

See discussions, stats, and author profiles for this publication at: <https://www.researchgate.net/publication/349364391>

Global guideline for the diagnosis and management of rare mould infections: an initiative of the European Confederation of Medical Mycology in cooperation with the International So...

Article in *The Lancet Infectious Diseases* · February 2021

DOI: 10.1016/S1473-3099(20)30784-2

CITATIONS

2

READS

254

56 authors, including:



Martin Hoenigl

University of California, San Diego

312 PUBLICATIONS 4,377 CITATIONS

[SEE PROFILE](#)



Thomas J Walsh

Weill Cornell Medicine of Cornell University and New York Presbyterian Hospital

1,066 PUBLICATIONS 83,401 CITATIONS

[SEE PROFILE](#)



Marcio Nucci

Federal University of Rio de Janeiro

307 PUBLICATIONS 13,257 CITATIONS

[SEE PROFILE](#)



Michaela Lackner

Medizinische Universität Innsbruck

235 PUBLICATIONS 2,989 CITATIONS

[SEE PROFILE](#)

Some of the authors of this publication are also working on these related projects:



Antifungal susceptibility of *Cryptococcus* species [View project](#)



Infection Prevention and control [View project](#)



Global guideline for the diagnosis and management of rare mould infections: an initiative of the European Confederation of Medical Mycology in cooperation with the International Society for Human and Animal Mycology and the American Society for Microbiology

Martin Hoenigl, Jon Salmanton-García, Thomas J Walsh, Marcio Nucci, Chin Fen Neoh, Jeffrey D Jenks, Michaela Lackner, Rosanne Sprute, Abdullah M S Al-Hatmi, Matteo Bassetti, Fabianne Carlesse, Tomas Freiburger, Philipp Koehler, Thomas Lehrnbecher, Anil Kumar, Juerge Prattes, Malcolm Richardson, Sanjay Revankar, Monica A Slavin, Jannik Stemler, Birgit Spiess, Saad J Taj-Aldeen, Adilia Warris, Patrick C Y Woo, Jo-Anne H Young, Kerstin Albus, Dorothee Arenz, Valentina Arsic-Arsenijevic, Jean-Philippe Bouchara, Terrence Rohan Chinniah, Anuradha Chowdhary, G Sybren de Hoog, George Dimopoulos, Rafael F Duarte, Petr Hamal, Jacques F Meis, Sayoki Mfinanga, Flavio Queiroz-Telles, Thomas F Patterson, Galia Rahav, Thomas R Rogers, Coleman Rotstein, Retno Wahyuningsih, Danila Seidel, Oliver A Cornely

With increasing numbers of patients needing intensive care or who are immunosuppressed, infections caused by moulds other than *Aspergillus* spp or *Mucorales* are increasing. Although antifungal prophylaxis has shown effectiveness in preventing many invasive fungal infections, selective pressure has caused an increase of breakthrough infections caused by *Fusarium*, *Lomentospora*, and *Scedosporium* species, as well as by dematiaceous moulds, *Rasamsonia*, *Schizophyllum*, *Scopulariopsis*, *Paecilomyces*, *Penicillium*, *Talaromyces* and *Purpureocillium* species. Guidance on the complex multidisciplinary management of infections caused by these pathogens has the potential to improve prognosis. Management routes depend on the availability of diagnostic and therapeutic options. The present recommendations are part of the One World—One Guideline initiative to incorporate regional differences in the epidemiology and management of rare mould infections. Experts from 24 countries contributed their knowledge and analysed published evidence on the diagnosis and treatment of rare mould infections. This consensus document intends to provide practical guidance in clinical decision making by engaging physicians and scientists involved in various aspects of clinical management. Moreover, we identify areas of uncertainty and constraints in optimising this management.

Background

Although invasive aspergillosis and mucormycosis have been the most commonly documented invasive mould infections,¹ mycoses caused by rare moulds are increasing.² These pathogens include dematiaceous moulds that cause phaeohyphomycosis, *Fusarium*, *Lomentospora*, *Scedosporium*, *Rasamsonia*, *Scopulariopsis*, *Penicillium*, *Talaromyces* species other than *T marneffeii*, *Paecilomyces*, *Purpureocillium* and *Schizophyllum* species, and other basidiomycetes.^{3–6} Maximising survival to these infections requires readily available guidance to allow rapid diagnostic and therapeutic intervention.⁷ Current guidelines are limited to individual rare mould pathogens or specific patient groups,^{8–10} or do not exist for many rare mould infections.

The European Confederation of Medical Mycology (also known as ECMM),¹¹ together with the International Society for Human and Animal Mycology (also known as ISHAM) and the American Society for Microbiology (also known as ASM), issue this comprehensive guidance document as part of their One World—One Guideline initiative,^{7,12} to facilitate clinical decision making and simultaneously provide an overview of the areas of uncertainty in invasive mould infections. We aimed to address limitations of previous recommendations by engaging physicians and scientists involved in all aspects

of the management of rare mould infections. In addition, the guideline group includes experts from all UN regions, and provides management approaches for settings with different availability of diagnostic and therapeutic options.

In January, 2018, experts were identified based on their publication activity in the field of rare mould infections in the previous 5 years, their involvement in patient management, and their distribution across the world regions as defined by the UN. Experts were invited in February, 2018, to develop this guideline, and video-conferences to discuss the methods and a mandatory video tutorial on guideline methodology were held between February and March, 2018. Supervision of the group was provided by the coordinators (MH, DS, and OAC). Documents were shared among the authors on a password-protected OneDrive repository, and were centrally managed and kept up to date with any new developments. Once all tables were finalised, a writing group contributed the first draft, which was circulated to all participants for approval in Jan 3, 2020. Recommendations were consensus-based; if no consensus was achieved, a majority vote of over 50% was used.

In April, 2020, a 4 week public consultation phase took place. Received comments were evaluated and used to modify the manuscript as appropriate, resulting in a

Lancet Infect Dis 2021

Published Online
February 16, 2021
[https://doi.org/10.1016/S1473-3099\(20\)30784-2](https://doi.org/10.1016/S1473-3099(20)30784-2)

Section of Infectious Diseases and Tropical Medicine, Medical University of Graz, Graz, Austria (M Hoenigl MD, J Prattes MD); Division of Infectious Diseases and Global Public Health, Department of Medicine (M Hoenigl, J D Jenks MD), Clinical and Translational Fungal Research Working Group (M Hoenigl, J D Jenks), and Division of General Internal Medicine, Department of Medicine (J D Jenks), University of California San Diego, San Diego, CA, USA; Faculty of Medicine (J Salmanton-García PhD, R Sprute MD, P Koehler MD, J Stemler MD, K Albus MSc, D Arenz PhD, D Seidel PhD, Prof O A Cornely MD), Cologne Excellence Cluster on Cellular Stress Responses in Aging-Associated Diseases (J Salmanton-García, P Koehler, K Albus, D Arenz, D Seidel, Prof O A Cornely), and Clinical Trials Center Cologne (Prof O A Cornely), University of Cologne, Cologne, Germany; German Centre for Infection Research, partner site Bonn-Cologne, Cologne, Germany (R Sprute, P Koehler, J Stemler, D Seidel, Prof O A Cornely); Department of Medicine, Department of Pediatrics, and Department of Microbiology and Immunology, Weill Cornell Medicine, New York, NY, USA (Prof T J Walsh MD); New York

Presbyterian Hospital, Weill Cornell Medical Center, New York, NY, USA (Prof T J Walsh); Department of Internal Medicine, Federal University of Rio de Janeiro, Rio de Janeiro, Brazil (M Nucci MD); Faculty of Pharmacy, and Collaborative Drug Discovery Research Group, Pharmaceutical and Life Sciences, Community of Research, Universiti Teknologi MARA, Selangor, Malaysia (C F Neoh PhD); Institute of Hygiene and Medical Microbiology, Department of Hygiene, Medical Microbiology and Public Health, Medical University Innsbruck, Innsbruck, Austria (M Lackner PhD); Department of Microbiology, Natural & Medical Sciences Research Center, University of Nizwa, Nizwa, Oman (A M S Al-Hatmi PhD); Division of Infections Diseases, Department of Health Sciences, IRCCS San Martino Polyclinic Hospital, University of Genoa, Genoa, Italy (Prof M Bassetti MD); Department of Pediatrics, and Pediatric Oncology Institute IOP-GRAACC-UNIFESP, Federal University of São Paulo, São Paulo, Brazil (F Carlesse MD); Centre for Cardiovascular Surgery and Transplantation, and Faculty of Medicine, Masaryk University, Brno, Czech Republic (T Freiburger MD); Center for Integrated Oncology Aachen Bonn Cologne Duesseldorf, Cologne, Germany (P Koehler); Division of Pediatric Hematology and Oncology, Hospital for Children and Adolescents, University Hospital, Frankfurt, Germany (T Lehnbecher MD); Department of Microbiology, Amrita Institute of Medical Sciences and Research Centre, Amrita Vishwa Vidyapeetham, Kochi, India (Prof A Kumar MD); Division of Infection, Immunity and Respiratory Medicine, University of Manchester, Manchester, UK (Prof M Richardson PhD); Mycology Reference Centre Manchester, Manchester University NHS Foundation Trust, Manchester, UK (Prof M Richardson); Division of Infectious Diseases, Wayne State University, Detroit, MI, USA (S Revankar MD);

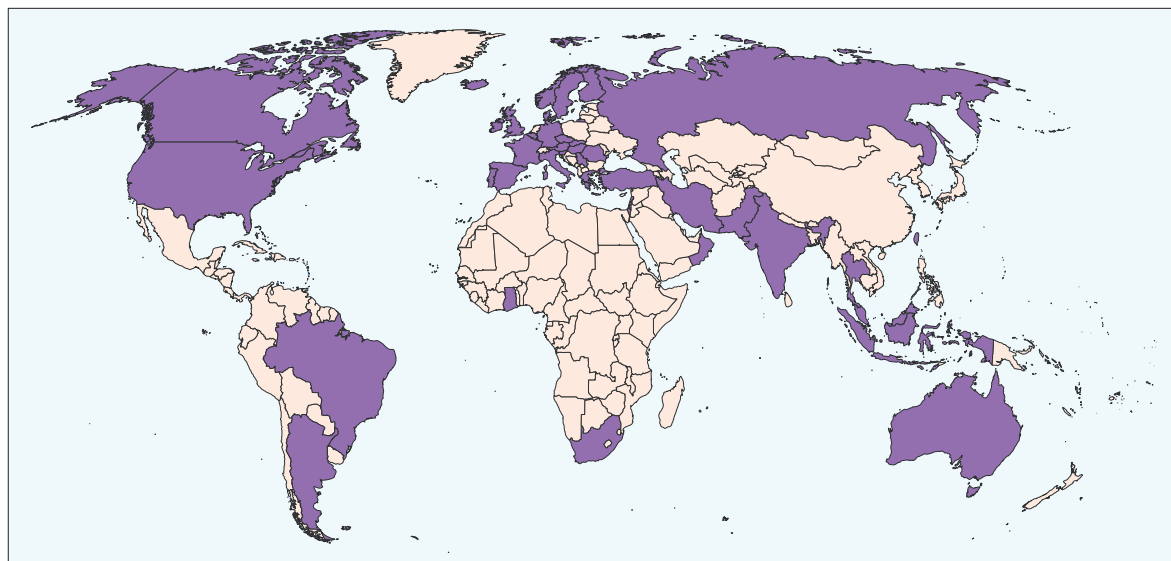


Figure 1: Countries whose national mycology societies endorse this Rare Mould Guideline. Purple indicates endorsement.

final author review in July 2, 2020. Detailed methods on how the guideline group worked and the worldwide distribution of experts involved in the process is displayed in the appendix pp 5–8, and closely follows the recent guideline on mucormycosis.⁷

A total of 55 scientific societies focusing on medical mycology, microbiology, and infectious diseases reviewed and endorsed the guidance document (figure 1).

Fusariosis

Epidemiology of fusariosis

Fusarium spp are the most clinically prevalent rare moulds causing superficial infections, such as keratitis, in immunocompetent hosts, and severe disseminated infections (frequently presenting as fungaemia) in immunocompromised individuals. These fungi are ubiquitous in nature and are found in soil and air.¹³ Of particular importance are the species complexes *Fusarium solani* (causing more than 50% of severe cases) and *Fusarium oxysporum* (causing 20% of severe cases).^{13,14} The main routes of infection are inhalation of airborne microconidia or direct inoculation through traumatic injury, including burns. In immunocompromised hosts, especially patients with an haematological malignancy and neutropenia, or undergoing haematopoietic stem cell transplantation or solid organ transplantation, fusariosis manifests as an invasive infection mainly affecting the skin, deep soft tissue, the lungs, and sinuses.^{14,15} *Fusarium* spp frequently disseminate in the host, with positive blood cultures in as much as 70% of cases in immunocompromised patients.¹⁵ This ease in propagation might be related to the ability of some *Fusarium* spp to form in-vivo adventitious conidia (aleurioconidia), which can then break away from invading hyphae and enter the blood stream.¹⁶ Necrotic

erythematous papular or nodular skin lesions are often evident in immunocompromised patients with systemic fusariosis, and are a distinctive characteristic of these infections.¹⁷

The incidence and prevalence of *Fusarium* spp infections vary depending on the underlying disease and geographical region, reaching 20 per 1000 recipients of allogeneic haematopoietic stem cell transplantation with HLA-mismatched related donors in Brazil and the USA.^{18,19}

Diagnosis of fusariosis

Blood cultures are positive in 40% of invasive cases,²⁰ with faster detection of growth in fungal blood culture bottles compared with standard aerobic bottles.²¹ Direct examination of tissue, especially skin biopsy, allows for a rapid evaluation before culture results are available, if the tissue sample can be examined in a timely way.²⁰ To diagnose fungal keratitis, histopathological examination and culture of corneal scrapings are used.¹⁷ In fresh tissue, the hyphae are morphologically similar to those of *Aspergillus* spp—that is, appearing as hyaline septate filaments that typically dichotomise in acute angles, or sometimes reaching 90°. Adventitious sporulation can be present, and the presence of reniform adventitious conidia is highly suggestive of fusariosis (figure 2, appendix pp 11–19).²²

First-line treatment of fusariosis in adults

Evidence

To our knowledge, there are no randomised trials evaluating the efficacy of antifungal drugs for the treatment of invasive fusariosis. The largest study published to date is a multicentre retrospective study of 236 patients with invasive fusariosis, diagnosed between

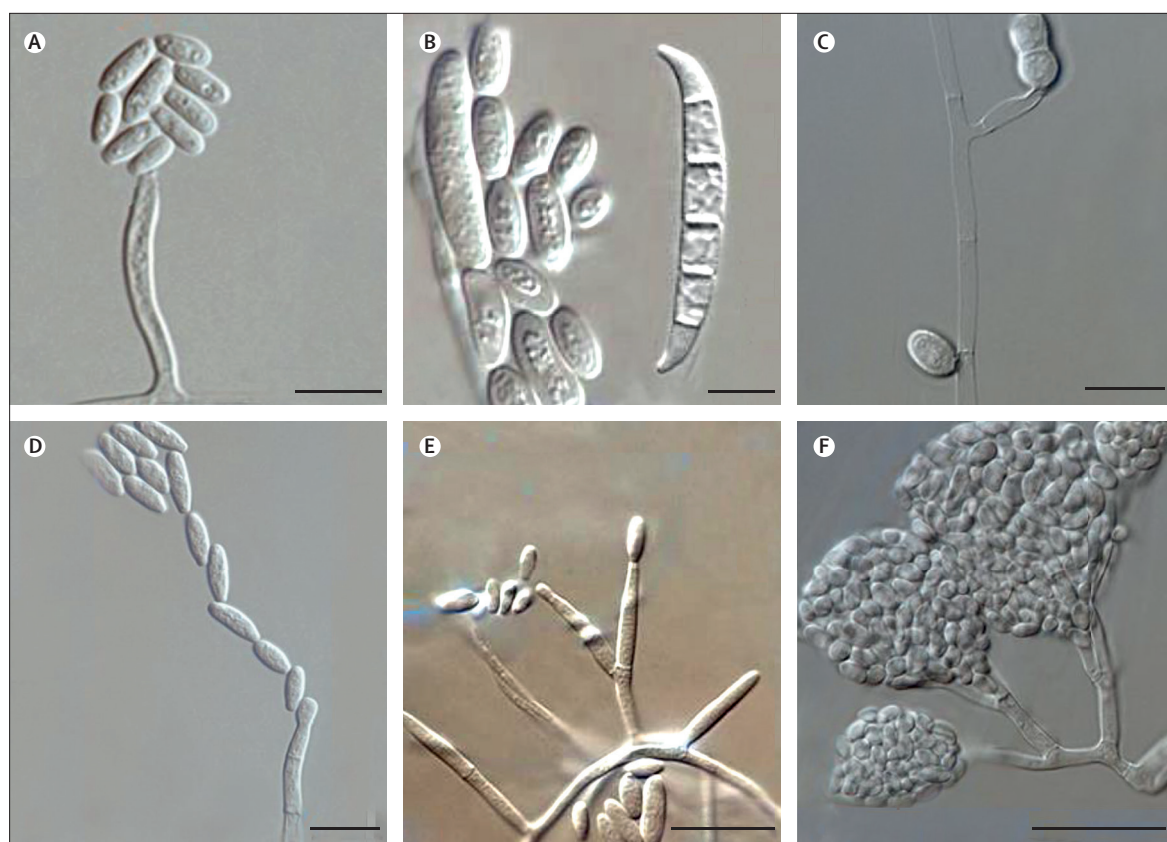


Figure 2: Microscopic morphology of *Fusarium* spp.²³

Scale bar=10 μm. (A) Microconidia on conidiogenous cells or monophialides (*Fusarium acutatum* [*Fusarium fujikuroi* species complex]). (B) Microconidia and macroconidia (*Fusarium metavorans* [*Fusarium solani* species complex]). (C) Young (bottom) and mature (top) chlamydospores (*Fusarium keratoplasticum* [*F solani* species complex]). (D) Microconidia in chain (*Fusarium musae* [*F fujikuroi* species complex]). (E) Monophialides with microconidia (*Fusarium pseudensiforme* [*F solani* species complex]). (F) Monophialides with microconidia (*Fusarium petrophilum* [*F solani* species complex]).

1985 and 2011 in 44 centres from 11 countries worldwide.¹⁵ Among 206 patients who received treatment for invasive fusariosis, 185 received monotherapy: 110 received amphotericin B deoxycholate, 38 were treated with voriconazole, 34 were treated with a lipid formulation of amphotericin B (20 patients with liposomal formulation, six with colloidal dispersion, and eight with lipid complex, which in a previous study was less well tolerated and caused more acute infusion-toxicity than the liposomal formulation²⁴), and three received other therapies. The 90 day probability of survival was 27% for patients treated with amphotericin B deoxycholate, 53% for patients receiving voriconazole, and 48% for patients receiving a lipid formulation of amphotericin B.

Other studies reported lower numbers of patients receiving primary treatment with a single agent for invasive fusariosis: either voriconazole (55 patients, including with localised disease, had response rates ranging from 44% to 100%),^{5,13,25–28} amphotericin B lipid complex (28 patients, 43% response rate),²⁹ liposomal amphotericin B (ten patients, response rates of either 0% or 100%; appendix p 23 for additional

references),^{5,30} and amphotericin B deoxycholate (five patients, 20% response rate).³⁰ Single case reports have reported successful treatment with either isavuconazole, terbinafine, or posaconazole, and no response to treatment with echinocandin therapy.^{27,31,32}

Combination therapy with voriconazole plus liposomal amphotericin B or another agent was reported in most studies, and is the preferred initial approach in many specialised centres because of the frequently observed high minimum inhibitory concentration of voriconazole, whereas other centres prefer monotherapy.^{5,13,15,25,27,28,32,33} Response rates with combination therapy overall were similar to monotherapy, and there are no randomised controlled trials comparing monotherapy with combination therapy. In one retrospective study, combination therapy was used in 21 (9%) of 236 patients.¹⁵ Response rates in patients treated with combination therapy were not significantly different than those of patients treated with monotherapy.¹⁵ However, as combination therapy might have been used in the most critically ill patients, no conclusions about the efficacy of combination therapy over monotherapy can be drawn from this study.

University of Melbourne, Melbourne, VIC, Australia (Prof M A Slavin MD); National Centre for Infections in Cancer, Peter MacCallum Cancer Centre, Melbourne, VIC, Australia (Prof M A Slavin); Department of Hematology and Oncology, University Hospital Mannheim, Heidelberg University, Mannheim, Germany (B Spiess PhD); Department of Laboratory Medicine and Pathology, Hamad Medical Corporation, Doha, Qatar (S J Taj-Aldeen PhD); Medical Research Council Centre for Medical Mycology, University of Exeter, Exeter, UK (A Warris MD); Department of Microbiology, University of Hong Kong, Hong Kong, China (P C Y Woo MD); University of Minnesota, Minneapolis, MN, USA (Prof J A H Young MD); Medical Center Hamburg-Eppendorf, University of Hamburg, Hamburg, Germany (D Arenz); National Reference Laboratory for Medical Mycology, Institute of Microbiology and Immunology, Faculty of Medicine, University of Belgrade, Belgrade, Serbia (V Arsic-Arsenijevic MD); Host-Pathogen Interaction Study Group, and Laboratory of Parasitology and Mycology, Angers University Hospital, Angers University, Angers, France (J-P Bouchara PhD); Department of Microbiology, University of Colombo, Colombo, Sri Lanka (T R Chinniah MD); Department of Medical Mycology, Vallabhbhai Patel Chest Institute, University of Delhi, Delhi, India (A Chowdhary MD); Department of Medical Microbiology and Infectious Diseases (Prof J F Meis MD) and Center of Expertise in Mycology (G S de Hoog PhD, Prof J F Meis), Radboud University Medical Center-Canisius Wilhelmina Hospital, Nijmegen, Netherlands; Critical Care Department, Attikon University Hospital, National and Kapodistrian University of Athens, Greece (G Dimopoulos MD); University Hospital Puerta de Hierro Majadahonda, Madrid, Spain (R F Duarte MD); Department of Microbiology, Faculty of Medicine and

Dentistry, University Hospital Olomouc, Palacky University Olomouc, Olomouc, Czech Republic (P Hamal MD); National Institute for Medical Research, Tanzania (S Mfinanga MD); Muhimbili University of Health and Allied Sciences, Dar es Salaam, Tanzania (S Mfinanga); Nelson Mandela African Institution of Science and Technology, Arusha, Tanzania (S Mfinanga); Department of International Public Health, Liverpool School of Tropical Medicine, Liverpool, UK (S Mfinanga); Department of Public Health, Clinics Hospital, Federal University of Parana, Curitiba, Brazil (F Queiroz-Telles MD); UT Health San Antonio and South Texas Veterans Health Care System, San Antonio, TX, USA (Prof T F Patterson MD); Sheba Medical Center, and Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel (G Rahav MD); Department of Clinical Microbiology, Trinity College Dublin, St James's Hospital Campus, Dublin, Ireland (T R Rogers MD); Division of Infectious Diseases, University of Toronto, Toronto, ON, Canada (C Rotstein MD); Department of Parasitology, Faculty of Medicine, Universitas Indonesia, Jakarta, Indonesia (R Wahyuningsih MD); Department of Parasitology, Faculty of Medicine, Universitas Kristen Indonesia, Jakarta, Indonesia (R Wahyuningsih); European Confederation of Medical Mycology Council, Basel, Switzerland (M Hoenigl, V Arsic-Arsenijevic, P Hamal, Prof J F Meis, Prof O A Cornely)

Correspondence to: Dr Martin Hoenigl, Division of Infectious Diseases and Global Public Health, Department of Medicine, University of California, San Diego, CA 92103, USA
hoeniglmartin@gmail.com

See Online for appendix

Recommendations

We strongly recommend voriconazole or a lipid formulation of amphotericin B for the primary treatment of invasive fusariosis. Amphotericin B deoxycholate should not be used if 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 in achieving voriconazole trough concentrations within the targeted range, and because minimum inhibitory concentrations for azoles and polyenes are often high. Primary combination therapy, with a potential early step down to monotherapy later (once minimum inhibitory concentrations of the azole and polyenes become available) is an approach we strongly recommend (figure 3).

Lomentosporiosis

Epidemiology of lomentosporiosis

Lomentospora prolificans (formerly *Scedosporium prolificans*) is morphologically and clinically distinct from *Scedosporium* spp, although before phylogenetic profiling both genera were classed together.³⁴ *L. prolificans* is ubiquitously found as a soil saprophyte, predominantly in the arid climates of Australia, southwestern USA, and Spain, which is reflected by the proportionally high number of reported cases in these regions.^{35–37} Prevalence and incidence data for lomentosporiosis are largely unknown. In a US study, *L. prolificans* accounted for one (2%) of 53 mould infections and one (6%) of 16 non-*Aspergillus* infections identified in recipients of liver and heart transplants; in another US mixed-cohort study, eight (35%) of 23 non-*Aspergillus* mould infections were reported to be *L. prolificans*.^{5,38} A map outlining the worldwide distribution of lomentosporiosis is included in the appendix p 36.

Diagnosis of lomentosporiosis

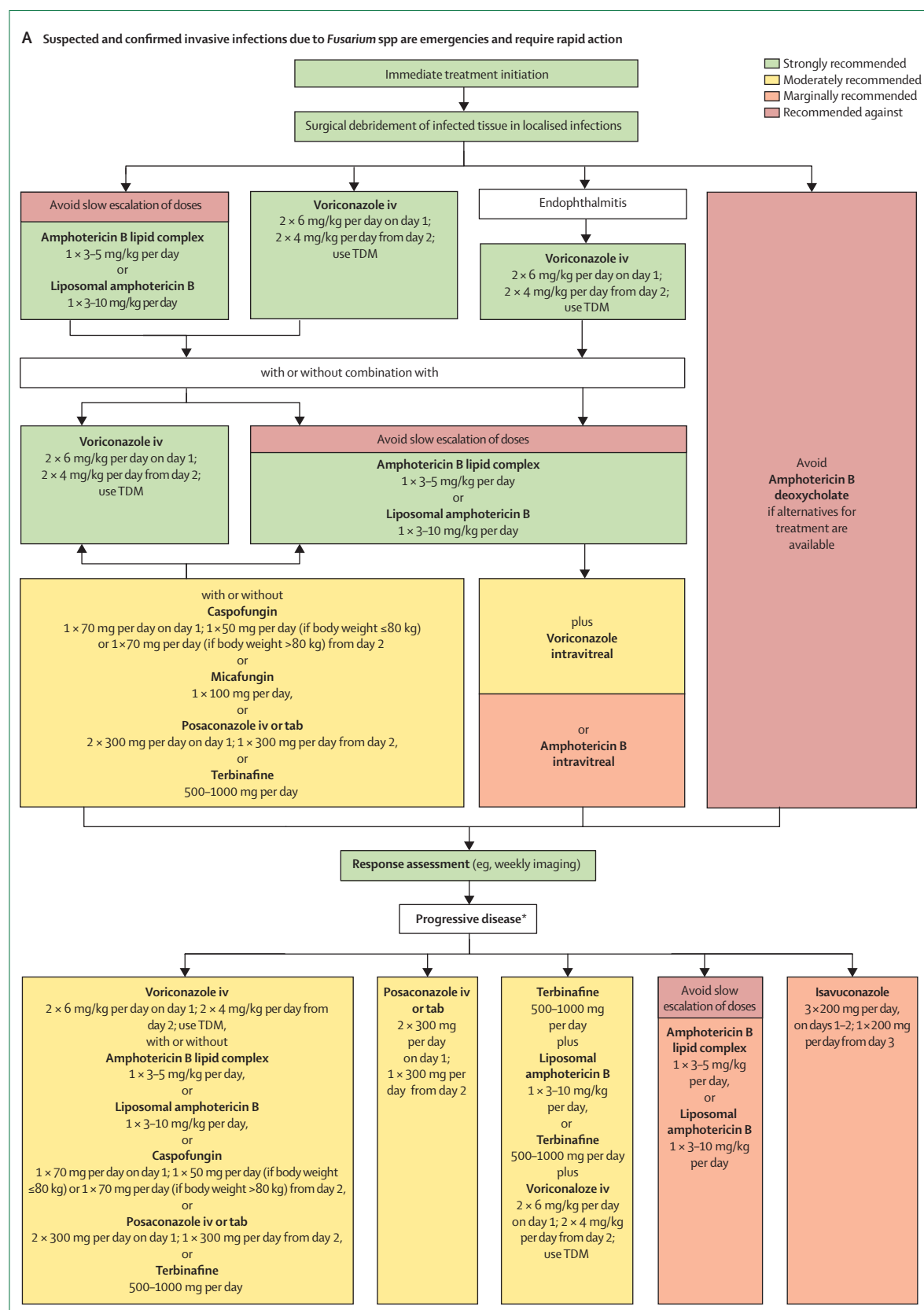
The definitive diagnosis of *L. prolificans* infection relies on the isolation of the fungus from biopsies, sterile body fluids, and blood cultures.^{8,39} For respiratory tract samples of patients with cystic fibrosis, a special selective medium, SceSel+, has shown improved rates of isolation when compared with other mediums, as it inhibits the overgrowth of aspergilli.^{40,41} Other selective fungal culture media that have been successfully used are the inhibitory mould agar and the brain heart infusion agar.⁴² If none of the three are available, specimens can be cultured on sabouraud dextrose agar or horse blood agar at 30°C or 37°C.^{43,44} By contrast with *Scedosporium*, *L. prolificans* is unable to grow in the presence of cycloheximide.⁴⁵ Species identification is achieved through macroscopic and microscopic examination of the colonies. *L. prolificans* is usually characterised by the black colour of its colonies and its characteristic flask-shaped and annellated conidiogenous cells, but identification should be confirmed by subsequent internal transcribed spacer gene sequencing.⁴⁵ *L. prolificans* can form pigmented hyphae, observable under

direct microscopy in infected tissue sections; the organism is therefore classified as a cause of phaeohyphomycosis (figure 4, appendix pp 36–43).^{8,39}

First-line treatment of lomentosporiosis in adults

Evidence

L. prolificans appears to be intrinsically resistant to most antifungals,^{46,47} with voriconazole showing the highest in-vitro activity against this fungus.⁴⁷ In the largest case series of lomentosporiosis infections published to date, combination antifungal therapy was associated with higher 28 day survival than monotherapy (15 [63%] of 24 survived vs four [25%] of 16).⁵ Combinations of voriconazole and terbinafine have shown in-vitro synergism.^{46,48} In several case reports and case series, combination antifungal therapy successfully treated lomentosporiosis with various organ involvement patterns and mixed underlying disease, particularly with voriconazole (6 mg intravenously twice daily loading dose, followed by 4 mg intravenously twice daily) plus terbinafine (500 mg daily orally), plus or minus other antifungals.⁴⁹ In one case report, voriconazole plus terbinafine and surgical debridement resulted in suppression of *L. prolificans* osteomyelitis in an immunocompetent woman,⁵⁰ and in a small case series, all three patients treated with voriconazole plus terbinafine combination therapy survived.⁵ In two larger case series, eight (45%) of 18 individuals treated with voriconazole plus terbinafine combination therapy were alive at day 42,⁵¹ and ten (63%) of 16 patients treated with voriconazole plus terbinafine combination therapy plus or minus other antifungals were alive at day 28.⁵² In the second case series,⁵² survival at 84 days and 360 days was significantly higher in patients who received voriconazole plus terbinafine combination therapy plus or minus other antifungals than in patients who received other antifungal therapies.⁵² Combination therapy with voriconazole plus either amphotericin B or micafungin has resulted in treatment response and survival in patients with mixed underlying disease in several case series,^{51,52} although outcomes did not differ compared with patients treated with voriconazole plus terbinafine combination therapy plus or minus other antifungals. In patients with haematological malignancy in one case series, two (50%) of four who were treated with voriconazole plus terbinafine combination therapy survived, whereas none of the three who received itraconazole plus terbinafine or amphotericin B survived.⁴⁴ In a case series of three patients with cystic fibrosis, combination therapy with voriconazole plus micafungin, terbinafine, or inhaled amphotericin B resulted in clinical improvement but not in eradication of the fungus.⁵³ Surgery as an adjuvant treatment has been shown to be significantly associated with survival.⁵² Resection of surgically amenable lesions is an important adjunct to the management of infections caused by *L. prolificans*.⁵⁴ Correction of underlying immune



(Figure 3 continues on next page)

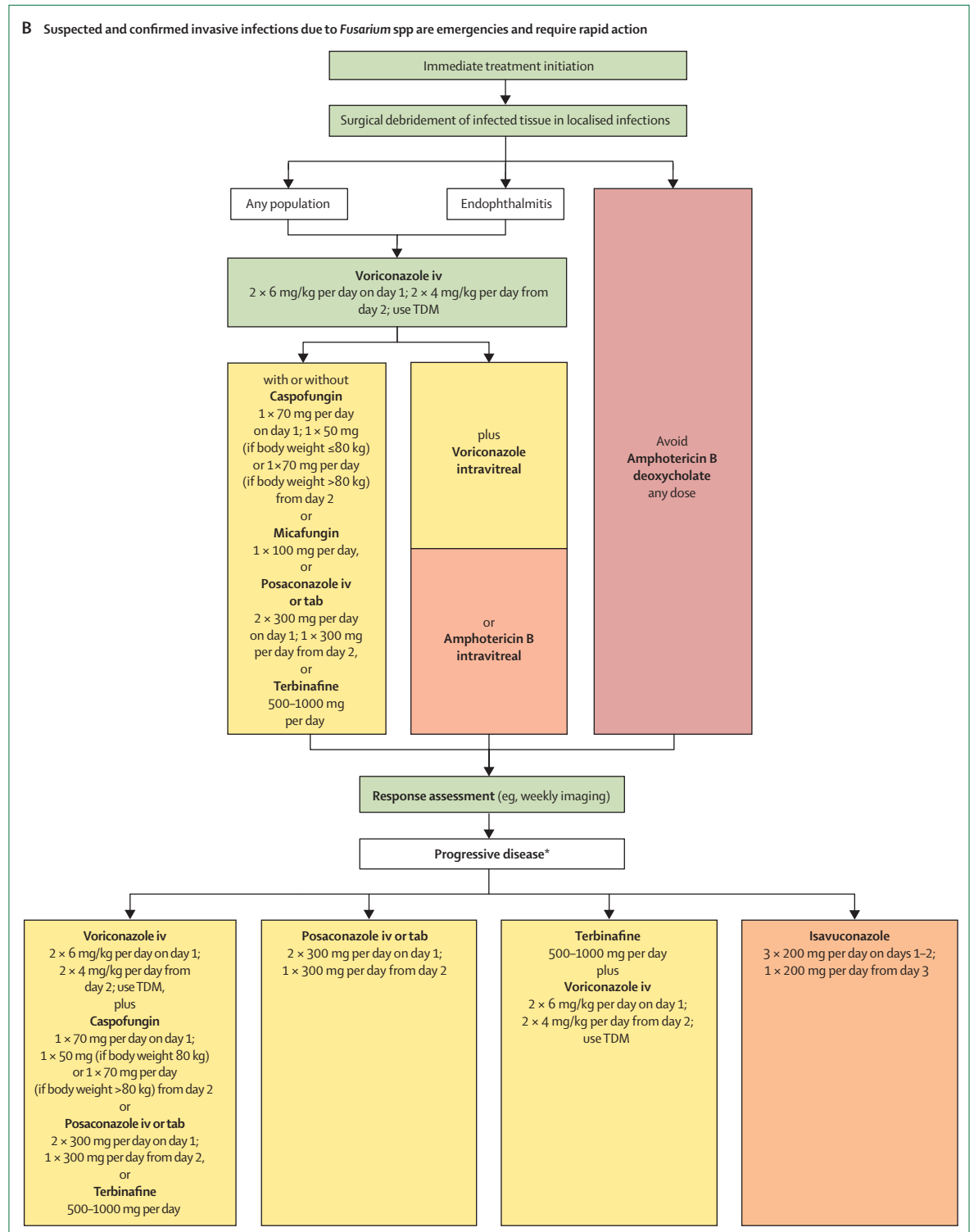


Figure 3: Treatment recommendations for fusariosis

(A) Optimal treatment pathway for fusariosis in adults when all treatment modalities and antifungal drugs are available. (B) If lipid formulation of amphotericin B is not available. iv=intravenously. tab=tablets. TDM=therapeutic drug monitoring. *Choice of salvage treatment always depends by the treatment that the patient did not respond to.

deficiencies is also an important adjunct to antifungal therapy.

Recommendations

The guideline group strongly supports first-line voriconazole-based combination antifungal therapy for the treatment of infections caused by *L. prolificans*, particularly voriconazole plus terbinafine plus or minus other antifungal agents. Monotherapy with voriconazole is moderately supported (appendix pp 44–50).

Scedosporiosis

Epidemiology of scedosporiosis

Scedosporium spp are ubiquitous saprophytes mostly found in temperate areas, with regional differences in species distribution.⁵⁵ In the clinical setting, the most commonly isolated species worldwide are *Scedosporium boydii* and *Scedosporium apiospermum*.

Scedosporium spp initiate two distinct diseases: mycetoma and scedosporiosis. In immunocompetent patients, *Scedosporium* spp are an important cause of eumycotic mycetoma and the most common cause of this infection in the USA.⁵⁶ Solid organ transplantation and treatment for haematological disease are major risk factors for scedosporiosis. Patients predominantly present with pulmonary, cutaneous, or cerebral infections.^{45,51} Secondary CNS infections can appear without an evident dissemination. Infection can also affect the paranasal sinuses or bones.^{45,51}

Scedosporium spp have been recovered from respiratory secretions of patients with chronic pulmonary conditions, such as cystic fibrosis, ranking as the second most frequently isolated fungal pathogen after *Aspergillus* spp.^{35,53} The relevance of *Scedosporium* spp in the context of chronic pulmonary conditions is unknown, but it might be the first step towards invasive disease.^{40,57} Colonisation by *Scedosporium* spp has also been described in patients with cancer.⁵⁸ Near drowning, tsunami, and earthquake victims are at high risk for developing scedosporiosis.⁵⁹ Near drowning has been associated with *S. apiospermum* cerebral infection resulting from haematogenous spread from the lungs as the primary site of infection, or penetration through the cribriform plate with direct invasion of the CNS.^{60–62} Eye infections after traumatic injuries are also common.⁶³

In one study in the USA, *S. apiospermum* accounted for six (11%) of 53 mould infections and three (19%) of 16 non-*Aspergillus* spp infections identified in recipients of liver and heart transplants.³⁸ The incidence of scedosporiosis was 0.93 per 100 000 patient-inpatient days, with a marked increase from 1993 to 2005 in a US cancer centre.⁵⁸

Diagnosis of scedosporiosis

The 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 microscopical and histopathological



Figure 4: Microscopic morphology of *Lomentospora* spp²³

Scale bars=10 µm. (A–F) Conidiogenous cells of *Lomentospora prolificans*, locally aggregated in small flask-shaped brushes. Darker and more inflated conidia may arise alongside hyphae. Smooth-walled conidia aggregate together in slimy heads.

examination of clinical specimens is important for the diagnosis of hyalohyphomycosis, and further discrimination based on microscopy is rarely possible.^{8,39} Branching patterns of *Scedosporium* spp often resemble *Aspergillus* spp, with dichotomously branching septate hyphae sometimes seen in tissue, although branching off to the side at a 60–70° angle, which is different from the 45° angle seen with *Aspergillus* spp. In addition, distinctive coremia or an ascocarp, as well the presence of pyriform adventitious conidia, might identify the mould as *Scedosporium* spp. After a few days, the mould colony takes on a tan colour and has sporulating structures that differ from *Aspergillus* spp (figure 5, appendix pp 52–59).²³

First-line treatment of scedosporiosis in adults

Evidence

Outcomes of voriconazole-based therapy were superior to therapy with any formulation of amphotericin B in several studies.^{51,64} In vitro resistance to amphotericin B formulations, as well as breakthrough infections, have been reported repeatedly.⁵¹ The use of amphotericin B

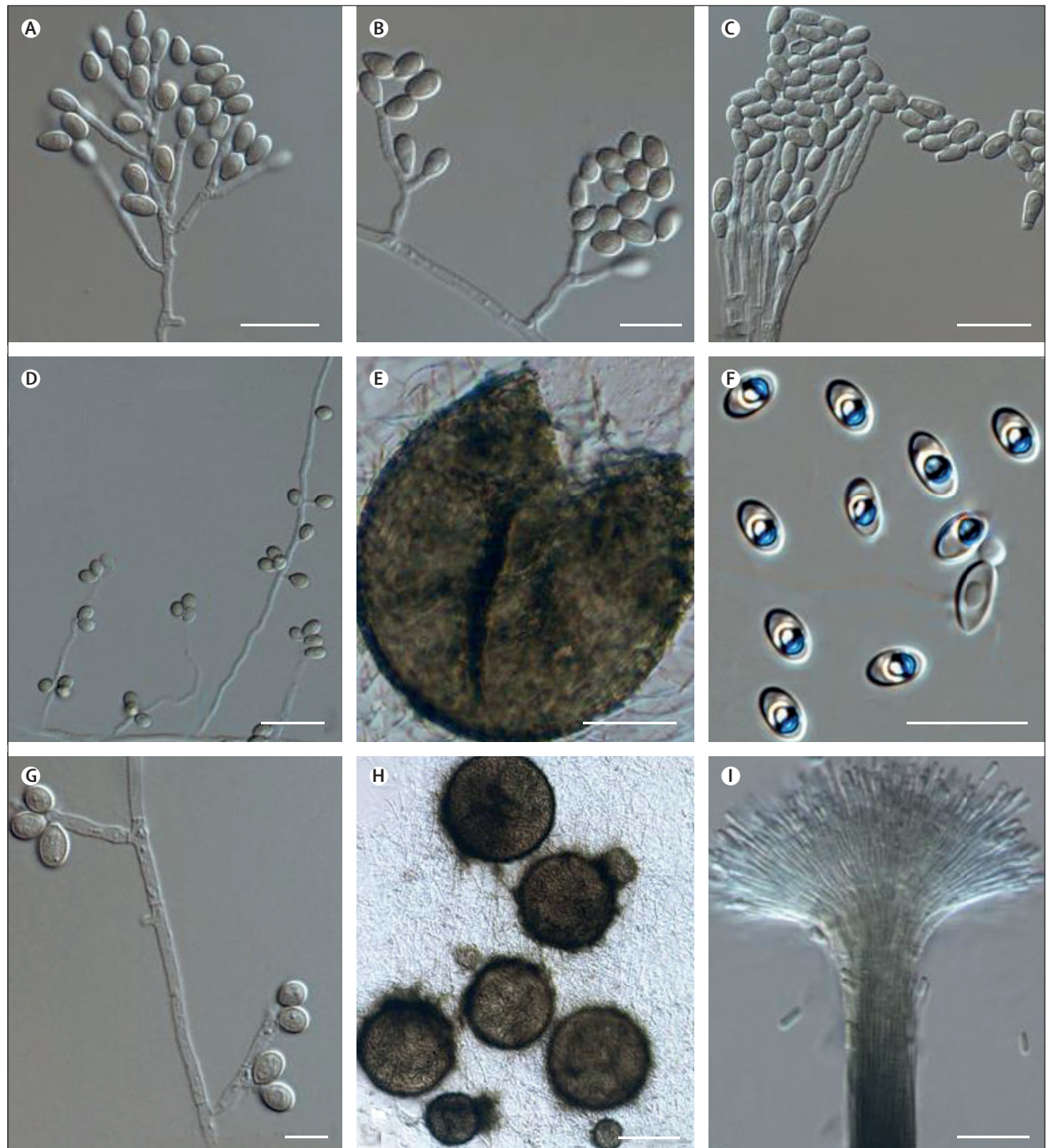


Figure 5: Microscopic morphology of *Scedosporium* spp.²³

Scale bars=10 µm. (A and B) Conidiogenous cells percurrent, lateral or terminal, subhyaline, smooth-walled, usually cylindrical, producing subhyaline, obovoidal, or ellipsoidal conidia (*Scedosporium apiospermum*). (C and D) Conidiogenous cells percurrent, lateral, or terminal (*Scedosporium aurantiacum*). Erect synnemata producing conidi (if synanamorph present). (E and F) Ascogonia and ascospores (*Scedosporium boydii*). (G) Conidiophores and conidia (*Scedosporium dehoogii*). (H and I) Cleistothecia and graphium-like synanamorph (*Scedosporium minutisporum*).

formulations should be restricted to settings in which there is no other antifungal therapy available. There is scarce evidence to support the use of isavuconazole, itraconazole, or posaconazole.^{31,35,44,58} Antifungal combination therapy showed higher efficacy and improved survival compared with amphotericin B monotherapy in multiple studies.^{43,51,53,58} There is a paucity of data

evaluating combination therapy versus voriconazole monotherapy.

Recommendations

First-line treatment with voriconazole is strongly supported across all patterns of organ involvement. Use of amphotericin B formulations is discouraged whenever

	First-line	First-line alternative	Second-line	Treatments to avoid	Salvage treatments
Fusariosis	Voriconazole, or voriconazole plus L-AmB, or voriconazole plus ABLC	L-AmB, or ABLC	Isavuconazole, or posaconazole	D-AmB	Posaconazole
Lomentosporosis	Voriconazole plus terbinafine	Voriconazole	Isavuconazole, or posaconazole	L-AmB	Voriconazole
Scedosporiosis	Voriconazole	Voriconazole in combination with L-AmB, ABLC, echinocandins, or terbinafine	Isavuconazole, or posaconazole, or itraconazole	L-AmB	Voriconazole echinocandins, or posaconazole
Phaeohyphomycosis: localised infection	Voriconazole	L-AmB with or without echinocandins, or triazole	Isavuconazole	D-AmB	Isavuconazole, or posaconazole, or voriconazole
Phaeohyphomycosis: cutaneous or subcutaneous infection	Itraconazole or voriconazole	L-AmB with or without echinocandins, or triazole	Isavuconazole	D-AmB	Isavuconazole, or posaconazole, or voriconazole
Phaeohyphomycosis: disseminated infection	Posaconazole, or voriconazole plus echinocandins, or voriconazole plus terbinafine	L-AmB with or without echinocandins, or triazole	Isavuconazole	D-AmB	Isavuconazole, or posaconazole, or voriconazole
Phaeohyphomycosis: <i>Exserohilum rostratum</i>	Voriconazole with or without L-AmB	..	L-AmB plus triazoles other than voriconazole	D-AmB	..
<i>Rasamsonia</i> spp	Caspofungin, or micafungin	Caspofungin plus L-AmB or posaconazole, or micafungin plus L-AmB or posaconazole	..	Azole monotherapy	..
<i>Schizophyllum commune</i>	L-AmB; stepdown to posaconazole	..	Voriconazole
<i>Schizophyllum</i> spp other than <i>S commune</i> and other basidiomycetes (eg, <i>Coprinopsis cinerea</i> , <i>Hormographiella aspergillata</i>)	L-AmB with or without inhaled L-AmB, or L-AmB with or without voriconazole	..	Voriconazole	Echinocandins	L-AmB, or voriconazole
<i>Scopulariopsis</i> spp	Isavuconazole, or voriconazole	L-AmB with or without voriconazole	Posaconazole with or without micafungin with or without terbinafine
<i>Penicillium</i> spp: disseminated infection	L-AmB with or without other antifungals	Voriconazole
<i>Penicillium</i> spp: lung infection	Posaconazole	Voriconazole
Non-marneffe <i>Talaromyces</i> spp	L-AmB	Voriconazole, or echinocandins plus terbinafine
<i>Paecilomyces</i> spp	L-AmB	Itraconazole, or posaconazole
<i>Purpureocillium</i> spp	Voriconazole	..	Itraconazole or L-AmB or posaconazole	..	Itraconazole, or L-AmB, or posaconazole
<i>Purpureocillium</i> spp: cutaneous or subcutaneous infection	Voriconazole plus terbinafine	..	Itraconazole or L-AmB or posaconazole	..	Itraconazole, or L-AmB, or posaconazole

Figure 6: Recommended systemic antifungal treatment for adults with rare mould infections

The choice of salvage treatment always depends on the treatment that the patient did not respond to. Detailed recommendations regarding doses can be found in the appendix p 19. L-AmB=liposomal amphotericin B. ABLC=amphotericin B lipid complex. D-AmB=amphotericin B deoxycholate.

voriconazole is available. The guideline group marginally supports the use of isavuconazole, itraconazole, or posaconazole for first line-treatment, and moderately supports voriconazole-based antifungal combination therapy (appendix pp 59–67).

Other rare mould infections

This guideline also covers dematiaceous moulds causing phaeohyphomycosis, *Rasamsonia* spp, *Schizophyllum* spp and other basidiomycetes, *Scopulariopsis*, *Paecilomyces*, *Penicillium*, *Talaromyces*, and *Purpureocillium* spp.⁶ A

summary of antifungal treatment recommendations for these agents is displayed in figure 6.

Details on epidemiology, as well as evidence and recommendations for the diagnosis (including photoplates and pathways) and treatment are outlined in the appendix pp 67–161.

Constraints in optimising management

The identification of rare moulds is complicated by the constant change in the nomenclature, which in turn compromises targeted treatment.⁶⁵ Advocates for nomenclatural stability of medically important fungi have maintained that new names for fungal species should not be adapted for clinical use until confirmed by independent laboratories.⁶⁶ Most microbiologists are not familiar with some of the rarest fungal species because they are either rarely encountered or are mistaken for contaminants. This unawareness can be decisive, especially in the case of dematiaceous fungi, in which pathogenicity and resistance to existing antifungal agents varies substantially.^{67,68} Members of the dematiaceous fungi group are emerging opportunists, affecting debilitated and immunosuppressed patients,^{45,69} although they are also known to cause trauma-associated infections and might complicate severe viral infections in otherwise healthy individuals.^{70–72} Optimised treatment of infections due to these rare moulds will remain a challenge while no reliable biomarkers are available.⁷³ Obtaining a tissue diagnosis in deep-seated infections is technically challenging, expensive, and poses a substantial risk to the patients. Diagnosis through conventional microscopy and culture is also difficult, as it is subject to personal interpretation. Molecular testing is expensive, as sequencing will be required for definitive identification. Intrinsic resistance to antifungal agents varies greatly among moulds, with the genera *Fusarium*, *Lomentospora*, and *Scedosporium* being multi-resistant to most currently available antifungals.^{45,68,74} Antifungal susceptibility testing for rare moulds is not standardised and break-points are not available.⁷⁴ A substantial proportion of infections due to rare moulds involve the cornea, especially in low-income to middle-income countries. Treatment of mycotic keratitis is a daunting task because it can include intravitreal injections that can be administered only in tertiary care centres, and topical preparations of amphotericin B and voriconazole are not readily available in these settings.⁷⁵ Both liposomal amphotericin B and voriconazole are costly and beyond the reach of most patients in low-income to middle-income countries, where health-care costs are met by the patients themselves. The availability of cheap and substandard generic antifungals in some of these countries also poses an important and unique challenge in the form of treatment failure and induction of antifungal resistance. Furthermore, given the rareness of these infections, there are no health economic analyses for the corresponding diseases.

Contributors

MH and OAC coordinated the work of the authors and guided the development of the guideline. MH, JS, TJW, MN, CFN, JDJ, ML, RS, AA-H, MB, FC, TF, PK, TL, AK, JP, MR, SR, MAS, JS, BS, SJT-A, AW, PCYW, J-AHY, DS, and OAC wrote the initial manuscript draft. All authors contributed to the literature review, compilation of data, and interpretation and assessment of recommendations. All authors participated in review and revisions, approved the final manuscript and are accountable for all aspects of the work and for ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All authors had access to and verified the data here presented. The contribution of the American Society for Microbiology to this document was a review conducted by Stuart M Levitz MD (University of Massachusetts, Worcester, MA, USA), Audrey N Schuetz MD (Mayo Clinic, Rochester, MN, USA), and Sean X Zhang MD (Johns Hopkins University, Baltimore, MD, USA).

Declaration of interests

MH reports research funding from Gilead, Astellas, Scynexis, and Pfizer; and is supported by the National Institutes of Health. TJW reports grants and personal fees from Allegran, Amplyx, Astellas, Leditant, Medicines Company, Merck, and Scynexis; grant funding from Tetrachase and Viosera, and personal fees from ContraFect, Gilead, Methylgene, and Pfizer. MN reports personal fees from AbbVie, Astellas, Basilea, Bioscanna, Gilead, Janssen, Merck Sharp and Dohme, and Pfizer. JDJ reports research grants from Pfizer and support from the National Institutes of Health. MB reports grants and personal fees from Angelini, Astellas, Bayer, Basilea, Cidara, Gilead, Menarini, Merck Sharp and Dohme, Pfizer, Roche, and Shionogi. FC reports personal fees from Astellas, Pfizer, Teva, and United Medical. TF reports personal fees from the Czech Republic Ministry of Health. PK reports non-financial scientific grants from Miltenyi Biotec and the Cologne Excellence Cluster on Cellular Stress Responses in Aging-Associated Diseases; and lecture honoraria from, or being an advisor to, Akademie für Infektionsmedizin, Ambu GmbH, Astellas, European Confederation of Medical Mycology, Gilead Sciences, Gesundheits- und Pflegezentrum Ruesselsheim Academy Ruesselsheim, Merck Sharp and Dohme, Noxxon, and University Hospital of Munich. TL reports grant and personal fees from Gilead; and personal fees from Astellas, Basilea, and Merck Sharp and Dohme. JP reports personal fees from Gilead and Pfizer; and is a stock holder of Gilead. SR reports grants and personal fees from Merck Sharp and Dohme and Pfizer, and support for pharmaceutical company-initiated clinical study paid to institution from Astellas. MAS reports grants from Merck Sharp and Dohme, Gilead, and F2G; and personal fees from Gilead, Merck Sharp and Dohme, and Pfizer. AW reports grant and personal fees from Gilead. J-AHY reports support for pharmaceutical company-initiated clinical studies paid to institution from Cidara and Scynexis. PH reports support by the Grant of the Czech Ministry of Health (no. NV 17-31269A). RFD reports personal fees from Astellas, Gilead, Merck Sharp and Dohme, and Pfizer. TFP reports grants from Cidara; and personal fees from Basilea, Gilead, Mayne, Merck Sharp and Dohme, Pfizer, Scynexis, Sfunga, and Toyama. TRR reports grants from Menarini and Gilead; and personal fees from Gilead, Menarini, and Pfizer. FQT reports grants from Merck Sharp and Dohme and Pfizer; and personal fees from Teva. OAC is supported by the German Federal Ministry of Research and Education, is funded by the Deutsche Forschungsgemeinschaft under Germany's Excellence Strategy (CECAD, EXC 2030, 390661388) and has received research grants from Actelion, Amplyx, Astellas, Basilea, Cidara, Da Volterra, F2G, Gilead, Janssen, Medicines Company, Melinta, Merck Sharp and Dohme, Octapharma, Pfizer, and Scynexis; is a consultant to Actelion, Allegra, Amplyx, Astellas, Basilea, Biosys, Cidara, Da Volterra, Entasis, F2G, Gilead, Matinas, MedPace, Menarini, Merck Sharp and Dohme, Mylan, Nabriva, Noxxon, Octapharma, Paratek, Pfizer, PSI, Roche Diagnostics, Scynexis, and Shionogi; and received lecture honoraria from Al-Jazeera Pharmaceuticals, Astellas, Basilea, Gilead, Grupo Biotoscana, Merck Sharp and Dohme, and Pfizer. All other authors declare no competing interests.

Acknowledgments

MH, TJW, MN, CFN, ML, AMSA-H, PK, AK, JP, MR, SR, AW, PCYW, VA-A, AC, GD, GSdH, PH, JFM, TRR, CR, and OAC are fellows of the ECMM. MH, JS-G, ML, RS, PK, JP, MR, JS, KA, DA, JFM, DS, and OAC

are members of the Excellence Center for Medical Mycology of the ECMM. We thank Christina Toebben and Nathalie Bauer for review and valuable contributions to the manuscript. We are indebted to Susann Blossfeld and Caroline Bruns for technical support with this manuscript.

References

- 1 Kontoyiannis DP, Marr KA, Park BJ, et al. Prospective surveillance for invasive fungal infections in hematopoietic stem cell transplant recipients, 2001–2006: overview of the Transplant-Associated Infection Surveillance Network (TRANSNET) database. *Clin Infect Dis* 2010; **50**: 1091–100.
- 2 Park BJ, Pappas PG, Wannemuehler KA, et al. Invasive non-*Aspergillus* mold infections in transplant recipients, United States, 2001–2006. *Emerg Infect Dis* 2011; **17**: 1855–64.
- 3 Lamoth F, Chung SJ, Damonti L, Alexander BD. Changing epidemiology of invasive mold infections in patients receiving azole prophylaxis. *Clin Infect Dis* 2017; **64**: 1619–21.
- 4 Stemler J, Salmanton-Garcia J, Seidel D, et al. Risk factors and mortality in invasive *Rasamsonia* spp infection: analysis of cases in the FungiScope registry and from the literature. *Mycoses* 2020; **63**: 265–74.
- 5 Jenks JD, Reed SL, Seidel D, et al. Rare mould infections caused by *Mucorales*, *Lomentospora prolificans* and *Fusarium*, in San Diego, CA: the role of antifungal combination therapy. *Int J Antimicrob Agents* 2018; **52**: 706–12.
- 6 Salmanton-García J, Koehler P, Kindo A, et al. Needles in a haystack: extremely rare invasive fungal infections reported in FungiScope-Global Registry for Emerging Fungal Infections. *J Infect* 2020; **81**: 802–15.
- 7 Cornely OA, Alastruey-Izquierdo A, Arenz D, et al. Global guideline for the diagnosis and management of mucormycosis: an initiative of the European Confederation of Medical Mycology in cooperation with the Mycoses Study Group Education and Research Consortium. *Lancet Infect Dis* 2019; **19**: e405–21.
- 8 Tortorano AM, Richardson M, Roilides E, et al. ESCMID and ECMM joint guidelines on diagnosis and management of hyalohyphomycosis: *Fusarium* spp, *Scedosporium* spp and others. *Clin Microbiol Infect* 2014; **20** (suppl): 27–46.
- 9 Chowdhary A, Meis JF, Guarro J, et al. ESCMID and ECMM joint clinical guidelines for the diagnosis and management of systemic phaeohyphomycosis: diseases caused by black fungi. *Clin Microbiol Infect* 2014; **20** (suppl): 47–75.
- 10 Blyth CC, Gilroy NM, Guy SD, et al. Consensus guidelines for the treatment of invasive mould infections in haematological malignancy and haemopoietic stem cell transplantation, 2014. *Intern Med J* 2014; **44**: 1333–49.
- 11 Cornely OA, Lass-Flörl C, Lagrou K, Arsic-Arsenijevic V, Hoenigl M. Improving outcome of fungal diseases—guiding experts and patients towards excellence. *Mycoses* 2017; **60**: 420–25.
- 12 Hoenigl M, Gangneux JP, Segal E, et al. Global guidelines and initiatives from the European Confederation of Medical Mycology to improve patient care and research worldwide: new leadership is about working together. *Mycoses* 2018; **61**: 885–94.
- 13 Muhammed M, Anagnostou T, Desalermos A, et al. *Fusarium* infection: report of 26 cases and review of 307 cases from the literature. *Medicine (Baltimore)* 2013; **92**: 420–16.
- 14 Guarro J. Fusariosis, a complex infection caused by a high diversity of fungal species refractory to treatment. *Eur J Clin Microbiol Infect Dis* 2013; **32**: 1491–500.
- 15 Nucci M, Marr KA, Vehreschild MJ, et al. Improvement in the outcome of invasive fusariosis in the last decade. *Clin Microbiol Infect* 2014; **20**: 580–85.
- 16 Schell WA. New aspects of emerging fungal pathogens. A multifaceted challenge. *Clin Lab Med* 1995; **15**: 365–87.
- 17 Nucci M, Anaissie E. *Fusarium* infections in immunocompromised patients. *Clin Microbiol Rev* 2007; **20**: 695–704.
- 18 Nucci M, Marr KA, Queiroz-Telles F, et al. *Fusarium* infection in hematopoietic stem cell transplant recipients. *Clin Infect Dis* 2004; **38**: 1237–42.
- 19 Nielsen SE, Nielsen E, Julian HO, et al. Incidence and clinical characteristics of fungal keratitis in a Danish population from 2000 to 2013. *Acta Ophthalmol* 2015; **93**: 54–58.
- 20 Nucci M, Carlesse F, Cappellano P, et al. Earlier diagnosis of invasive fusariosis with *Aspergillus* serum galactomannan testing. *PLoS One* 2014; **9**: e87784.
- 21 Hennequin C, Ranaivoarimalala C, Chouaki T, et al. Comparison of aerobic standard medium with specific fungal medium for detecting *Fusarium* spp in blood cultures. *Eur J Clin Microbiol Infect Dis* 2002; **21**: 748–50.
- 22 Liu K, Howell DN, Perfect JR, Schell WA. Morphologic criteria for the preliminary identification of *Fusarium*, *Paecilomyces*, and *Acremonium* species by histopathology. *Am J Clin Pathol* 1998; **109**: 45–54.
- 23 De Hoog GS, Guarro J, Gené J, et al. Atlas of clinical fungi, 3rd edn. 2019. Utrecht/Rus: Westerdijk Institute, Universitat Rovira i Virgili. Reus. <http://www.clinicalfungi.org/> (accessed July 3, 2020).
- 24 Fleming RV, Kantarjian HM, Husni R, et al. Comparison of amphotericin B lipid complex (ABLC) vs ambisome in the treatment of suspected or documented fungal infections in patients with leukemia. *Leuk Lymphoma* 2001; **40**: 511–20.
- 25 Lortholary O, Obenga G, Biswas P, et al. International retrospective analysis of 73 cases of invasive fusariosis treated with voriconazole. *Antimicrob Agents Chemother* 2010; **54**: 4446–50.
- 26 Perfect JR, Marr KA, Walsh TJ, et al. Voriconazole treatment for less-common, emerging, or refractory fungal infections. *Clin Infect Dis* 2003; **36**: 1122–31.
- 27 Stempel JM, Hammond SP, Sutton DA, Weiser LM, Marty FM. Invasive fusariosis in the voriconazole era: single-center 13-year experience. *Open Forum Infect Dis* 2015; **2**: ofv099.
- 28 Stanzani M, Tumietto F, Vianelli N, Baccarani M. Update on the treatment of disseminated fusariosis: focus on voriconazole. *Ther Clin Risk Manag* 2007; **3**: 1165–73.
- 29 Perfect JR. Treatment of non-*Aspergillus* moulds in immunocompromised patients, with amphotericin B lipid complex. *Clin Infect Dis* 2005; **40** (suppl): S401–08.
- 30 Musa MO, Al Eisa A, Halim M, et al. The spectrum of *Fusarium* infection in immunocompromised patients with haematological malignancies and in non-immunocompromised patients: a single institution experience over 10 years. *Br J Haematol* 2000; **108**: 544–48.
- 31 Cornely OA, Mullane KM, Ostrosky-Zeichner L, et al. Isavuconazole for treatment of rare invasive fungal diseases. *Mycoses* 2018; **61**: 518–33.
- 32 Herbrecht R, Kessler R, Kravanja C, Meyer MH, Waller J, Letscher-Bru V. Successful treatment of *Fusarium proliferatum* pneumonia with posaconazole in a lung transplant recipient. *J Heart Lung Transplant* 2004; **23**: 1451–54.
- 33 Horn DL, Freifeld AG, Schuster MG, Azie NE, Franks B, Kauffman CA. Treatment and outcomes of invasive fusariosis: review of 65 cases from the PATH Alliance registry. *Mycoses* 2014; **57**: 652–58.
- 34 Lackner M, de Hoog GS, Yang L, et al. Proposed nomenclature for *Pseudallescheria*, *Scedosporium* and related genera. *Fungal Divers* 2014; **67**: 1–10.
- 35 Heath CH, Slavin MA, Sorrell TC, et al. Population-based surveillance for scedosporiosis in Australia: epidemiology, disease manifestations and emergence of *Scedosporium aurantiacum* infection. *Clin Microbiol Infect* 2009; **15**: 689–93.
- 36 Rodriguez-Tudela JL, Berenguer J, Guarro J, et al. Epidemiology and outcome of *Scedosporium prolificans* infection, a review of 162 cases. *Med Mycol* 2009; **47**: 359–70.
- 37 Seidel D, Hassler A, Salmanton-García J, et al. Invasive *Scedosporium* spp and *Lomentospora prolificans* infections in pediatric patients: analysis of 55 cases from FungiScope and the literature. *Int J Infect Dis* 2020; **92**: 114–22.
- 38 Husain S, Alexander BD, Munoz P, et al. Opportunistic mycelial fungal infections in organ transplant recipients: emerging importance of non-*Aspergillus* mycelial fungi. *Clin Infect Dis* 2003; **37**: 221–29.
- 39 Cortez KJ, Roilides E, Quiroz-Telles F, et al. Infections caused by *Scedosporium* spp. *Clin Microbiol Rev* 2008; **21**: 157–97.
- 40 Sedlacek L, Graf B, Schwarz C, et al. Prevalence of *Scedosporium* species and *Lomentospora prolificans* in patients with cystic fibrosis in a multicenter trial by use of a selective medium. *J Cyst Fibros* 2015; **14**: 237–41.
- 41 Blyth CC, Harun A, Middleton PG, et al. Detection of occult *Scedosporium* species in respiratory tract specimens from patients with cystic fibrosis by use of selective media. *J Clin Microbiol* 2010; **48**: 314–16.

- 42 Hong G, Miller HB, Allgood S, Lee R, Lechtzin N, Zhang SX. Use of selective fungal culture media increases rates of detection of fungi in the respiratory tract of cystic fibrosis patients. *J Clin Microbiol* 2017; **55**: 1122–30.
- 43 Cobo F, Lara-Oya A, Rodríguez-Granger J, Sampedro A, Aliaga-Martínez L, Navarro-Marí JM. Infections caused by *Scedosporium/Lomentospora* species: clinical and microbiological findings in 21 cases. *Med Mycol* 2018; **56**: 917–25.
- 44 Cooley L, Spelman D, Thursky K, Slavin M. Infection with *Scedosporium apiospermum* and *S. prolificans*, Australia. *Emerg Infect Dis* 2007; **13**: 1170–77.
- 45 Ramirez-Garcia A, Pellon A, Rementeria A, et al. *Scedosporium* and *Lomentospora*: an updated overview of underrated opportunists. *Med Mycol* 2018; **56** (suppl): 102–25.
- 46 Cuenca-Estrella M, Gomez-Lopez A, Mellado E, Buitrago MJ, Monzon A, Rodriguez-Tudela JL. Head-to-head comparison of the activities of currently available antifungal agents against 3,378 Spanish clinical isolates of yeasts and filamentous fungi. *Antimicrob Agents Chemother* 2006; **50**: 917–21.
- 47 Meletiadis J, Meis JF, Mouton JW, Rodriguez-Tudela JL, Donnelly JP, Verweij PE. In vitro activities of new and conventional antifungal agents against clinical *Scedosporium* isolates. *Antimicrob Agents Chemother* 2002; **46**: 62–68.
- 48 Dolton MJ, Perera V, Pont LG, McLachlan AJ. Terbinafine in combination with other antifungal agents for treatment of resistant or refractory mycoses: investigating optimal dosing regimens using a physiologically based pharmacokinetic model. *Antimicrob Agents Chemother* 2014; **58**: 48–54.
- 49 Howden BP, Slavin MA, Schwarzer AP, Mijch AM. Successful control of disseminated *Scedosporium prolificans* infection with a combination of voriconazole and terbinafine. *Eur J Clin Microbiol Infect Dis* 2003; **22**: 111–13.
- 50 Wangchinda W, Chongtrakool P, Tanboon J, Jitmuang A. *Lomentospora prolificans* vertebral osteomyelitis with spinal epidural abscess in an immunocompetent woman: case report and literature review. *Med Mycol Case Rep* 2018; **21**: 26–29.
- 51 Seidel D, Meißner A, Lackner M, et al. Prognostic factors in 264 adults with invasive *Scedosporium* spp and *Lomentospora prolificans* infection reported in the literature and FungiScope. *Crit Rev Microbiol* 2019; **45**: 1–21.
- 52 Jenks JD, Seidel D, Cornely OA, et al. Voriconazole plus terbinafine combination antifungal therapy for invasive *Lomentospora prolificans* infections: analysis of 41 patients from the FungiScope registry 2008–2019. *Clin Microbiol Infect* 2020; **26**: 784.e1–784.e5.
- 53 Schwarz C, Brandt C, Melichar V, et al. Combined antifungal therapy is superior to monotherapy in pulmonary scedosporiosis in cystic fibrosis. *J Cyst Fibros* 2019; **18**: 227–32.
- 54 Jenks JD, Seidel D, Cornely OA, et al. Clinical characteristics and outcomes of invasive *Lomentospora prolificans* infections: analysis of patients in the FungiScope registry. *Mycoses* 2020; **63**: 437–42.
- 55 Kaltseis J, Rainer J, De Hoog GS. Ecology of *Pseudallescheria* and *Scedosporium* species in human-dominated and natural environments and their distribution in clinical samples. *Med Mycol* 2009; **47**: 398–405.
- 56 Pang KR, Wu JJ, Huang DB, Tying SK. Subcutaneous fungal infections. *Dermatol Ther* 2004; **17**: 523–31.
- 57 Zouhair R, Rougeron A, Razafimandimby B, Kobi A, Bouchara JP, Giraud S. Distribution of the different species of the *Pseudallescheria boydii/Scedosporium apiospermum* complex in French patients with cystic fibrosis. *Med Mycol* 2013; **51**: 603–13.
- 58 Lamaris GA, Chamilos G, Lewis RE, Safdar A, Raad II, Kontoyiannis DP. *Scedosporium* infection in a tertiary care cancer center: a review of 25 cases from 1989–2006. *Clin Infect Dis* 2006; **43**: 1580–84.
- 59 Signore SC, Dohm CP, Schütze G, Bähr M, Kermer P. *Scedosporium apiospermum* brain abscesses in a patient after near-drowning—a case report with 10-year follow-up and a review of the literature. *Med Mycol Case Rep* 2017; **17**: 17–19.
- 60 Chen TC, Ho MW, Chien WC, Lin HH. Disseminated *Scedosporium apiospermum* infection in a near-drowning patient. *J Formos Med Assoc* 2016; **115**: 213–14.
- 61 Nakamura Y, Suzuki N, Nakajima Y, et al. *Scedosporium aurantiacum* brain abscess after near-drowning in a survivor of a tsunami in Japan. *Respir Investig* 2013; **51**: 207–11.
- 62 Shimizu J, Yoshimoto M, Takebayashi T, Ida K, Tanimoto K, Yamashita T. Atypical fungal vertebral osteomyelitis in a tsunami survivor of the Great East Japan Earthquake. *Spine* 2014; **39**: e739–42.
- 63 Bansal Y, Chander J, Kaistha N, Singla N, Sood S, van Diepeningen AD. *Fusarium sacchari*, a cause of mycotic keratitis among sugarcane farmers—a series of four cases from North India. *Mycoses* 2016; **59**: 705–09.
- 64 Husain S, Muñoz P, Forrest G, et al. Infections due to *Scedosporium apiospermum* and *Scedosporium prolificans* in transplant recipients: clinical characteristics and impact of antifungal agent therapy on outcome. *Clin Infect Dis* 2005; **40**: 89–99.
- 65 Gilgado F, Cano J, Gené J, Guarro J. Molecular phylogeny of the *Pseudallescheria boydii* species complex: proposal of two new species. *J Clin Microbiol* 2005; **43**: 4930–42.
- 66 de Hoog GS, Chaturvedi V, Denning DW, et al. Name changes in medically important fungi and their implications for clinical practice. *J Clin Microbiol* 2015; **53**: 1056–62.
- 67 Revankar SG. Dematiaceous fungi. *Mycoses* 2007; **50**: 91–101.
- 68 Al-Hatmi AM, Meis JF, de Hoog GS. *Fusarium*: molecular diversity and intrinsic drug resistance. *PLoS Pathog* 2016; **12**: e1005464.
- 69 Hoenigl M, Valetitsch H, Stammberger H, Valentin T, Krause R, Buzine W. Sinusitis and frontal brain abscess in a diabetic patient caused by *Schizophyllum commune*: case report and review of the literature. *Mycoses* 2013; **56**: 389–93.
- 70 Poignon C, Blaize M, Vezinet C, Lampros A, Monsel A, Fekkar A. Invasive pulmonary fusariosis in an immunocompetent critically ill patient with severe COVID-19. *Clin Microbiol Infect* 2020; **26**: 1582–84.
- 71 Arastehfar A, Carvalho A, van de Veerdonk FL, et al. COVID-19 Associated pulmonary aspergillosis (CAPA)—from immunology to treatment. *J Fungi (Basel)* 2020; **6**: 91.
- 72 Hoenigl M. Invasive fungal disease complicating COVID-19: when it rains it pours. *Clin Infect Dis* 2020; published online Sept 5. <https://doi.org/10.1093/cid/ciaa1342>.
- 73 Jenks JD, Prattes J, Frank J, et al. Performance of the bronchoalveolar lavage fluid *Aspergillus* galactomannan lateral flow assay with cube reader for diagnosis of invasive pulmonary aspergillosis: a multicenter cohort study. *Clin Infect Dis* 2020; published online Aug 31. <https://doi.org/10.1093/cid/ciaa1281>.
- 74 Lackner M, de Hoog GS, Verweij PE, et al. Species-specific antifungal susceptibility patterns of *Scedosporium* and *Pseudallescheria* species. *Antimicrob Agents Chemother* 2012; **56**: 2635–42.
- 75 Troke P, Obenga G, Gaujoux T, et al. The efficacy of voriconazole in 24 ocular *Fusarium* infections. *Infection* 2013; **41**: 15–20.

© 2021 Elsevier Ltd. All rights reserved.