
Shigemura Infect 20151676

Imaging studies
Hematological/allogeneic SCT patients with respiratory symptoms or persistent neutropenic fever
To detect pulmonary infection and assess imaging characteristics of Hormographiella spp. infection
CT Sinuses
A
III
Suarez JCM 20111660
Bojic Mycoses 20131627
Lagrou JMM 20051644
Nanno TID 20161646
Godet Mycopathol 20171612
N=5

Hematological/allogeneic SCT patients
To detect sino-orbital-cerebral infection and assess imaging characteristics of sinusitis caused by Hormographiella spp.
MRIs
A
III
Heiblig Mycoses 20151641

Hematological patients with neurologic symptoms/seizures
To detect CNS involvement of Hormographiella spp. infection
MRI
A
III
Chauhan LabMed 20191616
Nanno TID 20161646
Heiblig Mycoses 20151641
Case reports

Any with CGD
To detect granulomatous inflammation and assess imaging characteristics
MRI
B
III
Davis PIDJ 20071624
De Ravin JCM 20141673
Ramesh JCI 20141682
Haidar Mycoses 20161675
Case reports: soft tissue / osteomyelitis due to Tropicoporus tropicalis

5-FC, 5-fluorocytosine; ABPM, allergic bronchopulmonary mycosis; AFST, antifungal susceptibility testing; AmB, amphotericin B; BDG, Beta-D-Glucan; CGD, chronic granulomatous disease; CLSI, Clinical and Laboratory Standards Institute; CT, computed tomography; ELISA, Enzyme-linked Immunosorbent Assay; FC, fluorocytosine; FCZ, fluconazole; GM, Galactomannan testing; GMS, Grocott-Gomori’s methenamine silver; HR, high-resolution; ICZ, itraconazole; ITS, internal transcribed spacer; ISA, isavuconazole; KCZ, ketoconazole; LSU, large subunit; MALDI-TOF MS, matrix assisted laser desorption ionization-time of flight mass spectrometry; MIC, minimal inhibitory concentration; MRI, magnetic resonance imaging; PAS, periodic acid-Schiff; pat., patient; PCR, polymerase chain reaction; PCZ, posaconazole; QoE, quality of evidence; SCT, stem cell transplant; SoR, strength of recommendation; TRB, terbinafine; VCZ, voriconazole.

**Recommendation** – The guideline group strongly recommends HR chest CT and CT of the sinuses and MRI of the brain to delineate the extent of involvement of the infection (Figure 24).
Figure 24. Optimal diagnostic pathway for infections caused by *Schizophyllum* spp. and other basidiomycetes, when all imaging and assay techniques are available

**Invasive infection due to *Schizophyllum* spp. and other Basidiomycetes**

- Any population
- Chronic granulomatous disease
- Hematological patients

**Imaging procedures** (CT scan, MRI, X-ray) on suspected sites of infection

**Direct microscopy**

**Culture from any site**
- multiple cultures might be necessary

**Antifungal susceptibility testing**
- to guide treatment

**Histology**

**For further species identification**
- ITS 1, ITS 2 and β-tubulin sequencing

**MALDI-TOF MS**

**Legend:**
- strongly recommended
- moderately recommended
- marginally recommended
- recommended against

CGD, chronic granulomatous disease; CT, computed tomography; ITS, internal transcribed spacer; MALDI-TOF MS, matrix-assisted laser desorption/ionization time-of-flight mass spectrometry; MRI, magnetic resonance imaging

**Treatment approaches to infections caused by *Schizophyllum* spp. and other basidiomycetes**

**Treatment in Adults**

**First line treatment for infections caused by *S. commune***

**Evidence** – For treatment of infections caused by *S. commune*, data are primarily obtained from case reports and small case series. Infections with systemic spread and proven or probable CNS involvement have primarily been treated with L-AmB, with step down therapy to oral azoles (*e.g.*, PCZ) after clinical
improvement and stabilization of the patient\textsuperscript{1609,1620,1652}. In patients with pulmonary infections including bronchopneumonia and pulmonary fungal balls VCZ, ICZ and FCZ have led to clinical improvement or cure\textsuperscript{1621,1670,1681} (Table 30).

### Table 30. First-line antifungal therapy for infections caused by *Schizephyllum* spp. and other basidiomycetes

<table>
<thead>
<tr>
<th>Population</th>
<th>Intention</th>
<th>Intervention</th>
<th>SoR</th>
<th>QoE</th>
<th>Reference</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any</td>
<td>To cure <em>S. commune</em> infection</td>
<td>L-AmB; optional: step down to PCZ</td>
<td>B</td>
<td>III+</td>
<td>Oliveira PLOS 2017\textsuperscript{1620}</td>
<td>N=1, success</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Hoenigl Mycoses 2013\textsuperscript{1622}</td>
<td>N=1, brain abscess, step down to PCZ solution, success</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Rihs JCM 1996\textsuperscript{1623}</td>
<td>N=1, brain abscess, success</td>
</tr>
<tr>
<td>Patients with pulmonary fungal ball</td>
<td>To cure</td>
<td>ICZ + tapering doses of systemic glucocorticoids</td>
<td>C</td>
<td>III</td>
<td>Chowdhary Mycoses 2013\textsuperscript{1624}</td>
<td>N=1, success</td>
</tr>
<tr>
<td>Any</td>
<td>To cure invasive pulmonary diseases/bronchopneumonia due to <em>S. commune</em></td>
<td>VCZ</td>
<td>C</td>
<td>III</td>
<td>Chowdhary AAC 2013\textsuperscript{1625}</td>
<td>N=2, success 2/2</td>
</tr>
<tr>
<td>Any</td>
<td>To cure invasive pulmonary diseases/bronchopneumonia due to <em>C. cinerea</em></td>
<td>Echinocandins</td>
<td>D</td>
<td>III</td>
<td>Lagrou JMM 2005\textsuperscript{1649}</td>
<td>N=4, progression while on CASPO/MICA</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Suarez JCM 2011\textsuperscript{1651}</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Chauhan LabMed 2019\textsuperscript{1652}</td>
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<td></td>
<td></td>
<td></td>
<td>Nanno TID 2016\textsuperscript{1653}</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Godet Mycopathol 2017\textsuperscript{1654}</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Ramesh JCI 2014\textsuperscript{1655}</td>
<td>Avoid echinocandins</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Conen CMI 2010\textsuperscript{1656}</td>
<td></td>
</tr>
<tr>
<td>Hematological malignancies patients</td>
<td>To cure <em>C. cinerea</em> infection</td>
<td>L-AmB iv +/- inhalative L-AmB OR VCZ 4 mg/kg bid after loading dose</td>
<td>B</td>
<td>III+</td>
<td>Godet Mycopathol 2017\textsuperscript{1657}</td>
<td>N=1, poor response to L-AmB but rapid improvement after addition of nebulized L-AmB</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Corzo-Leon Mycoses 2015\textsuperscript{1658}</td>
<td>N=1, bIFI under VCZ prophylaxis, treatment with L-AmB, died</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Heiblig Mycoses 2015\textsuperscript{1659}</td>
<td>N=1, stable disease</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Surmont MedMycol 2002\textsuperscript{1660}</td>
<td>N=1, improvement</td>
</tr>
<tr>
<td>Hematological malignancies patients</td>
<td>To cure pulmonary infection</td>
<td>D-AmB, ICZ</td>
<td>D</td>
<td>III</td>
<td>Verweij JCM 1997\textsuperscript{1661}</td>
<td>N=1, failure</td>
</tr>
<tr>
<td>Hematological malignancies patients</td>
<td>To cure disseminated infection</td>
<td>VCZ iv</td>
<td>C</td>
<td>III</td>
<td>Conen CMI 2010\textsuperscript{1662}</td>
<td>N=3, stable disease 1/3, success 2/3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Koncan JMBT 2016\textsuperscript{1663}</td>
<td>N=1, success</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Heiblig Mycoses 2015\textsuperscript{1664}</td>
<td>N=1, stable disease</td>
</tr>
<tr>
<td>Any</td>
<td>To cure respiratory diseases, ranging from saprobiic colonization to fungal pneumonia</td>
<td>ICZ</td>
<td>C</td>
<td>III</td>
<td>Chowdhary JCM 2013\textsuperscript{1665}</td>
<td>N=4, <em>Emmia lacera</em>, outcome unknown</td>
</tr>
<tr>
<td>Patients with CGD</td>
<td>To cure</td>
<td>VCZ</td>
<td>C</td>
<td>III</td>
<td>Ramesh JCI 2014\textsuperscript{1666}</td>
<td>N=1, <em>T. tropicalis</em>, success</td>
</tr>
<tr>
<td>Immunodeficiency patients</td>
<td>To cure disseminated infection</td>
<td>L-AmB, VCZ</td>
<td>D</td>
<td>III</td>
<td>Friman Scand JID 2006\textsuperscript{1667}</td>
<td>N=1, <em>Phlebia tremellosa</em>, failure</td>
</tr>
<tr>
<td>Patients with CGD</td>
<td>To cure</td>
<td>L-AmB 7.5 mg/kg qd, followed by L-AmB + ESA</td>
<td>C</td>
<td>III</td>
<td>Haidar Mycoses 2017\textsuperscript{1668}</td>
<td>N=1, <em>T. tropicalis</em>, success</td>
</tr>
</tbody>
</table>

**Standard dose unless stated otherwise:** bid, twice a day; bIFI, breakthrough invasive fungal infection; CASPO, caspofungin; CGD, chronic granulomatous disease; d, day(s); D-AmB, amphotericin B deoxycholate; ISA, isavuconazole; iv, intravenous; L-AmB, liposomal amphotericin B; MICA, micafungin; MIC, minimal inhibitory concentration; PCZ, posaconazole; po, orally; qd, once a day; QoE, quality of evidence; SoR, strength of recommendation; VCZ, voriconazole.
**Recommendations** – The guideline group moderately recommends first-line treatment with L-AmB (with the option to step down to PCZ later) based on descriptive case reports for infections with *S. commune*. Primary treatment with VCZ is marginally supported and may be used in patients intolerant to L-AmB.

**First line treatment for infections caused by C. cinerea**

**Evidence** - First line treatment for *infections caused by C. cinerea* is difficult to establish due to limited clinical data but *in vitro* data highlight that AmB and VCZ MICs are lower compared to those of CASPO and FCZ. Echinocandins should be avoided for the treatment of these infections due to higher MICs as well as reports of progression of disease in patients receiving echinocandins. L-AmB with dosages of 3 – 10 mg/kg has been used to treat *C. cinerea*-related infections and has led to cure in some patients. In cases of pulmonary infection caused by *C. cinerea* and nephrotoxicity associated with high-dose systemic L-AmB treatment, addition of inhaled L-AmB may allow dose reduction of systemic L-AmB and cure. VCZ may also be used as an alternative to L-AmB in cases where there are contraindications to L-AmB as well as for step down treatment after clinical improvement under L-AmB treatment.

**Recommendations** – Despite limited literature on the treatment of these infections, first-line treatment with systemic L-AmB +/- inhaled L-AmB or VCZ is moderately recommended for *C. cinerea*-related infections in patients with hematological malignancy. No data are available for other patient cohorts. Use of parenteral VCZ as first-line treatment is marginally recommended, whereas the guideline group recommends against the use of echinocandins.

**First line treatment for infections caused by other filamentous basidiomycetes**

**Evidence** - The relevance of *Emmia lacerata* (formerly *Ceriporia lacerate*) as a human pathogen remains unclear. In case series, *E. lacerata* was found to be a colonizer of the airways but also a cause for fungal
In vitro data showed the lowest MICs for PCZ and ISA compared to FCZ, 5-FC and echinocandins. Data on treatment is limited to three patients who received ICZ (n=2) or VCZ (n=1). Outcome is known for only one patient who received ICZ 200 mg tid and improved clinically.

Infections caused by Tropicoporus tropicalis (formerly Phellinus tropicalis) have been reported exclusively in patients with CGD causing pneumonia, abscesses, brain lesions or osteomyelitis. Reported MICs were low for AmB and all triazoles, whereas higher MICs were found for FCZ.

Several different antifungal strategies have been published. Most included L-AmB either in combination with VCZ or ISA. VCZ monotherapy was used in one patient successfully. Surgical treatment with resection of infected areas or drainage of abscess formations were performed in the majority of cases. Interestingly, the majority of T. tropicalis-related infections occurred while patients were on ICZ prophylaxis.

A single case of Phlebia tremellosa (formerly Merulius tremellosus) related infection in an immunocompromised host was published. Despite sequential therapy with L-AmB and VCZ the patient ultimately died.

Recommendations – Based on in vitro susceptibility data and a single case report, ICZ treatment is recommended marginally for the treatment of E. lacerata (formerly Ceriporia lacerata) infections. For patients with CGD and infection due to T. tropicalis the guideline group marginally recommends first line treatment with L-AmB +/- VCZ or ISA. VCZ monotherapy is an alternative option (marginally recommended).

Salvage treatment for basidiomycetes

Evidence – Few breakthrough infections with C. cinerea in patients with hematological malignancy have been reported. Different antifungal strategies including surgery have been used for management of these infections. However, the majority of patients had a fatal outcome despite salvage treatment because of progression of the infection or the underlying disease. Salvage treatment with L-AmB (5-10 mg/kg) alone
or in combination with VCZ and surgical debridement was associated with clinical and radiological improvement or cure in some of these patients. The addition of inhaled L-AmB (25 mg tiw) to systemic L-AmB led to cure and reduced nephrotoxicity in a patient (Table 31).

### Table 31. Antifungal salvage treatment for infections caused by Schizophyllum spp. and other basidiomycetes

<table>
<thead>
<tr>
<th>Population</th>
<th>Intention</th>
<th>Intervention</th>
<th>SoR</th>
<th>QoE</th>
<th>Reference</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematological malignancies patients</td>
<td>To cure pulmonary infection with C. cinerea</td>
<td>L-AmB 5-10 mg/kg + VCZ iv/PCZ +/- surgical debridement</td>
<td>B</td>
<td>III</td>
<td>Conen CMI 2010</td>
<td>N=2, success 1/2</td>
</tr>
<tr>
<td>Hematological malignancies patients</td>
<td>To cure C. cinerea infection</td>
<td>L-AmB 4 mg/kg iv bid after loading</td>
<td>B</td>
<td>III</td>
<td>Conen CMI 2010</td>
<td>N=2, stable 1/2, improved 1/2</td>
</tr>
<tr>
<td>Hematological malignancies patients</td>
<td>To cure C. cinerea infection</td>
<td>VCZ 4 mg/kg iv bid after loading</td>
<td>B</td>
<td>III</td>
<td>Conen CMI 2010</td>
<td>N=2, stable disease</td>
</tr>
<tr>
<td>Hematological patients/allo SCT patients</td>
<td>To cure pulmonary infection and reduce toxicity</td>
<td>Add nebulized AmB 25 mg tiw</td>
<td>C</td>
<td>III</td>
<td>Godet Mycopathol 2017</td>
<td>N=1, stable disease</td>
</tr>
<tr>
<td>Hematological patients/allo SCT patients</td>
<td>To cure C. cinerea infection</td>
<td>Echinocandin</td>
<td>D</td>
<td>III</td>
<td>Conen CMI 2010</td>
<td>N=1, failure</td>
</tr>
<tr>
<td>Patients with CGD</td>
<td>To cure</td>
<td>ISA + dose-reduced L-AmB</td>
<td>C</td>
<td>II</td>
<td>Haidar Mycoses 2017</td>
<td>N=1, response</td>
</tr>
</tbody>
</table>

**Standard dose unless stated otherwise:** bid, twice a day; CGD, chronic granulomatous disease; ISA, itraconazole; iv, intravenous; L-AmB, liposomal amphotericin B; PCZ, micafungin; QoE, quality of evidence; SCT, stem cell transplantation; SoR, strength of recommendation; tiw, three times a week; VCZ, voriconazole.

**Recommendations** – Use of L-AmB (5-10 mg/kg) or parenteral VCZ are moderately recommended for salvage treatment of C. cinerea-related infections in hematological patients. Combination of both +/- surgical debridement is marginally recommended as is the combination of ISA with a reduced dose of L-AmB.

The guideline group recommends against the use of echinocandins for basidiomycetes.

**Other treatment options for basidiomycetes**

**Evidence** – There is a single case report of a patient with biphenotypic acute leukemia developing C. cinerea-related infection during induction chemotherapy while on primary prophylaxis. In this patient L-AmB 5 mg/kg was successfully used as secondary prophylaxis during allogeneic HSCT for a total of 45 days. This patient did not suffer from relapsing disease and was considered cured from her IFI. In CGD patients with basidiomycetes infection, cultures from infected sites may be positive for years. However, they should not be classified as contaminants but should be considered as the causative agent in this setting. Secondary prophylaxis with VCZ or PCZ was used in two patients for several years without recurrence of infection.
For deep-seated basidiomycete infections surgical intervention may be of benefit for the patient. Case reports of successful treatment of such infections including surgery (debridement, excision of lung nodules, wedge resection, excision of infected tissue), plus antifungal treatment, highlight the potential benefits of surgery in this setting. However, surgery was not able to control fungal infection in a patient with post-surgical eye infection or in an allogeneic HSCT patient with pulmonary infection who showed progress of disease after resection of the lung nodules. Thus, surgery and antifungal treatment should always be combined if feasible.

Table 32. Other treatment options for infections caused by *Schizophyllum* spp. and other basidiomycetes

<table>
<thead>
<tr>
<th>Population</th>
<th>Intention</th>
<th>Intervention</th>
<th>SoR</th>
<th>QoE</th>
<th>Reference</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematological patients planned for allo-SCT</td>
<td>Secondary prophylaxis</td>
<td>L-AmB or inhaled AmB</td>
<td>C</td>
<td>III</td>
<td>Suarez JCM 2011</td>
<td>Case reports, CGD patients kept on VCZ for several months without recurrence or deterioration</td>
</tr>
<tr>
<td>Patients with CGD</td>
<td>Secondary prophylaxis</td>
<td>VCZ</td>
<td>C</td>
<td>III</td>
<td>Ramesh JCI 2014, Nguyen JACI 2009, Shigemura Infection 2015</td>
<td>Literature review, fungus was misinterpreted as contaminant, but should be considered as causative in this specific setting</td>
</tr>
<tr>
<td>Patients with CGD</td>
<td>To cure <em>Inonotus/Phellinus</em> spp. infection</td>
<td>Do not consider as contamination</td>
<td>C</td>
<td>III</td>
<td>Haidar Mycoses 2017</td>
<td></td>
</tr>
<tr>
<td>Post-surgical eye infection</td>
<td>To cure</td>
<td>Surgery/ vitrectomy</td>
<td>C</td>
<td>III</td>
<td>Jain JMM 2019</td>
<td>N=1, TPX + vitrectomy + systemic and topical antifungals</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>To cure</td>
<td>Surgical debridement</td>
<td>B</td>
<td>III</td>
<td>Heiblig Mycoses 2015</td>
<td>N=1, improved</td>
</tr>
<tr>
<td>Pulmonary infection</td>
<td>To cure</td>
<td>Surgical excision of lung nodules/wedge resection</td>
<td>B</td>
<td>III</td>
<td>Godet Mycospathol 2017</td>
<td>N=1, Progress of infection after surgery</td>
</tr>
<tr>
<td>Skin/subcutaneous infection</td>
<td>To cure</td>
<td>Surgical excision of infected tissue</td>
<td>B</td>
<td>III</td>
<td>Shigemura Infection 2015</td>
<td>N=2, success 1/2, stable disease 1/2</td>
</tr>
</tbody>
</table>

AmB, amphotericin B; CGD, chronic granulomatous disease; L-AmB, liposomal amphotericin B; QoE, quality of evidence; SCT, stem cell transplantation; SoR, strength of recommendation; TPK, total penetrating keratoplasty; VCZ, voriconazole.

**Recommendations** — Secondary prophylaxis for hematological patients during allogeneic HSCT with L-AmB is marginally recommended. In CGD patients with basidiomycete infections secondary prophylaxis with VCZ or PCZ is marginally recommended. Surgical resection of infected tissue and debridement are moderately recommended whenever feasible.
Treatment duration

Evidence - Treatment duration has been determined on a case-by-case basis and depends on the extent of surgery, the organs involved, the pathogen involved, status of underlying disease and ongoing immunosuppression. For CNS infections a treatment duration of 6 weeks or more has been reported\textsuperscript{1609,1652}, while for fungal rhinosinusitis with mucosal and/or bone invasion a treatment duration of >2 months has been reported\textsuperscript{1606}. For bone infections a treatment duration of up to several years has been published\textsuperscript{1692}.

(Table 33).

Table 33. Treatment duration for infections caused by \textit{Schizophyllum} spp. and other basidiomycetes

<table>
<thead>
<tr>
<th>Population</th>
<th>Intention</th>
<th>Intervention</th>
<th>SoR</th>
<th>QoE</th>
<th>Reference</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any with CNS involvement</td>
<td>To cure</td>
<td>6 wk or more of therapy</td>
<td>B</td>
<td>III</td>
<td>Hoenigl Mycoses 2013\textsuperscript{1609}</td>
<td>N=2, duration determined case-by-case</td>
</tr>
<tr>
<td>Fungal rhinosinusitis with mucosal and/or bone invasion</td>
<td>To cure</td>
<td>2 mo or more</td>
<td>C</td>
<td>III</td>
<td>Michel MedMycol 2016\textsuperscript{1606}</td>
<td>Treatment duration determined case-by-case</td>
</tr>
</tbody>
</table>

CNS, central nervous system; mo, month(s); QoE, quality of evidence; SoR, strength of recommendation; wk, week(s)

Recommendation – Treatment duration should be determined on a case by case basis. For all types of CNS infections a treatment duration of 6 weeks or more is moderately recommended\textsuperscript{1609,1652}. For fungal rhinosinusitis with mucosal and/or bone invasion a treatment duration of 2 months or more is marginally recommended\textsuperscript{1606} (Figure 25).
Figure 25. Optimal treatment pathway for infections caused by *Schizophyllum* spp. and other basidiomycetes in adults when all treatment modalities and antifungal drugs are available

Suspected and confirmed invasive infections due to *Schizophyllum* spp. and other basidiomycetes are emergencies and require rapid action

Immediate treatment initiation

Surgery

Schizophyllum commune

Coprinopsis cinerea/Hormographiella aspergilata

Hematological malignancy

Response assessment (e.g. weekly imaging)

Progressive disease

Legend:
- strongly recommended
- moderately recommended
- marginally recommended
- recommended against

TDM, therapeutic drug monitoring

* Choice of salvage treatment always depends by the treatment that the patient failed to respond to

**Legend:**
- strongly recommended
- moderately recommended
- marginally recommended
- recommended against

TDM, therapeutic drug monitoring

* Choice of salvage treatment always depends by the treatment that the patient failed to respond to
Specific considerations on treatment of infections caused by Schizophyllum spp. and other basidiomycetes in children

Evidence – Pediatric data is limited only to case reports (Table 34).

Table 34. Therapy in children for Schizophyllum spp. and other basidiomycetes infections

<table>
<thead>
<tr>
<th>Population</th>
<th>Intention</th>
<th>Intervention</th>
<th>SoR</th>
<th>QoE</th>
<th>Reference</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>First-line antifungal therapy</td>
<td>To cure</td>
<td>VCZ iv</td>
<td>B</td>
<td>III</td>
<td>Lim AJD 2017[1865]</td>
<td>N=1, 22 mo, Earieilla scabrosa, failure</td>
</tr>
<tr>
<td>Any</td>
<td>To cure</td>
<td>L-AmB 7.5-10 mg/kg qd, VCZ iv, surgical debridement</td>
<td>B</td>
<td>III</td>
<td>Heiblig Mycoses 2015[1941]</td>
<td>N=1, 19 yrs, stable disease</td>
</tr>
<tr>
<td>AML</td>
<td>To cure</td>
<td>No treatment</td>
<td>D</td>
<td>III</td>
<td>Kbuaji JCM 2009[1621]</td>
<td>N=1, 14 yrs, fatal outcome</td>
</tr>
<tr>
<td>Antifungal salvage treatment</td>
<td>To cure</td>
<td>VCZ 200 mg po bid +/- other antifungals</td>
<td>B</td>
<td>III</td>
<td>Ramesh JCI 2014[1682]</td>
<td>N=1, 24 yrs, T. tropicalis retropharyngeal abscess, survived</td>
</tr>
<tr>
<td></td>
<td>To cure</td>
<td>L-AmB 7.5-10 mg/kg qd, VCZ iv, surgical debridement</td>
<td>B</td>
<td>III</td>
<td>Sigemura Infection 2015[1695]</td>
<td>N=1, 23 yrs, Phellinus mori, VCZ + MICA, survived</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Davis PIDJ 2007[1814] (molecular work presented by Sutton JCM 2005[1861])</td>
<td>N=1, 21 yrs, paraspinal abscess and sacral osteomyelitis, T. tropicalis, survived</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>De Ravin JCM 2014[1679]</td>
<td>N=1, 10 yrs, Phellinus spp., paravertebral abscess, + surgery, survived</td>
</tr>
<tr>
<td>Children with soft tissue infection</td>
<td>To cure</td>
<td>PCZ 100 mg qd + alternate regimen of PCZ 100 mg/200 mg for consolidation 2 wk after clinical improvement</td>
<td>C</td>
<td>III</td>
<td>Correa Martinez NMI 2017[1690]</td>
<td>N=1, C. cinerea</td>
</tr>
</tbody>
</table>

Recommendations - According to data in adults, the recommendation for therapy includes VCZ alone or in combination with L-AmB (moderate recommendation).

7. Scopulariopsis

Epidemiology of infections caused by Scopulariopsis spp.

Scopulariopsis is found in soil and plant material with a worldwide distribution[1693]. Some species have teleomorphs, which are classified in the genus Microascus[1694]. Scopulariopsis brevicaulis is the most relevant species in humans[1695]. Single cases of infections caused by Scopulariopsis acremonium, Scopulariopsis brumptii and Scopulariopsis candida have been reported, mostly from Western Europe and North-
America. *Scopulariopsis* is typically associated with onychomycosis or other superficial infections. Severe *Scopulariopsis*-related systemic infections have been reported, mainly in immunosuppressed patients with underlying malignancy, HSCT and SOT recipients, affecting lungs, paranasal-sinuses and soft tissues. Infections have rarely occurred in immunocompetent patients following traumatic injuries or surgery affecting the eye or deep soft tissue. Dissemination to the CNS or other organs and fungemia have been noted in severely ill patients. Heart infections due to *Scopulariopsis* have been described mainly in patients who underwent prosthetic valve implantation. In a retrospective study in a US Cancer Center, ~2% of fungal infections of the brain in bone marrow transplant patients were caused by *Scopulariopsis*. The National Institutes of Health reported that in patients with positive bronchoalveolar lavage BDG tests ~3% of confirmed fungal infections were due to *Scopulariopsis*. In patients post-lung transplantation an incidence of 0.2% was reported in a center in Spain. (Figure 26).

**Figure 26.** Worldwide distribution of infections caused by *Scopulariopsis* spp. (reported cases between 1936 and 2019 per million population)
Cases of Scopulariopsis-related infections reported in the medical literature were identified in a PubMed search on October 30, 2019 using the search string “Scopulariopsis OR Microascus” that yielded 554 publications. In total, 86 cases were identified from 24 countries, 61 since the year 2000. Most cases were reported from the United States (n=41), France (n=10) and Spain (n=5). The number of cases reported between 1936 and 2019 is presented as cases per million population per country. The resident population per country was obtained from www.worldometers.info. *One case was reported from Brunei Darussalam (2.3 cases per million population between 1936 and 2019).

**Diagnosis of Scopulariopsis**

**Diagnosis – Microbiology – Conventional Methods**

Evidence – The definitive diagnosis of Scopulariopsis-related infections has traditionally relied on the isolation of Scopulariopsis spp. from infected tissue or body fluids, with histological findings showing dichotomously branched septate hyphae, and culture confirmation of Scopulariopsis spp. See also Figure 27 with microscopic morphology from the Atlas of Clinical Fungi project.
Figure 27. Microscopic morphology of *Scopulariopsis* spp. 19

Culture is essential, and histological findings alone are insufficient for the diagnosis of these infections as Scopulariopsis spp. can be difficult to distinguish from Aspergillus spp., Fusarium spp., and Scedosporium spp. by histology and morphological appearance alone\(^{1746}\) (Table 35).

**Recommendations** – The guideline group strongly recommends that infected tissue or body fluids be obtained for culture and also microscopic/histological evaluation, when possible.

**Diagnosis – Microbiology – Serology**

**Evidence** – In multiple case reports, Aspergillus GM and BDG have been negative\(^{1711,1732,1766}\) (Table 35).

**Recommendations** – Aspergillus GM and BDG are not recommended as part of the diagnostic evaluation for Scopulariopsis-related infections.

**Diagnosis – Microbiology – Molecular-based**

**Evidence** – PCR assays have been developed that can identify Scopulariopsis isolates to the genus level\(^{1767}\) and species level\(^{1706,1726,1732,1764,1766}\), in two reports PCR has been performed directly on sputum samples\(^{1706,1768}\) (Table 35).

**Recommendations** – The guideline group marginally supports the use of molecular-based diagnostic tests to diagnose Scopulariopsis-related infections, if available.

**Diagnosis – Microbiology – Species identification**

**Evidence** – Using PCR assays\(^{1769-1771}\) and phylogenetic analysis using multi-gene sequences\(^{1772}\), identification to the species level has been reported in some studies, although the specificity of PCR varies from study to study and has been as low as 70% in some studies\(^{561,1768}\). MALDI-TOF MS has been used to identify Scopulariopsis isolates in one case report\(^{1773}\) and the combination of PCR and MALDI-TOF MS in another case report\(^{1701}\) (Table 35).
Recommendations – The guideline group strongly recommends species identification using ITS2 or D1/D2 or 18S PCR or phylogenetic analysis for species identification from isolates and marginally the use of MALDI-TOF MS for the same purpose.

Microbiology – Susceptibility testing

Evidence – Scopulariopsis species typically demonstrate high MICs to many antifungal agents including FCZ, ICZ, S-FC, and AmB. Antifungal susceptibility testing using CLSI and EUCAST testing can determine MICs, while having been shown to poorly correlate with E-test. However, there are not enough data documenting a correlation between MICs and clinical outcome nor has a clinically meaningful cutoff value been established (Table 35).

Recommendations – Given that Scopulariopsis spp. typically demonstrate high MICs to many antifungal agents, CLSI or EUCAST testing is strongly recommended to determine antifungal susceptibility, and moderately for guiding antifungal treatment.

Diagnosis - Pathology

Evidence – Histological findings showing dichotomously branched septate hyphae have been reported in multiple studies to be suggestive of Scopulariopsis infection, including in those with underlying hematological malignancies, solid organ transplant patients, and a patient with endocarditis. Scopulariopsis spp. can be difficult to distinguish from Aspergillus spp., Fusarium spp., and Scesosporium spp. by morphology alone (Table 35).

Recommendations – The guideline group strongly recommends histopathological examination of biopsy tissue in cases of suspected Scopulariopsis infection.

Diagnosis – Imaging

Evidence – Scopulariopsis spp. rarely cause invasive infections in humans and the diagnosis is typically made in immunocompromised individuals. As with other invasive fungal infections, imaging studies have
played a crucial role in determining the likely site of Scopulariopsis infection and assisting in the procurement of infected tissue or body fluids (Table 35).

### Table 35. Microbiological, histopathological and imaging diagnostics of Scopulariopsis infections

<table>
<thead>
<tr>
<th>Population</th>
<th>Intention</th>
<th>Intervention</th>
<th>SoR</th>
<th>QoE</th>
<th>Reference</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any</td>
<td>To diagnose</td>
<td>Culture and microscopy</td>
<td>A</td>
<td>II</td>
<td>Arroyo JCM 2017</td>
<td>H&amp;E, GMS, and PAS stainings revealed numerous septate hyphae with dichotomous branching. Cultures confirmed Scopulariopsis spp.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Sattler MMCR 2014</td>
<td>Allergic sinusitis; Hyaline septate hyphae and globose to pyriform truncate spores at direct examination. Cultures confirmed Scopulariopsis spp.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Salmon CMI 2010</td>
<td>Biopsy showed numerous septate hyphae by direct observation after Chlorazol-Black staining. Microscopic examination of histological sections stained with lactophenol blue, PAS, H&amp;E and GMS stainings revealed branched septate hyphae and many vesicular swellings of different sizes. Cultures confirmed Scopulariopsis spp.</td>
</tr>
<tr>
<td>Any</td>
<td>To determine antifungal susceptibility</td>
<td>EUCAST method</td>
<td>A</td>
<td>III</td>
<td>Alastruey-Izquierdo AAC 2018</td>
<td>S. brevicaulis had high MICs for all antifungals</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Sandoval-Denis JCM 2013</td>
<td>N=97, Echinocandins had better in vitro activities than azoles</td>
</tr>
<tr>
<td>Any</td>
<td>To guide antifungal treatment</td>
<td>CLSI MIC testing</td>
<td>A</td>
<td>IIu</td>
<td>Cawcutt CRM 2015</td>
<td>N=1, Endocarditis; susceptible to CASPO, MICA and TRB, treatment with CASPO + VCZ, success</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Savill Infection 2016</td>
<td>N=1, Cutaneous infection; susceptible to MICA, but no correlation between MIC and clinical outcome</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Shaver AJT 2014</td>
<td>N=1, Lung transplant patient; susceptible to echinocandins, failure</td>
</tr>
</tbody>
</table>

#### Serology assays

| Any        | To diagnose | Aspergillus GM EIA | D   | III | Salmon CMI 2010 | N=1, disseminated S. brevicaulis. Serum Aspergillus GM +, thought to be false + due to cross-reactivity with S. brevicaulis cell wall components |
|            |            |                |     |     | Miossec JCM 2011 | N=1, Scopulariopsis fungemia. Aspergillus GM assays ×5 were negative, starting 11 d after transplant |
|            |            |                |     |     | Iwen MedMycol 2012 | N=1, Invasive Scopulariopsis infection. Aspergillus GM negative |

#### Aplastic anemia

| Any        | To diagnose | Aspergillus GM from serum and BAL, BDG from serum and BAL | D   | III | Rose Infect 2014 | N=1. Invasive Scopulariopsis infection. BDG and GM (both serum and BAL) negative |

#### Nucleic-acid based assays/MALDI-TOF MS

<p>| Any        | To diagnose | PCR directly from sputum/tissue | C   | II  | Salmon CMI 2010 | N=1, Disseminated S. brevicaulis detected by PCR from sputum and tissue and culture |
|            |            | Universal 28S PCR + RFLP directly from sputum | C   | II  | Bontems BJD 2009 | N=17, S brevicaulis isolated in culture from infected nails, 12/17 were correctly identified by PCR-RFLP (spec. 71%) |</p>
<table>
<thead>
<tr>
<th>Module</th>
<th>Procedure</th>
<th>Case Series</th>
<th>Study References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any with non-dermatophyte onychomycosis</td>
<td>To detect</td>
<td>Development of PCR for detection in nail (keratin)</td>
<td>C III</td>
</tr>
<tr>
<td>Any</td>
<td>To identify species</td>
<td>PCR-RFLP</td>
<td>A IIu</td>
</tr>
<tr>
<td>Any</td>
<td>To identify species</td>
<td>ITS 1/2 and intervening 5.8S rDNA, tub2 and tef2 gene regions</td>
<td>A IIlu</td>
</tr>
<tr>
<td>Onychomycosis</td>
<td>To identify Scopulariopsis</td>
<td>PCR to 28S rDNA</td>
<td>B II</td>
</tr>
<tr>
<td>Onychomycosis</td>
<td>To identify Scopulariopsis</td>
<td>PCR to 28S rDNA</td>
<td>B II</td>
</tr>
<tr>
<td>Any</td>
<td>To identify isolates</td>
<td>ITS2 or D1/D2 or 18S PCR sequencing from isolates</td>
<td>A III</td>
</tr>
<tr>
<td>AML</td>
<td>To identify Scopulariopsis</td>
<td>MALDI-TOF MS and PCR</td>
<td>C III</td>
</tr>
<tr>
<td>Any</td>
<td>To identify Scopulariopsis</td>
<td>MALDI-TOF MS</td>
<td>C III</td>
</tr>
<tr>
<td>Any</td>
<td>To diagnose</td>
<td>Histopathological examination of biopsy tissue</td>
<td>A II</td>
</tr>
<tr>
<td>Any</td>
<td>To diagnose</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any</td>
<td>To diagnose</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
**Imaging studies**

<table>
<thead>
<tr>
<th></th>
<th>To assess the cause of pulmonary symptoms</th>
<th>Chest radiograph and CT</th>
<th>B</th>
<th>II</th>
<th>Pat TID 2016</th>
<th>N=1, pneumonia, S. brumptii</th>
</tr>
</thead>
<tbody>
<tr>
<td>SOT patients</td>
<td></td>
<td>Chest CT</td>
<td>A</td>
<td>II</td>
<td>Shaver AJT 2014</td>
<td>N=1, pneumonia, pleural effusion, S. brumptii</td>
</tr>
</tbody>
</table>

|                         | To assess the clinical manifestations and imaging characteristics of sinusitis caused by *Scopulariopsis* | CT scan of the sinuses | A | II | Gluck IJPO 2011 | Sinus opacification in pediatric patients presenting with sinusitis that was later proven to be caused by *Scopulariopsis* |
| Sinusitis               |                                                          |                         |   |    | Sattler MMCR 2014 | N=1, Mucosal thickening at the floor of the left maxillary sinus that penetrated into the premolar dentition in an apparently immunocompetent patient |
|                         |                                                          |                         |   |    | Kammoun JMM 2018 | N=1, Orbital cellulitis resulted from erosion and calcification of the frontal sinus by *Scopulariopsis* spp. |

**Recommendations** – As with other invasive fungal infections, imaging studies such as chest CT for pulmonary symptoms or CT of the sinuses for sinusitis are strongly recommended to assist in diagnosis, when applicable (Figure 28).
Figure 28. Optimal diagnostic pathway for *Scopulariopsis* infections when all imaging and assay techniques are available

**Legend:**
- strongly recommended
- moderately recommended
- marginally recommended
- recommended against

CT, computed tomography; ITS, internal transcribed spacer; MALDI-TOF MS, matrix-assisted laser desorption/ionization time-of-flight mass spectrometry; PCR, polymerase chain reaction; RFLP, restriction fragment length polymorphism; β, translational elongation factor 1α

### Treatment approaches to *Scopulariopsis* infections

#### Treatment in adults

**Evidence** - *Scopulariopsis* spp. usually exhibit high MICs to all currently available antifungal agents. ICZ, FCZ and 5-FC have almost no activity against *Scopulariopsis* spp.
Therefore, drugs that should be considered for the treatment of invasive disease include AmB, VCZ, PCZ, echinocandins, and TRB. Some reports also suggest a high percentage of *in vitro* synergism with antifungal combinations of AmB and ANID (>80%) or PCZ, CASPO and TRB (~100%). However, the relevance of these *in vitro* data is not clear, because there are not enough data documenting a correlation between MICs and the clinical outcome.

Adequate debridement or excision of necrotic tissue and the early start of systemic antifungal treatment appear to be the major means of halting progression of the disease. In patients with invasive *Scopulariopsis* infection, various combinations of D-AmB, lipid-based AmB formulations, azoles and echinocandins have been reported (Table 36).

### Table 36. Therapy for *Scopulariopsis* infections

<table>
<thead>
<tr>
<th>Population</th>
<th>Intention</th>
<th>Intervention</th>
<th>SoR</th>
<th>QoE</th>
<th>Reference</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any</td>
<td>To cure</td>
<td>L-AmB 3-10 mg/kg qd + VCZ</td>
<td>B</td>
<td>III</td>
<td>Kurata IJH 2018</td>
<td>N=1, failure</td>
</tr>
<tr>
<td>Any</td>
<td>To cure</td>
<td>VCZ iv, step down to therapy po later</td>
<td>B</td>
<td>III</td>
<td>Kammoun JMM 2018</td>
<td>N=1, success</td>
</tr>
<tr>
<td>Any</td>
<td>To cure</td>
<td>VCZ + Echinocandin + TRB 250 mg qd</td>
<td>C</td>
<td>III</td>
<td>Taton TID 2017</td>
<td>N=1, success</td>
</tr>
<tr>
<td>AML with skin infection</td>
<td>To cure</td>
<td>Echinocandin</td>
<td>D</td>
<td>III</td>
<td>SavrI Infection 2016</td>
<td>N=1, failure</td>
</tr>
<tr>
<td>Any</td>
<td>To cure</td>
<td>AmB lipid formulations +/- other antifungals</td>
<td>B</td>
<td>III</td>
<td>Sabtavani SMI 2010</td>
<td>N=1, success</td>
</tr>
<tr>
<td>Any</td>
<td>To cure</td>
<td>L-AmB + echinocandin</td>
<td>C</td>
<td>III</td>
<td>salmon CMI 2010</td>
<td>N=1, failure</td>
</tr>
<tr>
<td>Any</td>
<td>Cure</td>
<td>ISA</td>
<td>B</td>
<td>III</td>
<td>Cornely Mycoses 2018</td>
<td>N=2, success</td>
</tr>
</tbody>
</table>

### Antifungal salvage treatment

| Any        | To cure | PCZ | B   | III | Cawcutt CMR 2015 | N=1, PCZ salvage after CASPO and VCZ, stable disease |
| Any        | To cure | PCZ + TRB salvage after AmB and MICA, success | N=1, success |
| Rakita AJT 2015 | N=1, PCZ + TRB salvage after VCZ, success |
| Arroyo JCM 2017 | N=1, PCZ + MICA salvage, followed by PCZ mono after AmB and VCZ; success |

| AML        | To cure bronchial infection | VCZ iv + CASPO | D   | III | Yang DMDI 2012 | N=1, S. brevicaulis, salvage after L-AmB and VCZ |
**Recommendation** - According to available data and drug safety profiles\(^{1790}\), the group moderately recommends L-AmB (monotherapy or combination therapy with VCZ or another antifungal), VCZ monotherapy, or ISA monotherapy as the preferred treatment regimens. Other combination therapy regimens should be considered according to results of \textit{in vitro} studies\(^{1779,1782}\). Antifungal regimens that include PCZ delayed release tablet alone or in combination with TRB or MICA are moderately recommended for salvage therapy\(^{1758,1760,1776,1785}\).

The duration of therapy should be individualized, and based on the site and extent of infection, and on the immune status of the patient (Figure 29).
Figure 29. Optimal treatment pathway for *Scopulariopsis* infections in adults when all treatment modalities and antifungal drugs are available

**Suspected and confirmed invasive infections due to *Scopulariopsis* spp. are emergencies and require rapid action**

**Immediate treatment initiation**

- **Isavuconazole**
  - 3 x 200 mg/d d1-2;
  - 1 x 200 mg/d from d3

- **Amphotericin B lipid complex**
  - 1 x 2-10 mg/kg/d or
  - **Liposomal Amphotericin B**
    - 1 x 3-10 mg/kg/d
    ±
    - **Voriconazole iv**
      - 2 x 6 mg/kg/d d1;
      - 2 x 4 mg/kg/d from d2;
      - use TDM
      or
      - **Other antifungals**

- **Voriconazole iv**
  - 2 x 6 mg/kg/d d1;
  - 2 x 4 mg/kg/d from d2;
  - use TDM

**Response assessment**

(e.g., weekly imaging)

- **Progressive disease**

- **Posaconazole iv/tab**
  - 2 x 300 mg/d d1;
  - 2 x 300 mg/d from d2
  ±
  - **Micafungin**
    - 1 x 100 mg/d
  ±
  - **Terbinafine**
    - 500-1000 mg/d

**Legend:**
- strongly recommended
- moderately recommended
- marginally recommended
- recommended against

TDM, therapeutic drug monitoring

* Choice of salvage treatment always depends by the treatment that the patient failed to respond to
Specific considerations on treatment of Scopulariopsis infection in children

Evidence – Only scarce data exist on invasive infections by Scopulariopsis spp. in children. In these studies, all children had an underlying Hematological malignancy and/or received a HSCT (Table 37).

Table 37. First-line antifungal therapy in children for Scopulariopsis infections

<table>
<thead>
<tr>
<th>Population</th>
<th>Intention</th>
<th>Intervention</th>
<th>SoR</th>
<th>QoE</th>
<th>Reference</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any</td>
<td>To cure</td>
<td>D-AmB iv</td>
<td>D</td>
<td>III</td>
<td>Krischer JCM 1995</td>
<td>N=1, 12 yrs, cutaneous infection + lung involvement, Microspus; D-AmB, followed by ABCD, failure Review of N=5, 17-40 yrs, AmB +/- ICZ or miconazole; failure 5/5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Neglia AJM 1987</td>
<td>N=1, 17 yrs, lung infection, AmB, + surgery, died</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Krisel CID 1994</td>
<td>N=1, 12 yrs, sino-nasal infection, cAmB + G-CSF + ICZ for 6 mo, surgery, survived</td>
</tr>
<tr>
<td>AML + BMT</td>
<td>To cure</td>
<td>VCZ + CASPO</td>
<td>C</td>
<td>III</td>
<td>Steinbach J Infect 2004</td>
<td>N=1, 10 yrs, skin and blood infection, survived</td>
</tr>
<tr>
<td>AML</td>
<td>To cure</td>
<td>c-AmB iv for 7 d, then switched to CASPO 7 mg/kg qd iv + VCZ 7 mg/kg qd iv for 3 mo; then VCZ 150 mg po bid + CASPO 1.5 mg/kg iv tiw for 3 mo; followed by 6 mo VCZ 150 mg bid</td>
<td>B</td>
<td>III</td>
<td>Petit TLID 2011</td>
<td>N=1, 11 mo, lung infection, survived</td>
</tr>
<tr>
<td>AML</td>
<td>To cure</td>
<td>VCZ 150 mg iv bid initially, after positive culture and susceptibility testing followed by L-AmB, surgery</td>
<td>B</td>
<td>III</td>
<td>Gluck I JP 2011</td>
<td>N=1, 17 yrs, sino-nasal infection, survived</td>
</tr>
</tbody>
</table>

Standard pediatric dose unless stated otherwise; ABCD, amphotericin B colloidal dispersion; AmB, amphotericin B; AML, acute myeloid leukemia; bid, twice a day; BMT, bone marrow transplant; CASPO, caspofungin; cAmB, oral encochleated amphotericin B; D-AmB, amphotericin B deoxycholate; G-CSF, granulocyte colony stimulating factor; ICZ, itraconazole; iv, intravenous; L-AmB, liposomal amphotericin B; mo, month(s); po, orally; qd, once a day; QoE, quality of evidence; SoR, strength of recommendation; tiw, three times a week; VCZ, voriconazole; wk, week(s); yrs, years.

Recommendations – Treatment recommendations are extrapolated from those for adult patients, and L-AmB or VCZ or both in combination are moderately recommended.

8. Penicillium

Epidemiology of infections caused by Penicillium spp.

Several Penicillium spp. have been redefined as Talaromyces; for example, P. marneffei and P. purpurogenum are now named Talaromyces marneffei and Talaromyces purpurogenus, respectively, and are therefore not included in this section. Penicillium spp. are ubiquitous in nature and are used in drug
and food production industries; e.g., *P. chrysogenum* (formerly *P. notatum*) is used to produce the antibioti-
cotic penicillin and *P. camemberti* and *P. roqueforti* are used in cheese making. Penicillium spp. have
been recognized as environmental allergens, which are frequently associated with hypersensitivity pneu-
monitis in exposed workers, with unknown clinical significance. Penicillium spp. are rarely patho-
genic in humans and are usually considered as laboratory contaminants or non-pathogenic colonizers in
clinical material. However it is important to recognize that pathogenic species such as *P. chryso-
genum*, *Penicillium citrinum*, *P. decumbens*, *P. commune*, *P. oxalicum* and *P. purpurogenum* (*T. purpurogenus*) grow well at 37°C, whereas the majority of common laboratory
contaminants do not grow at body temperature. Penicillium spp. have been reported as a cause of oppor-
tunistic infections leading to mycotic keratitis, endophthalmitis and lung infection. Dissemi-
nated infections such as endocarditis (following valve prosthesis insertion), CNS infection and fungemia
also have been reported less frequently. In addition to immunocompromised humans, fatal
*Penicillium* infections in dogs have been described (Figure 30).

**Figure 30.** Worldwide distribution of infections caused by *Penicillium* spp. (reported cases between
1963 and 2018 per million population). The red cloud marks regions where penicilliosis (caused by vari-
ous *Penicillium* spp.) is endemic.
Cases of severe *Penicillium*-related infections reported in the medical literature were identified in a PubMed search on September 12, 2019. The search string included all *Penicillium* spp. listed in the Index Fungorum database (accessed September 12, 2019) and “(infection OR invasive OR disseminated OR patient [Title/Abstract] OR case [Title/Abstract] OR cases [Title/Abstract] OR report [Title/Abstract] OR isolate [Title/Abstract]) NOT marneffei [Title]” that yielded 834 publications. In total, 75 cases from 13 countries were identified, 34 since the year 2000. Most cases were reported from the United States (n=40), Nigeria (n=8), Spain (n=6), and United Kingdom (n=5). Few cases of invasive *Penicillium*-related infections were reported from endemic countries. The number of cases reported between 1963 and 2018 is presented as cases per million population per country. The resident population per country was obtained from www.worldometers.info. The grey cloud marks regions where penicilliosis is endemic and from where travel-related cases are possible (South East Asia, North India, Bhutan and Nepal, North Korea, Papua-New Guinea, and North Australia).

**Diagnosis of Penicillium infections**

**Evidence** - Conventional diagnosis using microscopy and culture is essential for identification of *Penicillium* spp. A positive culture from deep sterile tissues confirms the diagnosis. Definitive diagnosis of *Penicillium*-related infections needs to recognize invasive fungal elements by histological examination of tissue sections. Infections caused by *Penicillium* spp. may be overlooked or misdiagnosed as aspergillosis due to nonspecific clinical and radiological findings. In addition, direct microscopic examination of both genera shows similar hyaline septate hyphae (hyalohyphomycosis) (Figure 31).
Figure 31. Microscopic morphology of *Penicillium* spp.¹⁹


conidiophores arising from submerged hyphae, relatively wide, with tuberculate walls, stage-branched
penicillin; **Panel I, P. spinulosum**, conidiophores, smooth- to rough-walled; penicilli monoverticillate, flask-shaped phialides. Scale bars = 10 µm.

In routine laboratory evaluation, identification does not usually go beyond the genus level due to a huge number of species and the lack of expertise in identification at species level. Morphological identification to the species level is very difficult therefore molecular identification using ITS and β-tubulin sequencing is the gold standard, with MALDI-TOF MS being an alternative. Serological cross-reaction in the GM assay or *Aspergillus*-specific lateral flow device test has been observed. Clinical diagnosis using imaging techniques or non-culture-based tests such as BDG have been used to diagnose *Penicillium* infections. Antifungal susceptibility testing results are variable and species-specific. Terbinafine and echinocandins showed the best *in vitro* activity against *Penicillium* spp., AmB showed intermediate antifungal activity, while the azole MICs differed between isolates, especially in *P. citrinum, P. oxalicum* and *Penicillium rubens* (Table 38).

### Table 38. Microbiological, histopathological and imaging diagnostics of *Penicillium* infections

<table>
<thead>
<tr>
<th>Population</th>
<th>Intention</th>
<th>Intervention</th>
<th>SoR</th>
<th>QoE</th>
<th>Reference</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any</td>
<td>To diagnose</td>
<td>Tissue biopsy</td>
<td>A</td>
<td>III</td>
<td>Mok JCM 1997</td>
<td>Lyzatopoulous J Infect 2002; Hesse MMCR 2017; Chowdhary OFID 2014</td>
</tr>
<tr>
<td>Any</td>
<td>To diagnose</td>
<td>Microscopy</td>
<td>A</td>
<td>III</td>
<td>Geltner Transpl 2013; Chowdhary OFID 2014</td>
<td></td>
</tr>
<tr>
<td>Any</td>
<td>To identify species</td>
<td>Microscopy</td>
<td>B</td>
<td>IIr</td>
<td>Visagie StudMycol 2014</td>
<td></td>
</tr>
<tr>
<td>Any</td>
<td>To guide treatment and correlate MIC with outcome</td>
<td>Antifungal susceptibility testing, EUCAST method</td>
<td>B</td>
<td>III</td>
<td>Alastruey-Izquierdo AAC 2018; Hamigera, Paecilomyces, Rasamsonia, Sagenomella, Talaromyces, and Trichocoma also show <em>Penicillium</em>-like “brush” structures</td>
<td></td>
</tr>
<tr>
<td>Any</td>
<td>To guide treatment and correlate MIC with outcome</td>
<td>Antifungal susceptibility testing, CLSI method</td>
<td>B</td>
<td>III</td>
<td>Chowdhary OFID 2014; Geltner Transplantation 2013; Barcus ACMA 2005; Lyzatopoulous J Infect 2002; Kantarcioğlu Mycoses 2004</td>
<td></td>
</tr>
<tr>
<td><strong>Any</strong></td>
<td><strong>Serology assays</strong></td>
<td><strong>Nucleic-acid based assays</strong></td>
<td><strong>Imaging studies</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>To determine in vitro activity by generating MIC</td>
<td>Any Imaging studies</td>
<td>Any Immunodiagnosis</td>
<td>Any To detect sinusitis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antifungal susceptibility testing, CLSI method</td>
<td>To detect Penicillium spp. other than T. marneffei</td>
<td>Beta-tubulin sequencing (from sinus content)</td>
<td>To determine in vitro activity by generating MIC</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>Galactomannan EIA</td>
<td>B</td>
<td>Craniot CT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>To detect Penicillium spp. other than T. marneffei</td>
<td>II</td>
<td>PET/CT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>Aspergillus-specific Lateral Flow Device</td>
<td>II</td>
<td>To detect sinusitis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>To detect Penicillium spp. other than T. marneffei</td>
<td>I</td>
<td>To detect disemination</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>BDG in serum</td>
<td>I</td>
<td>To detect and assess brain lesions / abscesses</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>To detect Penicillium spp. other than T. marneffei</td>
<td>I</td>
<td>MRI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>To detect and assess brain lesions / abscesses</td>
<td>C</td>
<td>To detect and assess pneumonia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C</td>
<td></td>
<td></td>
<td>To detect and assess pneumonia</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Antifungal susceptibility testing:**
- **CLSI method**
- **Beta BDG**
- **Galactomannan EIA**
- **Aspergillus-specific Lateral Flow Device**
- **To detect sinusitis**
- **Histopathology of biopsy tissue**
- **To detect disemination**
- **Cranial CT**
- **PET/CT**
- **To detect and assess brain lesions / abscesses**
- **MRI**
- **To detect and assess pneumonia**
- **Chest radiography**
- **Chest CT**

**Nucleic-acid based assays:**
- **MALDI-TOFF MS**
- **MALDI-TOFF MS**
- **Panfungal, Penicillium just to the genus level**

**Clinical studies:**
- **Yadav IJPM 2019**
- **McShane Th 1879**
- **Zhang MCO 2016**
- **N=1, fungus ball, P. roqueforti**
- **Bauce ACMA 2005**
- **Lau BMCM 2016**
- **N=77 clinical isolates**
- **Mohammadi JRMS 2017**
- **Oshikata BMCPM 2013**
- **N=1**
- **Chen BMCID 2013**
- **N=1**
- **Reboux JMM 2019**
- **N=1**

**Imaging studies:**
- **Yadav IJPM 2019**
- **Ye IJMM 2015**
- **Ye IJMM 2015**
- **Sun CMJ 2006**
- **Ye IJMM 2015**
- **Ye IJMM 2015**
- **Yadav IJPM 2019**
- **Jung KJMS 2012**
- **Santos MedMycol 2006**
- **N=1, 8 yo, CGD**
- **Jin HIVM 2009**
- **N=19**

**Antifungal susceptibility testing:**
- **Beta BDG**
- **Galactomannan EIA**
- **Aspergillus-specific Lateral Flow Device**
- **To detect sinusitis**
- **Histopathology of biopsy tissue**
- **To detect disemination**
- **Cranial CT**
- **PET/CT**
- **To detect and assess brain lesions / abscesses**
- **MRI**
- **To detect and assess pneumonia**
- **Chest radiography**
- **Chest CT**

**Nucleic-acid based assays:**
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**Clinical studies:**
- **Yadav IJPM 2019**
- **McShane Th 1879**
- **Zhang MCO 2016**
- **N=1, fungus ball, P. roqueforti**
- **Bauce ACMA 2005**
- **Lau BMCM 2016**
- **N=77 clinical isolates**
- **Mohammadi JRMS 2017**
- **Oshikata BMCPM 2013**
- **N=1**
- **Chen BMCID 2013**
- **N=1**
- **Reboux JMM 2019**
- **N=1**

**Imaging studies:**
- **Yadav IJPM 2019**
- **Ye IJMM 2015**
- **Ye IJMM 2015**
- **Sun CMJ 2006**
- **Ye IJMM 2015**
- **Ye IJMM 2015**
- **Yadav IJPM 2019**
- **Jung KJMS 2012**
- **Santos MedMycol 2006**
- **N=1, 8 yo, CGD**
- **Jin HIVM 2009**
- **N=19**

**Antifungal susceptibility testing:**
- **Beta BDG**
- **Galactomannan EIA**
- **Aspergillus-specific Lateral Flow Device**
- **To detect sinusitis**
- **Histopathology of biopsy tissue**
- **To detect disemination**
- **Cranial CT**
- **PET/CT**
- **To detect and assess brain lesions / abscesses**
- **MRI**
- **To detect and assess pneumonia**
- **Chest radiography**
- **Chest CT**

BDG, Beta-D-Glucan; CGD, chronic granulomatous disease; CLSI, Clinical and Laboratory Standards Institute; CT, computed tomography; EIA, enzyme-linked immunoassay; EUCAST, European Committee for Antimicrobial Susceptibility Testing; ITS, internal transcribed spacer; MRI, magnetic resonance imaging; PCR, polymerase chain reaction; PET, positron emission tomography; pt, patient; QoE, quality of evidence; rRNA, ribosomal ribonucleic acid; SoR, strength of recommendation; yo, years old

**Recommendations** – The guideline group strongly recommends conventional diagnostic techniques such as microscopy and culture as well as histopathological analysis of tissue sections. Molecular diagnosis in clinical specimens is moderately supported, while ITS and β-tubulin sequencing of isolates is strongly recommended for species identification. The group marginally supports GM, BDG and the *Aspergillus* LFD for diagnosis of *Penicillium*-related infections. MIC determination is moderately recommended to guide treatment. Imaging is variably recommended depending on the case and patient condition, but strongly recommended to clinically diagnose invasive infections (Figure 32).
Figure 32. Optimal diagnostic pathway for *Penicillium* infections, when all imaging and assay techniques are available

**Invasive infection due to *Penicillium* spp.**

Any population

**Imaging procedures** (CT scan, MRI, X-ray) on suspected sites of infection

- *Aspergillus* LFD
- 1,3-β-D-Glucan
- Galactomannan in BAL and serum

**Direct microscopy**

**Culture from any site**

- Antifungal susceptibility testing to guide treatment

**Histology**

For further species identification

**ITS 1, ITS 2 and β tubulin sequencing**

For further species identification

**MALDI-TOF MS**

**Legend:**

- strongly recommended
- moderately recommended
- marginally recommended
- recommended against

CT, computed tomography; ITS, internal transcribed spacer; LFD, lateral-flow-device; MALDI-TOF MS, matrix-assisted laser desorption/ionization time-of-flight mass spectometry; MRI, magnetic resonance imaging
**Treatment approaches for infections caused by *Penicillium* spp.**

**Treatment in adults**

**Evidence** – Data guiding the treatment of *Penicillium* infections is scarce and mainly obtained from case reports. For first-line antifungal therapy, L-AmB has been used in many instances with variable results for invasive infections. Failure has been reported with both AmB alone or in combination with other antifungal agents, while successful treatment with AmB has been reported in other case series. Clinical failure of itraconazole has been reported in other case series. A finding not uncommon in other *Penicillium* spp. such as *P. citrinum* and *P. rubens*. PCZ has been successfully used to treat infections caused by *P. oxalicum* with high MICs against VCZ. Treatment durations of 6 weeks have been reported in patients with successful outcome. Parenteral VCZ resulted in satisfactory global response in 9 of 10 patients in one study. In invasive infections, surgical resection of pulmonary nodules resulted in a successful outcome in most reported cases. (Table 39).

<table>
<thead>
<tr>
<th>Table 39. Therapy for <em>Penicillium</em> infections</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Population</strong></td>
</tr>
<tr>
<td>Exogenous endophthalmitis</td>
</tr>
<tr>
<td>Exogenous endophthalmitis</td>
</tr>
<tr>
<td>Exogenous endophthalmitis</td>
</tr>
<tr>
<td>Endogenous endophthalmitis</td>
</tr>
<tr>
<td>Any with pulmonary infection due to <em>P. oxalicum</em></td>
</tr>
<tr>
<td>Any with disseminated infection</td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

**Antifungal salvage treatment**

| Any | To cure | VCZ iv | B | III | Perfect CID 2003 | N=10, response 9/10 |

**Treatment duration**

| Any | To cure | ≤6 wk antifungal treatment | C | III | Chowdhary OFID 2014 | N=3, *P. oxalicum*, response to PCZ 2/3, failure 1/3 |

**Standard dose unless stated otherwise;** 5-FC, 5-Fluorocytosine; AmB, amphotericin B; d, day(s); FCZ, fluconazole; iv, intravenous; ICZ, itraconazole; L-AmB, liposomal amphotericin B; MICA, micafungin; PCZ, posaconazole; po, orally; qd, once a day; qds, four times a day; QoE, quality of evidence; SoR, strength of recommendation; VCZ, voriconazole; wk, week(s).
**Recommendations** – The guideline group moderately supports L-AmB alone or in combination with other antifungals for invasive infections caused by *Penicillium* spp. The guideline group marginally supports systemic treatment with lipid-based formulations of AmB for *Penicillium*-related endophthalmitis. The group moderately recommends salvage therapy with parenteral VCZ. Surgery is moderately recommended when feasible (Figure 33).

**Figure 33. Optimal treatment pathway for *Penicillium* infections in adults when all treatment modalities and antifungal drugs are available**

<table>
<thead>
<tr>
<th>Suspected and confirmed invasive infections due to <em>Penicillium</em> spp.</th>
<th>are emergencies and require rapid action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immediate treatment initiation</td>
<td></td>
</tr>
<tr>
<td>Dissemination</td>
<td>Endophthalmitis</td>
</tr>
<tr>
<td>Liposomal Amphotericin B</td>
<td>Amphotericin B lipid complex</td>
</tr>
<tr>
<td>1 x 3-10 mg/kg/d</td>
<td>1 x 2-10 mg/kg/d or Liposomal Amphotericin B 1 x 3-10 mg/kg/d</td>
</tr>
<tr>
<td>± Other antifungals</td>
<td></td>
</tr>
<tr>
<td>Response assessment (e.g. weekly imaging)</td>
<td></td>
</tr>
<tr>
<td>Progressive disease*</td>
<td>Voriconazole iv</td>
</tr>
<tr>
<td>2 x 6 mg/kg/d d1; 2 x 4 mg/kg/d from d2; use TDM</td>
<td></td>
</tr>
</tbody>
</table>

**Legend:**
- strongly recommended
- moderately recommended
- marginally recommended
- recommended against

TDM, therapeutic drug monitoring

* Choice of salvage treatment always depends by the treatment that the patient failed to respond to
Specific considerations on treatment of infections caused by *Penicillium* spp. in children

Evidence – Pulmonary infections caused by *Penicillium* spp. have been described in children following lung transplantation and in those with CGD\(^{1811}\) (Table 40).

<table>
<thead>
<tr>
<th>Population</th>
<th>Intention</th>
<th>Intervention</th>
<th>SoR</th>
<th>QoE</th>
<th>Reference</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung transplant</td>
<td>To cure</td>
<td>VCZ + ANID</td>
<td>C</td>
<td>III</td>
<td>Ammermann ClinTransplant 2017(^{1811})</td>
<td>N=3, <em>Penicillium</em> spp., 3/3 survived</td>
</tr>
</tbody>
</table>

Standard pediatric dose unless stated otherwise; ANID, anidulafungin; QoE, quality of evidence; SoR, strength of recommendation; VCZ, voriconazole.

Recommendations – VCZ is moderately recommended as a first-line treatment option, although quality of evidence is weak\(^{1811}\).

### 9. Non-\textit{marneffei} Talaromyces

**Epidemiology of infections caused by non-\textit{marneffei} Talaromyces spp.**

*Talaromyces* spp. belong to the order Eurotiales and are ubiquitously found in air, soil, and indoor environments. The vast majority of reported infections due to *Talaromyces* spp. are related to *T. marneffei* (formerly *P. marneffei*), which is endemic in China and in tropical regions of South East Asia, and are mostly associated with advanced HIV infection\(^{1851}\). Very few cases of talaromycosis caused by species other than *marneffei* have been reported from non-endemic regions \textit{e.g.}, Europe and America over the past 20 years\(^{1798,1884,1893-1898}\). Infections have occurred in immunocompromised patients with CGD, malignancy, or long-term corticosteroid treatment for other chronic diseases. Infections are caused by *T. puritygenus*, *T. stolli*, *T. piceae*\(^{1884,1897}\), and *T. amestolkiae*, and mainly affect the lung and rarely other organs\(^{1798,1898}\). Hematogenous spread is common in *T. marneffei*-related infections; conversely, dissemination has rarely been reported for other *Talaromyces* spp.\(^{1897}\) (Figure 34).
Figure 34. Worldwide distribution of infections caused by non-marneffei Talaromyces spp. (reported cases between 1998 and 2019 per million population)

Cases of severe Talaromyces-related infections reported in the medical literature were identified in a PubMed search on July 29, 2019. The search string included all Talaromyces spp. that were identified in the Index Fungorum database (accessed 27. July 2019): (Talaromyces and T. each plus the following: albobicillius, amelstokiae, apiculatus, assiutensis, atroroseus, aurantiacus, austrocalifornicus, bacillisporus, barcinensis, boninensis, brunneus, calidicanius, cecidicola, coallescens, convolutus, dendriticus, dextii, duclauxii, echinosporus, emodensis, erythromellis, euchlorocarpus, flavus, funiculosus, galapagensis, hachi-joensis, helicus, indigoticus, intermedius, islandicus, lagunensis, leycettanis, loliensis, luteus, macrospora, malagensis, mimosinus, minioluteus, muroii, palmae, panamensis, paucisporus, phialosporus, piceus, pinophilus, pittii, primulinus, proteolyticus, pseudostromaticus, purpureus, purpureogenus, rademirici, radicus, ramulosus, retardatus, rotundus, ruber, rubicundus, rugulosus, ryukyuensis, sabulosus, siamensis, stipitatus, stollii, subinflatus, sublevisporus, tardifaciens, thermocitrinus, trachyspermus, ucrainicus, udagawae, unicus, variabilis, varians, vermiculatus, flavus, vermiculatus, verruculosus, viridis, viridulus, wort-mannii) NOT marneffei [title]) that yielded 608 publications. In total, 10 cases were identified from 7 coun-
tries\textsuperscript{1116,1798,1884,1893-1898}. Number of cases reported between 1998 and 2019 is presented as cases per million population per country. The resident population per country was obtained from www.worldometers.info\textsuperscript{321}.

### Diagnosis of non-marneffei Talaromyces infections

**Evidence** - Non-marneffei Talaromyces spp. are rarely encountered in clinical specimens submitted to the diagnostic laboratory. Conventional diagnosis by microscopy and culture is essential to see the *Penicillium*-like structures\textsuperscript{1893,1895}. Histopathological examination is crucial to demonstrate invasiveness with septate hyphae\textsuperscript{1884}. Morphological identification is very challenging, therefore sequencing of the ITS and β-tubulin-encoding genes has been applied for species identification\textsuperscript{1856}. Imaging with CT scan helps with the localisation of fungal infections\textsuperscript{1894}. To guide treatment, antifungal susceptibility testing is important to correlate MIC with treatment outcome. In one study echinocandins seem to have the best \textit{in vitro} activity\textsuperscript{1604} (Table 41).

#### Table 41. Microbiological, histopathological and imaging diagnostics for non-marneffei Talaromyces infections

<table>
<thead>
<tr>
<th>Population</th>
<th>Intention</th>
<th>Intervention</th>
<th>SoR</th>
<th>QoE</th>
<th>Reference</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any</td>
<td>To diagnose</td>
<td>Tissue biopsy stained by GMS</td>
<td>A</td>
<td>III</td>
<td>Villanueva-Lozano JIC 2017\textsuperscript{1893}</td>
<td>By GMS staining, hyphal structures were shown and by PCR investigation Talaromyces sp. was identified</td>
</tr>
<tr>
<td>Any</td>
<td>To diagnose</td>
<td>Culture</td>
<td>A</td>
<td>III</td>
<td>Villanueva-Lozano JIC 2017\textsuperscript{1893}</td>
<td>N=1, BAL culture on PDA</td>
</tr>
<tr>
<td>Any</td>
<td>To diagnose</td>
<td>Microscopy</td>
<td>A</td>
<td>III</td>
<td>Villanueva-Lozano JIC 2017\textsuperscript{1893}</td>
<td>Microscopy revealed <em>Penicillium</em>-like structure, identified as <em>P. chrysogenum</em> by PCR</td>
</tr>
<tr>
<td>Any</td>
<td>To guide treatment and correlate MIC with outcome</td>
<td>Broth microdilution (M-38A2 CLSU)</td>
<td>B</td>
<td>III</td>
<td>Guevara-Suarez JCM 2016\textsuperscript{1893}</td>
<td>Susceptibility testing of <em>T. amestolkiae</em>, <em>Talaromyces purpurapurogenus</em>. Best in vitro effect had echinocandins, however, only a few Talaromyces isolates were tested in this study</td>
</tr>
</tbody>
</table>

**Nucleic-acid based assays/MALDI-TOF MS**

| Any        | To identify clinically important *T. marneffei* and non-marneffei spp. | Bruker MALDI-TOF MS system | C   | III | Lau BMCM 2016\textsuperscript{1896} | N=59 isolates with documented penicilliosis. Database is suboptimal. Among four species phylogenetically closely related to *T. marneffei*, only *Penicillium brevicompactum* and *P. chrysogenum* were identified, while Talaromyces aurantacus and Talaromyces stipitatus strains were not identified |
| Any        | To identify species | ITS1/ITS2/ITC sequencing for molecular species identification of Talaromyces- *Penicillium*-like fungi (25-30°C) yeast-like (35-37°C) forming red pigment | A   | III | Ryu LMO 2017\textsuperscript{1903} | Sanger sequencing of the ITS regions covering ITS1, 5.8S, and ITS2, and the β-tubulin gene from the genomic DNA revealed Talaromyces albobiverticillus |
**Recommendations** – The guideline group strongly recommends microscopy and culture to diagnose *Talaromyces*-related infections, as well as histopathological evaluation (GMS staining) of tissue biopsies to distinguish between true infection and colonization. Molecular identification of isolates by sequencing the ITS regions is strongly recommended, while MALDI-TOF MS is marginally recommended by the group for species identification. Antifungal susceptibility testing is moderately recommended to guide treatment and correlation between MIC and outcome. CT scan is strongly recommended to clinically diagnose the infections (Figure 35).
Figure 35. Optimal diagnostic pathway for non-*marneffei Talaromyces* infections, when all imaging and assay techniques are available

**Invasive infection due to non-*marneffei Talaromyces***

Any population

| Imaging procedures (CT scan, MRI, X-ray) on suspected sites of infection |

Direct microscopy

Culture from any site

| Antifungal susceptibility testing to guide treatment |

Histology

| GMS stain |

For further species identification

| ITS 1, ITS 2 and β tubulin sequencing |

For further species identification

| MALDI-TOF MS |

Legend:

- strongly recommended
- moderately recommended
- marginally recommended
- recommended against

CT, computed tomography; GMS stain, Grocott’s methenamine silver stain; ITS, internal transcribed spacer; MALDI-TOF MS, matrix-assisted laser desorption/ionization time-of-flight mass spectrometry; MRI, magnetic resonance imaging

1972 1973 1974

**Treatment approaches to non-*marneffei Talaromyces* infection**

1975 1976 **Treatment in adults**

1977 **Evidence** – In view of the infrequency/rarity of infections caused by *non-*marneffei Talaromyces* spp., information on antifungal treatment is available from a few published case reports. L-AmB has been suc-
cessfully used as a first-line treatment\textsuperscript{1798}. Salvage treatment of non-
marneffei \textit{Talaromyces}-related infections with a combination of AmB plus ICZ/TRB has been unsuccessful\textsuperscript{1798}. In invasive infections, surgical resection of pulmonary nodules resulted in a successful outcome\textsuperscript{1884} (Table 42).

### Table 42. Therapy for non-marneffei \textit{Talaromyces} infections

<table>
<thead>
<tr>
<th>Population</th>
<th>Intention</th>
<th>Intervention</th>
<th>SoR</th>
<th>QoE</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>First-line antifungal therapy</strong></td>
<td>To cure</td>
<td>L-AmB</td>
<td>B</td>
<td>IIIu</td>
<td>Lyratzopoulos J Infect 2002\textsuperscript{1798}</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Guevera-Suarez JCM 2016\textsuperscript{1604}</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Lyratzopoulos J Infect 2002\textsuperscript{1798}</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lipid formulations AmB + ICZ + TRB</td>
<td>C</td>
<td>III</td>
<td>Lyratzopoulos J Infect 2002\textsuperscript{1798}</td>
</tr>
<tr>
<td></td>
<td>To cure</td>
<td>VCZ iv</td>
<td>C</td>
<td>III</td>
<td>Santos Med Mycol 2006\textsuperscript{1884}</td>
</tr>
<tr>
<td></td>
<td>To cure</td>
<td>TRB and echinocandins</td>
<td>C</td>
<td>III</td>
<td>Guevera-Suarez JCM 2016\textsuperscript{1604}</td>
</tr>
<tr>
<td><strong>Antifungal salvage treatment</strong></td>
<td>To cure</td>
<td>Lipid formulations AmB + ICZ + TRB</td>
<td>C</td>
<td>III</td>
<td>Lyratzopoulos J Infect 2002\textsuperscript{1798}</td>
</tr>
<tr>
<td></td>
<td></td>
<td>TRB and echinocandins</td>
<td>C</td>
<td>III</td>
<td>Santos Med Mycol 2006\textsuperscript{1884}</td>
</tr>
<tr>
<td></td>
<td>To cure</td>
<td>VCZ iv</td>
<td>C</td>
<td>III</td>
<td>Santos Med Mycol 2006\textsuperscript{1884}</td>
</tr>
<tr>
<td></td>
<td>To cure</td>
<td>TRB and echinocandins</td>
<td>C</td>
<td>III</td>
<td>Santos Med Mycol 2006\textsuperscript{1884}</td>
</tr>
<tr>
<td></td>
<td>To cure</td>
<td>Surgery</td>
<td>B</td>
<td>IIIu</td>
<td>Santos Med Mycol 2006\textsuperscript{1884}</td>
</tr>
<tr>
<td><strong>Other treatment options</strong></td>
<td>To cure</td>
<td>Surgery</td>
<td>B</td>
<td>IIIu</td>
<td>Santos Med Mycol 2006\textsuperscript{1884}</td>
</tr>
<tr>
<td><strong>Treatment duration</strong></td>
<td>To cure</td>
<td>12 wk of therapy</td>
<td>C</td>
<td>III</td>
<td>Lyratzopoulos J Infect 2002\textsuperscript{1798}</td>
</tr>
<tr>
<td></td>
<td>To cure</td>
<td>12 wk of therapy</td>
<td>C</td>
<td>III</td>
<td>Santos Med Mycol 2006\textsuperscript{1884}</td>
</tr>
</tbody>
</table>

\textbf{Recommendations} – Treatment with L-AmB is moderately recommended by the group. The guideline group moderately recommends surgical resection, and marginally salvage therapy with VCZ or an echinocandin plus TRB (Figure 36).
Suspected and confirmed invasive infections due to non-*marneffei Talaromyces* spp. are emergencies and require rapid action

Immediate treatment initiation

Liposomal Amphotericin B
1 x 3-10 mg/kg/d

Response assessment
(e.g. weekly imaging)

Progressive disease

Voriconazole iv
2 x 6 mg/kg/d d1;
2 x 4 mg/kg/d from d2
or
Echinocandin
Terbinafine
500-1000 mg/d

Legend:
- strongly recommended
- moderately recommended
- marginally recommended
- recommended against

Specific considerations on treatment of non-*marneffei Talaromyces* infections in children

Evidence – Specific pediatric data and case reports are lacking.

Recommendations – Treatment recommendations follow those in adults.

10. *Paecilomyces*

Epidemiology of *Paecilomyces* infections

*Paecilomyces* spp. are members of the order Eurotiales. They are filamentous, saprophytic, and thermo-tolerant fungi that are ubiquitously found in soil, food products, decaying organic material, and house
In the past, *Paecilomyces* spp. were often considered as contaminants when isolated clinically, but recently they are becoming recognized worldwide as important cause of infections primarily in immunocompromised patients or patients with indwelling catheters. However, immunocompetent individuals can also be affected, e.g., by direct inoculation of fungus following trauma. The majority of these infections is caused by *P. variotii* spp. complex that is composed of *P. variotii* *sensu stricto*, *P. formosus*, *P. divaricatus*, *P. brunneolus*, and *P. dactylethromphus*. *P. variotii* is the asexual state of *Byssochlamys spectabilis*. Microbiological identification of *Paecilomyces* spp. is challenging due to its morphological similarity to some *Rasamsonia* and *Hamigera* spp. Phylogenetic analyses showed that *Purpureocillium lilacinum* (formerly *Paecilomyces lilacinus*) belongs to the order Hypocreales and thus shall not be considered together with *Paecilomyces* spp. Species identification is crucial for patient management since both species appear to have different susceptibility profiles and clinical response to antifungal agents. *P. variotii* infection can affect many different organ systems and presents with various manifestations including pneumonia, skin and soft tissue infections, endophthalmitis, peritonitis, osteomyelitis, and bloodstream infections, especially in immunocompromised patients (Figure 37).

**Figure 37.** Worldwide distribution of infections caused by *Paecilomyces* spp. (reported cases between 1971 and 2018 per million population)
Cases of severe *Paecilomyces*-related infections reported in the medical literature were identified in a PubMed search on October 31, 2019 including all *Paecilomyces* spp. identified in the Index Fungorum database (accessed 27. July 2019) in the PubMed search string (*Paecilomyces* plus the following: *antarcticus*, *aspergilloides*, *atrovirens*, *baarnensis*, *borysthenicus*, *breviramosus*, *brunneolus*, *brunneolus*, *burcii*, *byssophiloides*, *canadensis*, *cinnamomeus*, *clavisporus*, *cossus*, *cremosus*, *cylindricosporus*, *divaricatus*, *echinosporus*, *erectus*, *fimetarius*, *fulvus*, *fuscatus*, *gunnii*, *heliothis*, *hepiali*, *huaxiensis*, *indicus*, *isarioides*, *laeensis*, *longipes*, *loushanensis*, *mandshuricus*, *maximus*, *maximus*, *maximus*, *militaris*, *musicola*, *niphetodes*, *odonatae*, *parvisporus*, *pascuus*, *penicillatus*, *persimplex*, *puntonii*, *purpureus*, *ramosus*, *rariramus*, *saturatus*, *simplex*, *smilanensis*, *stipitatus*, *subglobosus*, *suffultus*, *tabacinus*, *taitungiacus*, *tenuis*, *variottii*, * verrucosus*, *verticillatus*, *victoriae*, *vinaceus*, *wawuensis*, *xylariiformis*, *zollerniae*) AND (infection OR invasive OR fungal infection OR fungemia OR blood OR disseminated OR subcutaneous OR case [Title/Abstract] OR report [Title/Abstract] OR case series [Title/Abstract] OR patient OR isolate) that yielded 662 publications. In total, 93 cases were identified from 23 countries, 67 since the year 2000\(^{572,1116,1903,1907,1914-1969}\). Most cases were reported from the United States (n=16), Spain (n=13) and Taiwan (n=14). The number of cases reported between 1971 and 2018 is presented as cases per million population per country. The resident population per country was obtained from www.worldometers.info\(^{121}\).

*Five cases were reported from Hong Kong SAR (0.7 cases per million population between 1971 and 2018)\(^{1925,1943,1944,1957}\).*

**Diagnosis of *Paecilomyces* infections**

A species distinction is achieved in the course of diagnosis on the basis of various microbiological and molecular criteria.

**Evidence** – The initial step in laboratory diagnosis is histopathological examination and microscopy, which reveal non-specific branched septate hyphae\(^{1965}\). Culture is essential for species identification. Based on the culture morphology on different growth media, species determination can be achieved\(^{1597,1915,1965,1970}\).
Histology is also required for identification of fungi, classification and evaluation of irregular hyphae.

Molecular-based methods can be used for species identification from DNA extracted from clinical isolates with subsequent Sanger sequencing, but not for the detection of fungal DNA directly from clinical material. Differentiation occurs via PCR-based DNA amplification of the rRNA gene regions ITS1 and ITS2 and of the 28S D1 and D2 regions. Additionally the amplification of the β-tubulin-encoding gene for species identification has been mentioned. Genbank analysis and sequence alignment are used for exact species assignment. Occasionally MALDI-TOF MS technology is used for species identification.

For susceptibility testing, the EUCAST and CLSI M38-A2 microdilution methodologies have shown AmB and echinocandins to be active against clinical *P. variotii* isolates. Among the triazoles, ICZ and PCZ showed clinically relevant activity against *P. variotii*. PCZ and TRB showed good in vitro activity with ICZ the second most active and VCZ the less active triazole.

Imaging technologies (chest CT) are mainly used for detection of suspected pulmonary infections.

(Table 43.)

<table>
<thead>
<tr>
<th>Population</th>
<th>Intention</th>
<th>Intervention</th>
<th>SoR</th>
<th>QoE</th>
<th>Reference</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any</td>
<td>To diagnose</td>
<td>Culture</td>
<td>A</td>
<td>III</td>
<td>Samson StudMycol 1974</td>
<td>Differentiate between <em>P. lilacinum</em> and <em>P. variotii</em></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Houbraken JCM 2010</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Barker MedMycol 2014</td>
<td>Sabouraud glucose brain heart infusion agar at 30°C</td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td>Abolghasemi Tanaffos 2015</td>
<td>Sabouraud dextrose agar</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Eren TID 2018</td>
<td>Potato dextrose agar</td>
</tr>
<tr>
<td>Any</td>
<td>To diagnose</td>
<td>Microscopy</td>
<td>A</td>
<td>III</td>
<td>Eren TID 2018</td>
<td>Gram and Giemsa staining</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Uzunoglu JMM 2003</td>
<td>Lactophenol cotton blue</td>
</tr>
<tr>
<td>Any</td>
<td>To guide treatment</td>
<td>ELICAST microdilution protocol</td>
<td>B</td>
<td>III</td>
<td>Castelli AAC 2008</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Feldman Mycoses 2016</td>
<td></td>
</tr>
<tr>
<td>Any</td>
<td>To guide treatment</td>
<td>Broth microdilution method according to CLSI guidelines (M38-A)</td>
<td>B</td>
<td>III</td>
<td>Aguilar AAC 1999</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Houbraken JCM 2010</td>
<td></td>
</tr>
</tbody>
</table>

**Nucleic acid-based assays/MALDI-TOF MS**

Any To identify species | PCR: ITS1, ITS2, and β-tubulin gene +/− 5.8S rDNA | A   | IIu | Houbraken JCM 2010 | |
|            |              |     |     | Uzunoglu JMM 2017 | |
|            |              |     |     | Kantarcioğlu Mycoses 2003 | |
|            |              |     |     | Barker MedMycol 2014 | |
| Any | To identify species | MALDI-TOF MS | B | III | Castelli AAC 2008<sup>1274</sup>  
Barker MedMycol 2014<sup>1277</sup>  
Chen F Microbiol 2015<sup>1276</sup> |
<table>
<thead>
<tr>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Tissue-based diagnosis</td>
<td>Any</td>
<td>To diagnose</td>
<td>Histopathological examination of biopsy tissue</td>
<td>A</td>
<td>III</td>
</tr>
<tr>
<td>Imaging studies</td>
<td>Any</td>
<td>To identify CNS infection</td>
<td>Cranial MRI</td>
<td>B</td>
<td>III</td>
</tr>
</tbody>
</table>
| | Any | To identify pulmonary infection | Chest (HR) CT | A | III | Marques EFIM 2019<sup>1280</sup>  
Abolghasemi Tanaffos 2015<sup>1281</sup> |

CLSI, Clinical and Laboratory Standards Institute; CT, computed tomography; EUCAST, European Committee for Antimicrobial Susceptibility Testing; HR, high-resolution; ITS, internal transcribed spacer; MALDI-TOF MS, matrix assisted laser desorption ionization-time of flight mass spectrometry; PCR polymerase chain reaction; QoE, quality of evidence; rRNA, ribosomal ribonucleic acid; SoR, strength of recommendation;

**Recommendations**  - Direct microscopy and culture followed by PCR sequencing of the ITS and D1/D2 regions for species identification are strongly recommended, as is histopathological examination of tissue. 

Antifungal susceptibility testing is moderately recommended to guide treatment. Imaging modalities such as chest CT are strongly recommended if applicable (Figure 38).
Figure 38. Optimal diagnostic pathway for *Paecilomyces* infections, when all imaging and assay techniques are available

![Diagnostic pathway diagram](image)

Legend:
- strongly recommended
- moderately recommended
- marginally recommended
- recommended against

CT, computed tomography; ITS, internal transcribed spacer; MALDI-TOF MS, matrix-assisted laser desorption/ionization time-of-flight mass spectrometry; MRI, magnetic resonance imaging

**Treatment approaches to *Paecilomyces* infections**

**Treatment in adults**

**Evidence** – L-AmB generally demonstrates good *in vitro* activity and different AmB formulations have been reported with varying but usually good responses. Antifungal combination therapies have only been described in individual cases (*e.g.*, L-AmB in combination with ICZ or AmB in combination with ANID), and were associated with favourable outcomes. ICZ and
PCZ show good activity against *P. variotii* and have been successfully used for salvage therapy. The appropriate length of treatment for *P. variotii* infections is unclear. Successful case reports cite treatment duration ranges from 4 to 12 weeks. For dialysis-associated peritonitis, shorter treatment duration of 10 days is reported in two cases in combination with peritoneal catheter removal.

Various authors have reported good treatment responses after surgical interventions and removal of venous or intraperitoneal catheter systems (Table 44).

### Table 44. Therapy for *Paecilomyces* infections

<table>
<thead>
<tr>
<th>Population</th>
<th>Intention</th>
<th>Intervention</th>
<th>SoR</th>
<th>QoE</th>
<th>Reference</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>First-line antifungal therapy</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any</td>
<td>To cure</td>
<td>L-AmB</td>
<td>B</td>
<td>II</td>
<td>Salle J Infect 2005(^{1011})</td>
<td>N=1, fungemia, response</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Chamilos J Infect 2005(^{1024})</td>
<td>N=1, <em>P. variotii</em>, + CVC removal, response, MICs VCZ 8 µg/ml, AmB 0.25 µg/ml, PCZ 0.06 µg/ml</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Steiner CRID 2013(^{1030})</td>
<td>N=1, pneumonia, <em>P. variotii</em>, failure</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Bellanger Myopathol 2017(^{1067})</td>
<td>N=1, fungemia, + ANID, success</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Dharmasena BMJ 1985(^{1229})</td>
<td>N=1, pneumonia, success</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Kantarcioglu Mycoses 2002(^{1234})</td>
<td>N=1, CNS infection, failure</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Cohen-Abbo Infection 1995(^{1234})</td>
<td>N=1, response</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Lam Eye 1999(^{1963})</td>
<td>N=1, endophthalmitis + fungemia, + surgery, success</td>
</tr>
<tr>
<td>Any</td>
<td>To cure</td>
<td>VCZ</td>
<td>D</td>
<td>III</td>
<td>Eren TID 2018(^{1979})</td>
<td>N=1, skin infection, + surgery, success</td>
</tr>
<tr>
<td>Any</td>
<td>To cure</td>
<td>PCZ tablet</td>
<td>C</td>
<td>III</td>
<td>Marques EJCRIM 2019(^{1924})</td>
<td>N=1, pulmonary mycetoma, died</td>
</tr>
<tr>
<td>Any</td>
<td>To cure</td>
<td>ICZ po</td>
<td>C</td>
<td>III</td>
<td>Abolghasemi Tanaffos 2015(^{1235})</td>
<td>N=1, pneumonia, success</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Vasudevan IJD 2013(^{1966})</td>
<td>N=1, subcutaneous hyalohypomycosis, success</td>
</tr>
<tr>
<td>Peritoneal dialysis patients</td>
<td>To cure peritonitis</td>
<td>L-AmB iv +/- ICZ po</td>
<td>B</td>
<td>II</td>
<td>Torres PDI 2014(^{1258})</td>
<td>N=3, + catheter removal N=3, + laparotomy N=1, success 2/3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Uzunoglu JMM 2017(^{1965})</td>
<td>N=1, success</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Marzec JCM 1993(^{1247})</td>
<td>N=4, + catheter removal N=4, success 4/4</td>
</tr>
<tr>
<td><strong>Antifungal salvage treatment</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any</td>
<td>To cure</td>
<td>PCZ</td>
<td>B</td>
<td>II</td>
<td>Feldmann Mycoses 2016(^{1903})</td>
<td>N=1, pneumonia, response</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Bellanger Myopathol 2017(^{1067})</td>
<td>N=1, fungemia, success</td>
</tr>
<tr>
<td>Any</td>
<td>To cure</td>
<td>ICZ po</td>
<td>B</td>
<td>III</td>
<td>Lee JHJT 2002(^{1944})</td>
<td>N=1, sternotomy wound infection, + surgery, success</td>
</tr>
<tr>
<td><strong>Other treatment options</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peritoneal dialysis patients</td>
<td>To cure</td>
<td>Catheter removal</td>
<td>A</td>
<td>III</td>
<td>Torres PDI 2014(^{1258})</td>
<td>N=3, initial response 3/3, success 2/3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Uzunoglu JMM 2017(^{1965})</td>
<td>N=1, success</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Marzec JCM 1993(^{1247})</td>
<td>N=4, success 4/4</td>
</tr>
<tr>
<td>Endophthalmitis</td>
<td>To cure</td>
<td>Vitrectomy and AmB 5 µg intravitreal</td>
<td>C</td>
<td>III</td>
<td>Tarkkanen AOS 2004(^{1962})</td>
<td>N=1, initial response but several re-apases</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Lam Eye 1999(^{1963})</td>
<td>N=1, endophthalmitis + fungemia, success</td>
</tr>
<tr>
<td>Any</td>
<td>To cure</td>
<td>Surgical debridement</td>
<td>B</td>
<td>III</td>
<td>Eren TID 2018(^{1979})</td>
<td>N=1, skin infection, + surgery, success</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Lee JHJT 2002(^{1944})</td>
<td>N=1, sternotomy wound infection, success</td>
</tr>
</tbody>
</table>

### Treatment duration

- PCZ show good activity against *P. variotii* and have been successfully used for salvage therapy. The appropriate length of treatment for *P. variotii* infections is unclear. Successful case reports cite treatment duration ranges from 4 to 12 weeks. For dialysis-associated peritonitis, shorter treatment duration of 10 days is reported in two cases in combination with peritoneal catheter removal.

- Various authors have reported good treatment responses after surgical interventions and removal of venous or intraperitoneal catheter systems (Table 44).
<table>
<thead>
<tr>
<th>Condition</th>
<th>Treatment</th>
<th>Duration</th>
<th>Study</th>
<th>Rating</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetic</td>
<td>To cure pneumonia</td>
<td>4 wk ICZ</td>
<td>Abolghasemi Tanaffos 2015</td>
<td>III</td>
<td>N=1, success</td>
</tr>
<tr>
<td>Solid organ transplant recipients</td>
<td>To cure skin infection</td>
<td>6 wk VCZ po</td>
<td>Eren TID 2018</td>
<td>III</td>
<td>N=1, success</td>
</tr>
<tr>
<td>Any</td>
<td>To cure pulmonary mycetoma</td>
<td>6 wk PCZ</td>
<td>Marques EJCRIM 2019</td>
<td>II</td>
<td>N=1, died</td>
</tr>
<tr>
<td>Peritoneal dialysis patients</td>
<td>To cure peritonitis</td>
<td>4-8 wk L-AmB iv + ICZ po</td>
<td>Marzec JCM 1993</td>
<td>III</td>
<td>N=3, initial response 3/3, success 2/3</td>
</tr>
<tr>
<td>Hematological malignancy</td>
<td>To cure fungemia</td>
<td>6-12 wk L-AmB, step down to PCZ po possible</td>
<td>Salle JInfect 2005</td>
<td>III</td>
<td>N=1, success</td>
</tr>
</tbody>
</table>

Standard dose unless stated otherwise: ANID, anidulafungin; AmB, amphotericin B; CNS, central nervous system; CVC, central venous catheter; d, day(s); ICZ, itraconazole; iv, intravenous; L-AmB, liposomal amphotericin B; MIC, minimal inhibitory concentration; PCZ, posaconazole; po, orally; qd, once a day; QoE, quality of evidence; SoR, strength of recommendation; VCZ, voriconazole; wk, week(s).

**Recommendation** – We moderately support the use of L-AmB (3-10 mg/kg qd) as a first-line antifungal monotherapy. We moderately recommend PCZ tablet (300 mg/d maintenance) or ICZ oral (400 mg/d) for salvage treatment. Treatment duration is a personalized decision and should be tailored to clinical signs.

In general, weeks to months of therapy are given and we marginally support 4 to 12 weeks of treatment.

We moderately support a recommendation of surgical debridement of infected tissues and strongly support removal of peritoneal catheters in peritoneal dialysis patients with peritonitis (Figure 39).
Figure 39. Optimal treatment pathway for *Paecilomyces* infections in adults when all treatment modalities and antifungal drugs are available

**Legend:**
- strongly recommended
- moderately recommended
- marginally recommended
- recommended against

**Suspected and confirmed invasive infections due to *Paecilomyces* spp. are emergencies and require rapid action**

- Immediate treatment initiation
- Removal of peritoneal catheters
- Surgery
- **Liposomal Amphotericin B**
  - 1 x 3-10 mg/kg/d
- **Response assessment**
  - (e.g. weekly imaging)

**Progressive disease**

- **Itraconazole**
  - 1 x 400 mg/d
- **Posaconazole iv/tab**
  - 2 x 300 mg/d d1;
  - 1 x 300 mg/d from d2

**Specific considerations on treatment of Paecilomyces infections in children**

**Evidence** – Only a few cases of *P. variotii*-related infection in children are described. In individual cases, successful treatment was achieved with AmB or VCZ[^234,238,235,236,237] (Table 45).
Table 45. Therapy in children for Paecilomyces infections

<table>
<thead>
<tr>
<th>Population</th>
<th>Intention</th>
<th>Intervention</th>
<th>SoR</th>
<th>QoE</th>
<th>Reference</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>First-line antifungal therapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Solid organ transplant recipient</td>
<td>Infectious source control/pneumonia</td>
<td>L-AmB qd or 10 mg/kg tiw +/- ICZ po OR VCZ 7 mg/kg bid</td>
<td>B</td>
<td>III</td>
<td>Das PedTransplant 20001321, Polat Mycopathol 20151331</td>
<td>N=1, 9 ys, Lung TX, pneumonia, several fungi in BAL, including Aspergillus versicolor, Aspergillus fumigatus, Aspergillus niger, Penicillium spp., P. variotii, questionable response, died from complications of bronchopneumonia, success</td>
</tr>
</tbody>
</table>

| Antifungal salvage treatment | | | | | | |
| Hematological malignancy | To cure fungemia | L-AmB | C | III | Chamilos J Infect 20051344 | N=1, 14 yrs, CVC infection, + catheter removal, success |

| Treatment duration | | | | | | |
| Any | To cure peritonitis | 4-6 wk of therapy | C | III | Rinaldi PedNephrol 20001352, Polat Mycopathol 20151331 | N=1, success |
| Any | To cure | 6-8 wk of therapy with L-AmB, followed by ICZ | C | III | Chamilos J Infect 20051344, Das PedTransplant 20001358 | N=1, fungemia, success |
| Any | To cure splenic abscess | 14 mo of therapy with FCZ +/- 5-FC | C | III | Wang DMID 20001357 | N=1, success |

Standard pediatric dose unless otherwise stated; 5-FC, 5-fluorocytosine; A Aspergillus; BAL, bronchoalveolar lavage; bid, twice a day; CVC, central venous catheter; FCZ, fluconazole; ICZ, itraconazole; L-AmB, liposomal amphotericin B; mo, month(s); po, orally; qd, once a day; QoE, quality of evidence; SoR, strength of recommendation; tiw, three times a week; VCZ, voriconazole; wk, week(s); yrs, years.

Recommendation – Although there is limited evidence to support a specific regimen, we moderately support the use of L-AmB (3 mg/kg qd or 10 mg/kg tiw), or VCZ as first-line treatment for Paecilomyces-related infections in children.

11. Purpureocillium

Epidemiology of Purpureocillium infections

P. lilacinum (formerly Paecilomyces lilacinus) is a saprobic, non-dermatophyte mold with a worldwide distribution and can be commonly found in soil. Due to its nematophagous potential it is widely used as a bio-control agent in agriculture and has been isolated from water streams in the Middle East, possibly as a run-off from agricultural use1981,1982.

P. lilacinum has a tropism for ocular structures, thus, the most frequent clinical manifestations in humans are keratitis and endophthalmitis, followed by cutaneous and subcutaneous infections1983. The most common route of infection is via external invasion but endogenous infections also have been reported, mainly in immunocompromised patients. In a US study in 2 referral centers, ~4% of cases of fungal keratitis were...
caused by *P. lilacinum*. Frequently, eye infections are associated with intra-ocular lens implantation, trauma and the use of soft contact lenses. Up to one third of reported *Purpureocillium*-associated keratitis cases required enucleation. Poor outcome is possibly related to the limited efficacy of topical natamycin, which is the treatment of choice for *Fusarium*-associated fungal keratitis, the main causative pathogen. The use of topical VCZ has demonstrated good effects in advanced cases of *Purpureocillium* keratitis. Cutaneous and sub-cutaneous infections mainly occur in transplant or other immunosuppressed patients, especially those with underlying malignancy. Cases of non-ocular, non-cutaneous infections caused by *P. lilacinum* have been described but these are in general rare. *P. lilacinum* presents moderate virulence. Infections are rarely disseminated, mainly in severely immunocompromised patients. In Spain, an incidence of 1% has been reported in patients following lung transplantation (Figure 40).

Figure 40. Worldwide distribution of infections caused by *Purpureocillium* spp. (reported cases between 1977 and 2019 per million population)

Cases of severe *Purpureocillium*-related infections reported in the medical literature were identified in a PubMed search on October 30, 2019 using the search string “*Purpureocillium atypicola* OR *Purpureocillium lavendulum* OR *Purpureocillium lilacinum* OR *Paecilomyces lilacinus* OR *Purpureocillium sodanum* OR *Purpureocillium takamizusanense*” that yielded 395 publications. Cases were identified in four additional
publications in the *Paecilomyces* search. Overall, 250 cases from 28 countries have been selected, 171 cases reported since the year 2000. Most cases were reported from the USA (n=113), Australia (n=26), Spain (n=17), India and Japan (each n=13). Nine patients with *Purpureocillium* -related infections that were reported during an outbreak due to contaminated skin lotion in Switzerland were excluded. Number of cases reported between 1977 and 2019 is presented as cases per million population per country. The resident population per country was obtained from www.worldometers.info. *One case of infection caused by *P. lilacinum* was reported from Iceland (3 cases per million population between 1977 and 2019).

**Diagnosis of *Purpureocillium* infections**

**Evidence** – Distinction between species is achieved in the course of diagnosis on the basis of various microbiological and molecular criteria. Direct microscopy of infected tissues is used for the characterization and identification of numerous hyaline and septate hyphae of molds. Rarely conidiophores and phialides can be observed. Culture is crucial for species identification. Based on culture morphology on different growth media the species determination can be performed. Histology is also required for identification of fungi and visualization of numerous separate hyphae and arthroconidia within granulomas. For susceptibility testing the use of E-test strips has been described for *Purpureocillium* spp. MICs were high for AmB, ICZ, PCZ, CASPO and MICA, while VCZ had a relatively low MIC.

Molecular methods are used for species identification, but not for detection of fungal DNA from clinical material. Differentiation occurs via PCR-based DNA amplification of rRNA gene regions, mainly 28S D1 and D2 regions, but also ITS1 and ITS2. PCR is performed from cultured clinical isolates. Genbank analysis and sequence alignment are used for the exact species assignment (Table 46).

| Table 46. Microbiological and histopathological diagnostics of *Purpureocillium* infections |
|-----------------------------------------------|---------------|-------------|-----------|-------------|-----------------|-------------|
| Population | Intention | Intervention | SoR | QoE | Reference | Comment |
| Microscopy, culture, MIC testing | To diagnose | Culture | A | III | Demitsu J Dermatol 2017 | Biopsy on SDA |
| | | | | | Saghrouni MedMycol 2013 | Biopsy on SDA |
| **Any** | To diagnose | Microscopy | A | III | Saghrouni MedMycol 2013
973 | KOH direct examination |
<table>
<thead>
<tr>
<th></th>
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<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Biopsy on brain heart infusion agar</td>
<td></td>
<td></td>
<td>Narita AMO 2015</td>
<td>Malt extract agar</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Malt extract agar</td>
<td></td>
<td></td>
<td>Antas Microbes Infect 2012</td>
<td>SDA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SDA</td>
<td></td>
<td></td>
<td>Antas Microbes Infect 2012</td>
<td>SDA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SDA</td>
<td></td>
<td></td>
<td>Naragamo MMJ 2014</td>
<td>SDA</td>
</tr>
<tr>
<td></td>
<td>To test susceptibility</td>
<td>E-test strips (bioMérieux, France)</td>
<td>B</td>
<td>III</td>
<td>Saghrouni MedMycol 2013</td>
<td>SDA</td>
</tr>
<tr>
<td></td>
<td>To identify species</td>
<td>PCR rRNA D1/D2 or ITS region</td>
<td>A</td>
<td>III</td>
<td>Demitsu JDermatol 2016</td>
<td>SDA</td>
</tr>
<tr>
<td></td>
<td>To identify cause of facial skin lesion</td>
<td>MALDI-TOF MS using a microflex LT instrument (Bruker Daltonics Germany)</td>
<td>B</td>
<td>III</td>
<td>Saghrouni MedMycol 2013</td>
<td>SDA</td>
</tr>
</tbody>
</table>

### Nucleic-acid based assays/MALDI-TOF MS

<table>
<thead>
<tr>
<th><strong>Any</strong></th>
<th>To diagnose in biopsy</th>
<th>In-house 18S rRNA PCR</th>
<th>C</th>
<th>III</th>
<th>Trinh TID 2017</th>
<th>SDA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>To identify species</td>
<td>PCR rRNA D1/D2 or ITS region</td>
<td>A</td>
<td>III</td>
<td>Demitsu JDermatol 2016</td>
<td>SDA</td>
</tr>
<tr>
<td></td>
<td>To identify cause of facial skin lesion</td>
<td>MALDI-TOF MS using a microflex LT instrument (Bruker Daltonics Germany)</td>
<td>B</td>
<td>III</td>
<td>Saghrouni MedMycol 2013</td>
<td>SDA</td>
</tr>
</tbody>
</table>

### Tissue-based diagnosis

<table>
<thead>
<tr>
<th><strong>Any</strong></th>
<th>To diagnose</th>
<th>Histopathology of biopsy tissue</th>
<th>A</th>
<th>III</th>
<th>Trinh TID 2017</th>
<th>SDA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Demitsu JDermatol 2016</td>
<td>SDA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Saghrouni MedMycol 2013</td>
<td>SDA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Antas Microbes Infect 2012</td>
<td>SDA</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Recommendations** - Direct microscopy, and culture followed by sequencing of the 28S D1 and D2 regions and of ITS1 and ITS2 for species identification are strongly recommended, as is histopathological examination of tissue. Identification of isolates with MALDI-TOF MS are moderately recommended. Antifungal susceptibility testing is moderately recommended to guide antifungal treatment.

If all diagnostic options are available, one should follow the management pathway (Figure 41).
**Figure 41.** Optimal diagnostic pathway for *Purpureocillium* infections, when all imaging and assay techniques are available

**Invasive infection due to *Purpureocillium* spp.**

Any population

- Imaging procedures (CT scan, MRI, X-ray) on suspected sites of infection
- Direct microscopy
- Culture from any site
  - Antifungal susceptibility testing to guide treatment
  - Histology

- For further species identification: D1/D2, ITS 1 and ITS 2 sequencing
- For further species identification: MALDI-TOF MS

**Legend:**

- strongly recommended
- moderately recommended
- marginally recommended
- recommended against

CT, computed tomography; ITS, internal transcribed spacer; MALDI-TOF MS, matrix-assisted laser desorption/ionization time-of-flight mass spectrometry; MRI, magnetic resonance imaging

---

**Treatment approaches to *Purpureocillium* infections**

**Treatment in adults**

**Evidence** - VCZ demonstrates generally good *in vitro* activity against *P. lilacinum* and several successful therapy approaches with VCZ have been reported. Furthermore, some reports of successful treatment with VCZ in combination with TRB have been published. For salvage therapy, the results for AmB have been mixed (not effective, effective). AmB
generally shows poor activity against *P. lilacinum* *in vitro*. PCZ and ICZ have been reported to be effective in individual cases but usually do not show *in vitro* activity against *Purpureocillium lilacinum*.

Appropriate length of treatment for *P. lilacinum* infections is unclear. Successful cases cover ranges from a few weeks to 7 months. Surgical debridement of infected tissue appears to be a major means of resolution of the infection if the lesions are localized (Table 47).

<table>
<thead>
<tr>
<th>Table 47. Therapy for <em>Purpureocillium</em> infections</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Population</strong></td>
</tr>
<tr>
<td>Hematological malignancy</td>
</tr>
<tr>
<td>Any</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
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<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Any with cutaneous / subcutaneous infection</td>
</tr>
<tr>
<td></td>
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<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Any</td>
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<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Any</td>
</tr>
<tr>
<td>Any with keratitis</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Clinical Condition</td>
</tr>
<tr>
<td>--------------------</td>
</tr>
<tr>
<td>Any with periarticular bursitis</td>
</tr>
<tr>
<td>Any with endophthalmitis</td>
</tr>
<tr>
<td>Any with keratitis</td>
</tr>
<tr>
<td>Any with endophthalmitis</td>
</tr>
<tr>
<td>Any with cutaneous/subcutaneous infection</td>
</tr>
<tr>
<td>Antifungal salvage treatment</td>
</tr>
<tr>
<td>Any with cutaneous infection</td>
</tr>
<tr>
<td>Immunocompetent patients with onychomycosis</td>
</tr>
<tr>
<td>Peritoneal dialysis patients with Peritoniitis</td>
</tr>
<tr>
<td>Other treatment options</td>
</tr>
<tr>
<td>Endophthalmitis</td>
</tr>
<tr>
<td>Immunocompetent patients with lung abscess</td>
</tr>
<tr>
<td>Immunocompetent patients with septic bursitis</td>
</tr>
<tr>
<td>Peritoneal dialysis patients with peri-</td>
</tr>
<tr>
<td>Treatment duration</td>
</tr>
<tr>
<td>McIntosh CEO 2013,206, N=1, immunocompromised patient, 6 mo of therapy with topical, oral and</td>
</tr>
<tr>
<td>Any</td>
</tr>
<tr>
<td>-----------------------------------------</td>
</tr>
<tr>
<td>Any</td>
</tr>
<tr>
<td>Solid organ transplant recipients</td>
</tr>
<tr>
<td>Immunocompetent patients</td>
</tr>
<tr>
<td>Peritoneal dialysis patients</td>
</tr>
<tr>
<td>Any</td>
</tr>
</tbody>
</table>

Standard dose unless stated otherwise: bid, twice a day; d, day(s); ICZ, itraconazole; iv, intravenous; L-AmB, liposomal amphotericin B; mo, month(s); PCZ, posaconazole; po, orally; qd, once a day; QoE, quality of evidence; SoR, strength of recommendation; TRB, terbinafine; VCZ, voriconazole; wk, week(s).

2186 Recommendations – The guideline group moderately supports first-line monotherapy with VCZ in all patients. ICZ (SUBA formulation preferred), PCZ and L-AmB are marginally recommended alternatives. For cutaneous and subcutaneous infections, combination therapy with VCZ plus TRB is moderately supported. For salvage therapy we marginally recommend L-AmB, PCZ or ICZ monotherapy. We moderately recommend a treatment duration of at least 3 months for ocular and cutaneous/subcutaneous infections. The guideline group strongly supports a recommendation for surgical debridement (Figure 42).
Figure 42. Optimal treatment pathway for *Purpureocillium* infections in adults when all treatment modalities and antifungal drugs are available

Suspected and confirmed invasive infections due to *Purpureocillium* spp. are emergencies and require rapid action

Immediate treatment initiation

Surgical debridement

- **Voriconazole iv**
  - 2 x 6 mg/kg/d d1; 2 x 4 mg/kg/d from d2; use TDM
- **Itraconazole**
  - 1 x 400 mg/d
- **Liposomal Amphotericin B**
  - 1 x 3-10 mg/kg/d
- **Posaconazole iv/tab**
  - 2 x 300 mg/d d1; 1 x 300 mg/d from d2
- **Voriconazole iv**
  - 2 x 6 mg/kg/d d1; 2 x 4 mg/kg/d from d2; use TDM
  - Terbinafine
  - 500-1000 mg/d

Response assessment (e.g. weekly imaging)

- **Progressive disease**
  - **Liposomal Amphotericin B**
    - 1 x 3-10 mg/kg/d
  - **Itraconazole**
    - 1 x 400 mg/d
  - **Posaconazole iv/tab**
    - 2 x 300 mg/d d1; 1 x 300 mg/d from d2

Legend:
- strongly recommended
- moderately recommended
- marginally recommended
- recommended against

* Choice of salvage treatment always depends by the treatment that the patient failed to respond to

Specific considerations on treatment of *Purpureocillium* infections in children

**Evidence** - Only a few cases are reported with good treatment response to AmB formulations\(^{1989,2083,2111}\). In an individual case, successful treatment is described with VCZ\(^{2073}\) (Table 48).
Table 48. Therapy in children for *Purpureocillium* infections

<table>
<thead>
<tr>
<th>Population</th>
<th>Intention</th>
<th>Intervention</th>
<th>SoR</th>
<th>QoE</th>
<th>Reference</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immunocompromised patients</td>
<td>To cure</td>
<td>AmB lipid formulations</td>
<td>C</td>
<td>III</td>
<td>Sillevis Smitt ADC 1997(^{111})</td>
<td>N=1, 12 yrs, lung infection, response</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Tan JCM 1992(^{201})</td>
<td>N=1, 18 mo, fungemia, D-AmB, success</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Silliman J Infect 1992(^{100})</td>
<td>N=1, 4 yrs, two abdominal wall abscesses, D-AmB, response</td>
</tr>
<tr>
<td>Immunocompetent patients with cutaneous infection</td>
<td>To cure</td>
<td>VCZ 400 mg</td>
<td>B</td>
<td>III</td>
<td>Saghrouni Med Mycol 2013(^{2073})</td>
<td>N=1, success</td>
</tr>
</tbody>
</table>

**Treatment duration**

| Immunocompetent patients | To cure cutaneous hyalohyphomycosis | B mo VCZ | C | III | Saghrouni Med Mycol 2013\(^{2073}\) | N=1, success |
| Immunocompromised patients | To cure lung infection | 4 wk AmB | C | III | Sillevis Smitt ADC 1997\(^{111}\) | N=1, 12 yrs, response |

*Standard pediatric dose unless otherwise stated; AmB, liposomal amphotericin B; mo, month(s); QoE, quality of evidence; SoR, strength of recommendation; VCZ, voriconazole; wk, week(s); yrs, years.*

### Recommendations

In line with recommendations in adults, the guideline group moderately supports the use of VCZ and marginally supports the use of L-AmB for treatment in children.

### Summary of Treatment Recommendations

The most important treatment recommendations of this guideline are summarized in Table 49.

### Table 49. Recommended systemic antifungal treatment in adults with other rare mold infections

<table>
<thead>
<tr>
<th>Mold infections caused by / Antifungal Treatment</th>
<th>First line</th>
<th>First Line Alternative</th>
<th>Second Line</th>
<th>Avoid</th>
<th>Salvage*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fusariosis</td>
<td>VCZ or VCZ + L-AmB/ABLC</td>
<td>L-AmB/ABLC</td>
<td>ISA or PCZ</td>
<td>D-AmB</td>
<td>PCZ</td>
</tr>
<tr>
<td>Lomentosporosis</td>
<td>VCZ + TRB</td>
<td>VCZ</td>
<td>ISA or PCZ</td>
<td>L-AmB</td>
<td>VZ</td>
</tr>
<tr>
<td>Scedosporiosis</td>
<td>VCZ</td>
<td>VCZ + L-AmB or VCZ + ABLC or VCZ + Echinocandins or VCZ + TRB</td>
<td>ISA or PCZ or ICZ</td>
<td>L-AmB</td>
<td>VCZ + Echinocandins or PCZ</td>
</tr>
<tr>
<td>Phaeohyphomycosis</td>
<td>VCZ</td>
<td>L-AmB +/- Echinocandin or Triazole</td>
<td>ISA</td>
<td>D-AmB</td>
<td>ISA or PCZ or VCZ</td>
</tr>
<tr>
<td>Phaeohyphomycosis: Cutaneous/Subcutaneous infection</td>
<td>ICZ or VCZ</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phaeohyphomycosis: Disseminated infection</td>
<td>PCZ or VCZ + Echinocandin OR TRB</td>
<td></td>
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<tr>
<td>Phaeohyphomycosis: <em>Exserohilium rostratum</em></td>
<td>VCZ +/- L-AmB</td>
<td>L-AmB + triazoles other than VCZ</td>
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<tr>
<td><em>Rasamsonia</em> spp.</td>
<td>CASPO or MICA</td>
<td>CASPO + L-AmB or PCZ, or MICA + L-AmB or PCZ</td>
<td></td>
<td></td>
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<tr>
<td>Azole monotherapy</td>
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<tr>
<td><em>Schizophyllum</em> spp. and other basidiomycetes: <em>Schizophyllum commune</em></td>
<td>L-AmB; Stepdown to PCZ</td>
<td>VCZ</td>
<td></td>
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<tr>
<td><em>Echinocandins</em></td>
<td>L-AmB or VCZ</td>
<td></td>
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<tr>
<td><em>Scopulariopsis</em> spp.</td>
<td>ISA or VCZ</td>
<td>L-AmB +/- VCZ</td>
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<tr>
<td>PCZ +/- MICA +/- TRB</td>
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<tr>
<td><em>Penicillium</em> spp.: dissemination</td>
<td>L-AmB +/- other antifungals</td>
<td>VCZ</td>
<td></td>
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<tr>
<td><em>Penicillium</em> spp.: lung infection</td>
<td>PCZ</td>
<td></td>
<td></td>
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</tr>
<tr>
<td><em>non-marneffei Talaromyces</em> spp.</td>
<td>L-AmB</td>
<td>VCZ or Echinocandine + TRB</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Paecilomyces</em> spp.</td>
<td>L-AmB</td>
<td>ICZ or PCZ</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Purpureocillium</em> spp.</td>
<td>VCZ</td>
<td>ICZ or L-AmB or PCZ</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Purpureocillium</em> spp.: cutaneous/subcutaneous infection</td>
<td>VCZ + TRB</td>
<td>ICZ or L-AmB or PCZ</td>
<td></td>
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</tr>
</tbody>
</table>

* Detailed recommendations regarding dosages can be found in Table 2.

**Legend:**
- strongly recommended
- moderately recommended
- marginally recommended
- recommended against

**TDM, therapeutic drug monitoring**

* Choice of salvage treatment always depends by the treatment that the patient failed to respond to
Future directions

Unmet needs

Despite recent advances in diagnostic testing and antifungal therapies, significant challenges remain in the management of rare mold infections. Diagnosis is based on conventional identification methods and culture, with molecular-based identification and testing often requiring referral to specialist laboratories with an expertise in phenotypic identification, including ECMM Excellence Centers\textsuperscript{17}. Even when available, molecular identification using standardized sequencing techniques is mostly restricted to identification of isolates, while more rapid tests that can be applied directly to clinical samples are needed\textsuperscript{2112}. A promising method for faster identification of fungal isolates is MALDI-TOF MS, though current CE certified databases need to be substantially enhanced to become clinically useful and additional research is needed to reliably identify molds. MALDI-TOF MS requires a large number of strains to generate reliable reference data for identification. In order to improve molecular identification methods and MALDI-TOF MS libraries or develop new diagnostic tools, comprehensive well-curated and publicly accessible collections of clinical isolates need to be maintained at central repositories for research purposes. Since randomized trials are impractical due to the rare occurrence of these infections, prospective and detailed clinical registries such as the FungiScope registry\textsuperscript{10,367}, are important to refine treatment strategies, which may be specifically tailored for a particular pathogen and clinical syndrome. Furthermore, development of unique animal models for some of these fungi is important for validation of some of the current therapeutic recommendations and for development of novel therapies, including immunomodulatory treatment. Finally, establishment of an online, searchable database of infections caused by rare molds, their clinical presentations and antifungal susceptibilities would assist in the management of difficult cases. In the digital era, we are now able to connect data sources globally to help optimize therapy of these often refractory infections.
**Priority research questions**

The immediate research questions are similar for the individual rare molds. Common research themes for the rare molds are the need to develop better diagnostic tools and antifungal agents, as well as to identify unique biomarkers, understand pathogenesis and elucidate host defense mechanisms.

1. Improved diagnostics: Culture-based diagnostics are slow or may be falsely negative due to various factors including ongoing antifungal treatment or prophylaxis. Biopsies are not always possible due to associated risks for the patients. Although non-culture-based diagnostics including point-of-care tests and molecular diagnostics have been developed for aspergillosis and to some extent also mucormycosis, the rare molds remain difficult to diagnose in a timely manner due to lack of rapid diagnostic tests. Research should focus on rapid diagnostic tests that may involve PCR testing. Although pan-fungal PCR targeting the ITS1 region of the ribosomal RNA gene can identify rare molds, this test is most accurate on fresh tissue in which hyphae are visible and less useful for samples containing low amounts of mold. Furthermore, multiplex PCR testing using the ITS1 and ITS2 regions as well as beta-tubulin on blood cultures, which have flagged positive has identified molds such as *Fusarium* spp. and *L. prolificans*. However, more sensitive targeted tests which could predict or identify development of invasive infection earlier than traditional methods and could impact on management of these infections, which are often only diagnosed with advanced infection, are needed.

Other advances include metabolite mass spectrometry of breath samples to identify volatile organic compound signatures specific for fungi, which has been successfully applied for diagnosis of invasive pulmonary aspergillosis and could be extended to invasive pulmonary infections with other molds. Metagenomic sequencing of blood or body fluids is now possible but while there is some experience in using this to detect bacteria and viruses, fungi have not been evaluated. The same applies for high resolution melting techniques. Inexpensive and portable se-
quencing machines will make these technologies widely available and may be a solution in countries without laboratory infrastructure\textsuperscript{2129}. Innovative technologies, such as clustered regularly interspaced short palindromic repeats (CRISPR)-based diagnostic tools, may lead to point-of-care assays\textsuperscript{2128}. PET CT or MRI scans with \textit{Aspergillus} antibodies or siderophores labelled to nuclear medicine isotopes have been used to diagnose aspergillosis\textsuperscript{2130,2131}, but rely on sensitive and specific fungal biomarkers that will need to be developed for these rare conditions\textsuperscript{2132}. Finally, future studies are needed to search for laboratory markers for treatment response assessment, including immunologic markers\textsuperscript{2121,2133}.

2. Improved treatments: With a limited number of antifungals currently available, there is an urgent need for studies designed to establish a correlation between \textit{in vitro} susceptibility results and \textit{in vivo} response, to better target treatment. Due to a number of new antifungal agents in the development pipeline, options for treating these difficult infections may improve in the near future\textsuperscript{2134}. Olorofim is currently being evaluated in human studies and has activity against \textit{L. prolificans}, \textit{Scedosporium} spp.\textsuperscript{560,2135}, and some \textit{Fusarium} spp.\textsuperscript{2136}. Evaluation of activity against the other rare molds is urgently required. Drugs in an earlier phase of development that have shown activity against rare molds include auranofin with \textit{in vitro} activity against \textit{Lomentospora} spp. and \textit{Scedosporium} spp., although the mechanism of action is yet unclear\textsuperscript{2137}. The glycosylphosphatidylinositol (GPI) synthesis inhibitor fosmanogepix, which weakens the cell wall and impairs fungal growth has \textit{in vitro} activity against \textit{Fusarium} spp., black molds, \textit{Lomentospora} spp., \textit{Scedosporium} spp., and \textit{P. lilacinum}\textsuperscript{2138}. This drug also was successful in a neutropenic mouse model of disseminated fusariosis\textsuperscript{2139}. To bring these promising new agents to clinical practice requires a concerted collaborative effort and partnerships between industry, regulators, and clinicians, which will be critical. Mechanisms of antifungal resistance in these rare molds should be further studied in order to develop new antifungal agents to overcome intrinsic resistance, an example being \textit{L. prolificans} and triazoles\textsuperscript{2140}.
Beyond drug therapy, adoptive T-cell therapy\textsuperscript{2141}, chimeric antigen receptor (CAR) T cells (artificially designed receptors that are introduced into T cells) \textsuperscript{2142} and neutrophils engineered with bifunctional small molecules that bind the antifungal targets and have immunostimulatory compounds to enhance the immune response\textsuperscript{2143} are possibly feasible approaches, which should be assessed.

3. The mycobiome: The third research question is understanding the mycobiome of sites such as the respiratory tract, the gastrointestinal tract, and skin in healthy subjects and during immunosuppression and if this is a factor in allowing rare molds to become invasive\textsuperscript{2144-2147}.

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