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Review
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Global guideline for the diagnosis and management of rare yeast infections: an initiative of the ECMM in cooperation with ISHAM and ASM

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Uncommon, or rare, yeast infections are on the rise given increasing numbers of patients who are immunocompromised or seriously ill. The major pathogens include those of the genera *Geotrichum*, *Saprochaete*, *Magnusiomyces*, and *Trichosporon* (ie, basidiomycetes) and *Kodamaea*, *Malassezia*, *Pseudozyma* (ie, now *Moesziomyces* or *Dirkmeia*), *Rhodotorula*, *Saccharomyces*, and *Sporobolomyces* (ie, ascomycetes). A considered approach to the complex, multidisciplinary management of infections that are caused by these pathogens is essential to optimising patient outcomes; however, management guidelines are either region-specific or require updating. In alignment with the One World–One Guideline initiative to incorporate regional differences, experts from diverse geographical regions analysed publications describing the epidemiology and management of the previously mentioned rare yeasts. This guideline summarises the consensus recommendations with regards to the diagnostic and therapeutic options for patients with these rare yeast infections, with the intent of providing practical assistance in clinical decision making. Because there is less clinical experience of patients with rare yeast infections and studies on these patients were not randomised, nor were groups compared, most recommendations are not robust in their validation but represent insights by use of expert opinions and in-vitro susceptibility results. In this Review, we report the key features of the epidemiology, diagnosis, antifungal susceptibility, and treatment outcomes of patients with *Geotrichum*, *Saprochaete*, *Magnusiomyces*, and *Trichosporon* spp infections.

Introduction

Emerging non-candidal and non-cryptococcal yeasts are increasingly recognised causes of invasive yeast infections in hospitalised inpatients.[1,2] Knowledge of infections that are caused by these so-called rare yeasts, however, is insufficient. Due to absence of clinical breakpoints, antifungal susceptibility profiles of these yeasts can be difficult to interpret.[3,4] Additionally, comparative trials on treatment efficacy are not feasible. As there are no pathogen-specific markers, culture-based methods are central to diagnosis. Optimising management relies on recognising disease patterns and access to diagnostic and therapeutic options.

Current recommendations hinge on clinical experience, expert opinion, or extrapolation from animal studies. Available guidelines are region-specific[5] or require updating.[3] Hence, the European Confederation for Medical Mycology (ECMM) has worked with the International Society for Human and Animal Mycology (ISHAM) and the American Society for Microbiology (ASM) to provide this guidance document to facilitate best-practice multidisciplinary care for patients with invasive rare yeast infections.

Scope

This Review presents the diagnostic and management recommendations for systemic infections caused by the basidiomycetous yeasts of the genera, *Trichosporon*, *Malassezia*, *Pseudozyma* (ie, now named *Moesziomyces* or *Dirkmeia*), *Rhodotorula*, *Sporobolomyces*, and the ascomycetous yeasts of the genera, *Geotrichum*, *Kodamaea*, *Saccharomyces*, *Saprochaete*, and *Magnusiomyces*.[6,7] This list is not exhaustive but includes the yeasts that are most well described in clinical settings. In this Review, key management aspects for patients with geotrichosis (appendix pp 17–63) or infections that are caused by *Saprochaete* and *Magnusiomyces* spp (appendix pp 142–55) and *Trichosporon* spp (appendix pp 162–79) are summarised. The appendix also describes the rationale and recommendations for managing patients with infections caused by the other rare yeasts that were previously listed. This Review does not include recommendations for managing patients with *Cryptococcus* spp infections or infections that are caused by those *Candida* spp that have been reassigned to non-*Candida* genera. For pragmatic reasons, and to place in appropriate clinical context, non-*Candida* genera will be discussed in a future guideline on candidiasis. Nonetheless, clinicians should be aware of nomenclature changes for fostering communication: the naming of uncommon yeasts might differ and yet refer to the same yeast (appendix p 8). Regional differences in prevalence render local epidemiological knowledge essential (appendix p 9).[8–12]

Notably, although there are few data to indicate that surgical intervention confers greater cure or survival for patients with rare yeast infections compared with for

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patients with common yeast infections, resection of infected foci, particularly cardiac valve replacement for endocarditis, is supported with moderate-to-strong recommendation, except for patients with *Malassezia* and *Sporobolomyces* spp infections where there are no data (appendix pp 58–60).

Guideline development and workflow

Physicians and scientists in multiple disciplines, incorporating internal medicine, surgery, pathology, and imaging, from all UN regions were invited to develop the guideline in alignment with ECMM's vision and on the basis of their involvement in care of patients with yeast infections (for details on authors, literature search terms, and workflow see appendix pp 11–16). This Review follows the structure of previous global guidelines in invasive fungal infections in accordance with the Grading of Recommendations Assessment, Development and Evaluation and Appraisal of Guidelines for Research and Evaluation systems, as previously described elsewhere.[13] We tabulated and assed the population, intervention, comparison, and outcome data; provided a strength of recommendation and quality of evidence grading, followed by support from the literature; and presented recommendations.[13]

To address the challenge of incorporating guideline members from multiple time zones, we convened repeated video conferences on the method that we adopted. All contributors viewed a video tutorial.[14] OAC, SC-AC, ALC, NPG, and JP supervised the workflow and timeline management.

All authors searched the literature using one or more of the major databases (ie, Web of Science, MEDLINE or PubMed [via the National Library of Medicine], Embase, and Scopus) for papers published in English. The following search strings were used as with the example given for *Geotrichum* spp infections: "Geotrichosis* OR Geotrichum*", "ped Geotrichum* AND child Geotrichum* AND neonate", "epidemiology Geotrichum* AND etiology*", "Geotrichum AND taxonomy*", "Geotrichum* AND susceptibility testing", and "Geotrichum* AND diagnosis*". For the epidemiology section, the following string was used "Geotrichum* [All Fields] AND (case[Title/Abstract] OR cases[Title/Abstract] OR patient[Title/Abstract] OR patients[Title/Abstract] OR report[Title/Abstract]) AND ('1999/01/01'[PDat] : '2019/12/31'[PDat])". Acknowledging the infrequent publications on rare yeast infections, a 20-year period of publication (ie, Jan 1, 1999, to Dec 31, 2019) was chosen to represent the distribution of worldwide reports. Similar search strings were used for the other yeast genera. Where taxonomic changes had occurred or synonyms were in use, search strings included these other fungal names.

Documents were shared among the authors on a password-protected, centrally managed OneDrive repository. Any discrepancies in recommendations were resolved by majority vote. Additional aspects or publications that were missing in the Review manuscript were contributed via a survey that was sent out to all authors. Once the group agreed on the final content, a writing group (SC-AC, ALC, JP, NPG, OAC, KA, JNdAJ, GG-E, JS-G, NG, AHG, CL-F, LO-Z, LP, TP, RR-R, DS, AS, and JS) wrote the first draft. On agreement by all authors of a final draft with recommendations that were based on consensus, a 4-week phase of public consultation followed, which included a review by the ASM. Comments that were received were evaluated and incorporated as appropriate. 45 scientific societies (in 31 countries) endorsed the document (appendix pp 14–17). For the yeast genera that were considered, evidence-based diagnostic pathways are given for each genus or genus group, where data are sufficient.

Geotrichosis

Epidemiology

Geotrichum spp are genetically closely related to yeasts of the genus *Saprochaete* and *Magnusiomyces*. As such, *Geotrichum clavatum* is now *Saprochaete clavata*, whereas *Geotrichum capitatum* is *Magnusiomyces capitatus*.[6] *Geotrichum candidum*, the only pathogenic species, is ubiquitous in soil, decaying organic matter and foods and is used in cheese manufacture.[15]

The few cases of invasive geotrichosis that are reported are mostly from Europe and the USA (appendix p 18). *G candidum* has accounted for only a small proportion of rare yeast infections, if at all.[1,10]

Predisposing risks largely include haematological diseases but also HIV/AIDS, uncontrolled diabetes, malignancy, and ingestion of contaminated cheese.[16,17] Bloodstream infection with or without skin lesions and pulmonary infections are the most frequent in patients who are immunocompromised,[17–19] but localised infections (eg, intestine, eyes, and heart valves) have occurred.[18,20] Mortality for *G candidum* infections is more than 60% in oncological patients but less than 40% for other patient groups.[17,21,22]

Diagnosis

Imaging findings of geotrichosis are non-specific (appendix p 20). Imaging studies are moderately supported to establish disease extent, including to the lungs, eyes, skin, heart, and skeleton.[21–24] CT scanning is preferred over chest radiography in lung disease. In eye or brain infections, MRI to define disease is moderately recommended. Transoesophageal echocardiography to confirm endocarditis is at least moderately supported. We strongly recommend follow-up imaging to monitor therapeutic response.

The few data for histopathology are for *G candidum* infection in skin or soft tissue or disseminated infection.[21,24] By use of periodic acid-Schiff or Gomori methenamine silver stains for fungi, or both, direct microscopy of specimens, including formalin-fixed paraffin-embedded tissue sections, has been useful (appendix p 24). *G candidum* hyphae are non-specific but

often are long, thin septate and regular with variable-angled branching.[25]

We strongly recommend histopathological examination of tissue. Diagnosis of geotrichosis by histopathology alone is not possible, hence further, we strongly recommend to culture specimens or to apply direct molecular detection and identification techniques.

Direct microscopy of clinical specimens can suggest a diagnosis of yeast infection that is consistent with *Geotrichum* spp (appendix pp 29–31). Yeast-to-hyphal structures can be seen on Gram stain of blood cultures.[19,21] Culture of clinical specimens is essential. The microscopic appearance of hyphae from cultured colonies are typically long structures with dichotomous or trichotomous branching, with segmentation into variably sized rectangular arthroconidia; no blastoconidia are evident (appendix p 30).

As fungaemia is common, optimising the yield of *Geotrichum* spp and other rare yeasts from blood cultures is pertinent. Data on use of dedicated fungal culture media, such as BACTEC Myco/F Lytic bottles (Becton Dickinson, Sparks, MD, USA) and the Isolator tube (Wampole Laboratories, Cranbury, NJ, USA), in addition to standard blood-culture media are sparse for the rare yeasts; studies indicate only a small (if any) benefit, although in one study, the inclusion of BACTEC Myco/F Lytic bottles assisted with recovery of two of eight *Trichosporon* spp isolates.[26,27]

Evidence for direct detection of *Geotrichum* spp in clinical specimens is also sparse, but panfungal PCR assays that are done on tissue, targeting the *ITS* or 28s ribosomal DNA regions, followed by DNA sequencing can be expected to have good specificity (ie, approximately 100%). The sensitivity is highest when the specimen is freshly obtained and when fungal forms are visualised.[28,29]

We strongly recommend Gram staining, seeking septation and arthroconidia formation for first clues of *G candidum*. We strongly recommend culture of specimens for pathogen identification and antifungal susceptibility testing. Molecular methods on fresh or formalin-fixed paraffin-embedded specimens for detecting *G candidum* is moderately supported; with no data, molecular-based detection in other specimens is weakly supported.

The reference European Committee on Antimicrobial Susceptibility Testing and the Clinical and Laboratory Standards Institute methods for antifungal susceptibility testing were developed for *Candida* and *Cryptococcus* spp.[30,31] Although the European Committee on Antimicrobial Susceptibility Testing protocol can apply to yeasts that ferment glucose, when interpreting susceptibility results for rare yeasts, it should be considered that the tests were developed for *Candida* and *Cryptococcus* spp.

Geotrichum spp ferment glucose, but data are insufficient to recommend one reference method over the other. Use of E-test (bioMerieux, Marcy-l'Étoile, France) and broth microdilution-based Sensititre (Thermofisher, Sydney, Australia) methods have rarely been reported.[17,22,32] As neither clinical breakpoints nor epidemiological cutoff values are defined for *G candidum*, classification of isolates as susceptible or resistant, or as wild type or non-wild type, should not be made.

Voriconazole, posaconazole, and micafungin have been the most active compounds against *Geotrichum* spp (appendix p 32).[17,22–24,33] As minimal inhibitory concentrations (MICs) are strain dependent, susceptibility testing of clinically significant *Geotrichum* spp isolates is reasonable.

Use of reference methods for antifungal susceptibility testing to guide antifungal treatment is moderately supported and might be useful for patients with infections that do not respond to treatment. We strongly recommend the use of these methods for epidemiological knowledge.

Species identification is important for extending epidemiological and clinical appreciation. There are no data to indicate that identification to species level can guide antifungal treatment.

All phenotypic identification systems, matrix-assisted laser desorption ionisation time-of-flight mass spectrometry (MALDI-TOF MS), and molecular approaches can contribute to species identification (appendix pp 51–54). Importantly, *G candidum* is urease-negative, distinguishing it from other arthroconida-producing yeasts.[12,19,22–24] Biochemical kits are being discontinued, and most likely, MALDI-TOF MS systems will replace them for yeast identification.

Sequence analysis of the *ITS* ribosomal DNA[34] or the *D1–D2* 28s ribosomal DNA regions[23,35,36] or species identification is better than morphological or biochemical approaches and has been used to benchmark the accuracy of other tests. Data are limited by small isolate numbers.

We strongly support species identification for epidemiological knowledge and moderately support it for use in guiding treatment. Morphological identification is moderately supported but molecular identification by *ITS* or 28s ribosomal DNA sequencing is strongly preferred. MALDI-TOF MS identification is supported with moderate strength; in-house mass spectrometry libraries should supplement commercial databases. Figure 1 shows a recommended diagnostic pathway.

Antifungal drug treatment and treatment duration

Treatment is diagnostic driven on isolation of *G candidum* from sterile body fluids or tissue. Data for antifungal selection are limited to in-vitro data, case reports, and case series.[17,19,21,22,24] Good treatment responses have been noted following amphotericin B formulation with or without flucytosine treatment[3] and with voriconazole.[17,23,24] The use of echinocandins might be associated with worse outcomes. Where an amphotericin B formulation is used, liposomal amphotericin B has been used successfully.[17,22,24]

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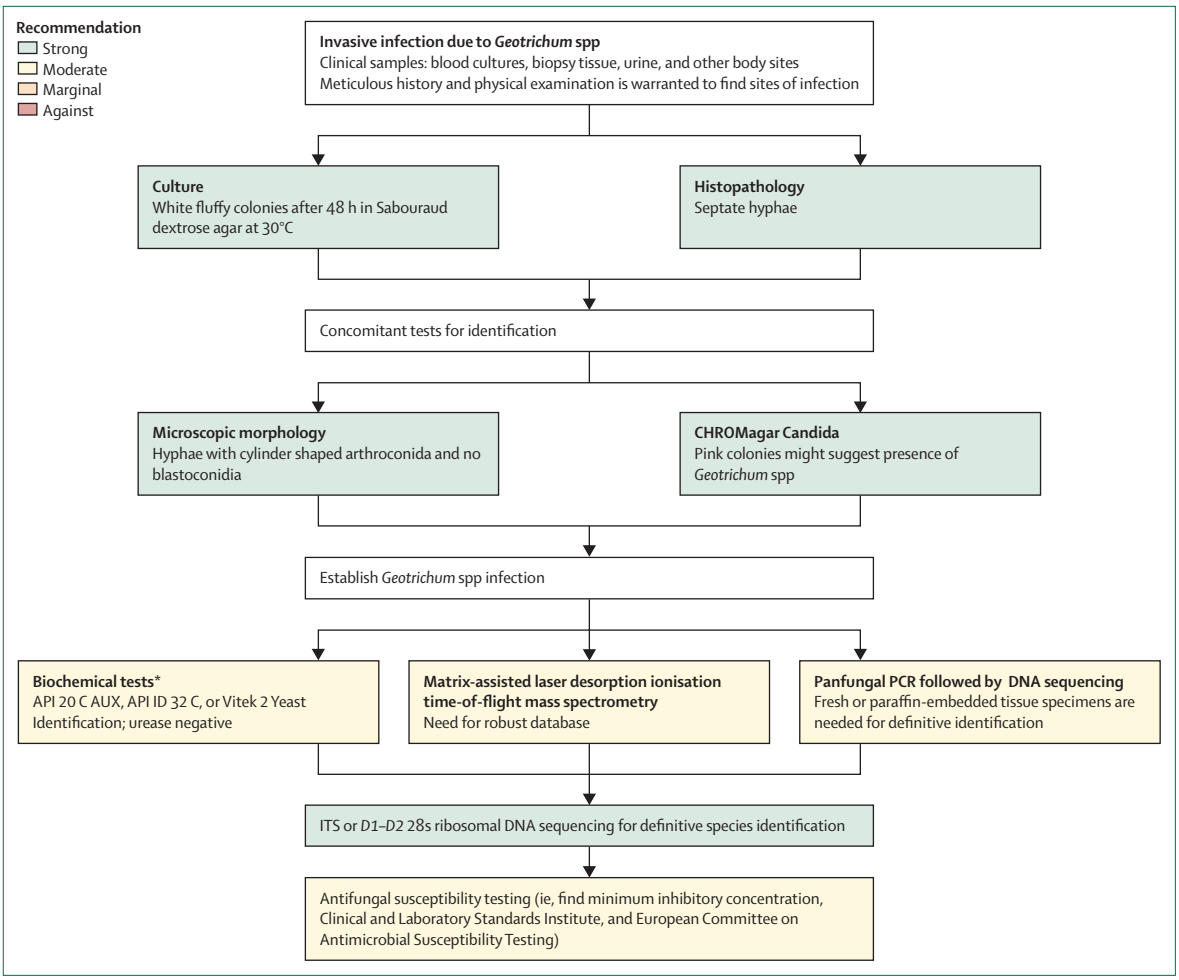

Figure 1: **Evidence-based diagnostic pathway for patients with invasive geotrichosis**
*Commercial biochemical tests are being discontinued.

Conventional amphotericin B can be used but with a worse safety profile.[37] There are no data on salvage therapy. For further information on evidence for antifungal drug treatment, see the appendix pp 61–63.

First-line antifungal treatment with amphotericin B formulation, with or without flucytosine, has moderate support, as does voriconazole. Echinocandin use is not supported. Where a treatment does not work, the guideline moderately recommends the use an antifungal agent of a different class, supported by susceptibility results. Treatment duration is empirical and should be individualised, guided by clinical response, site and extent of infection, and patient immune status. We moderately support a long period of treatment for end organ disease. Figure 2 summarises the treatment pathways.

Saprochaete or *Magnusiomyces* spp infections

Epidemiology

Saprochaete spp yeasts were previously of the genera *Geotrichum* or *Blastoschizomyces*, hence clinical data can be found under these names. *S clavata* are urease-negative environmental yeasts that occasionally colonise human skin, sputum, and the gastrointestinal tract, and rarely cause disease; *M capitatus* is a more common cause of infection. The geographical distribution of infections is shown in the appendix (p 143).[38–41]

Saprochaete or *Magnusiomyces* spp most frequently causes fungaemia, organ (eg, hepatosplenic abscesses), and disseminated disease (eg, skin, brain, or bone or joint) in haemato-oncology patients, including patients receiving echinocandins; in these patients, infection can present as nosocomial outbreaks.[42–44] However, these yeasts also cause disease in immunocompetent people.[39]

Diagnosis, species identification, and susceptibility

The principles and methods are as for the other rare yeasts, and imaging, histopathology, culture, and direct detection by molecular approaches are considered to be appropriate, taking into account the site or sites of infection.

Primarily, isolation of *Saprochaete* or *Magnusiomyces* spp is done from blood cultures or sterile body sites. Isolates

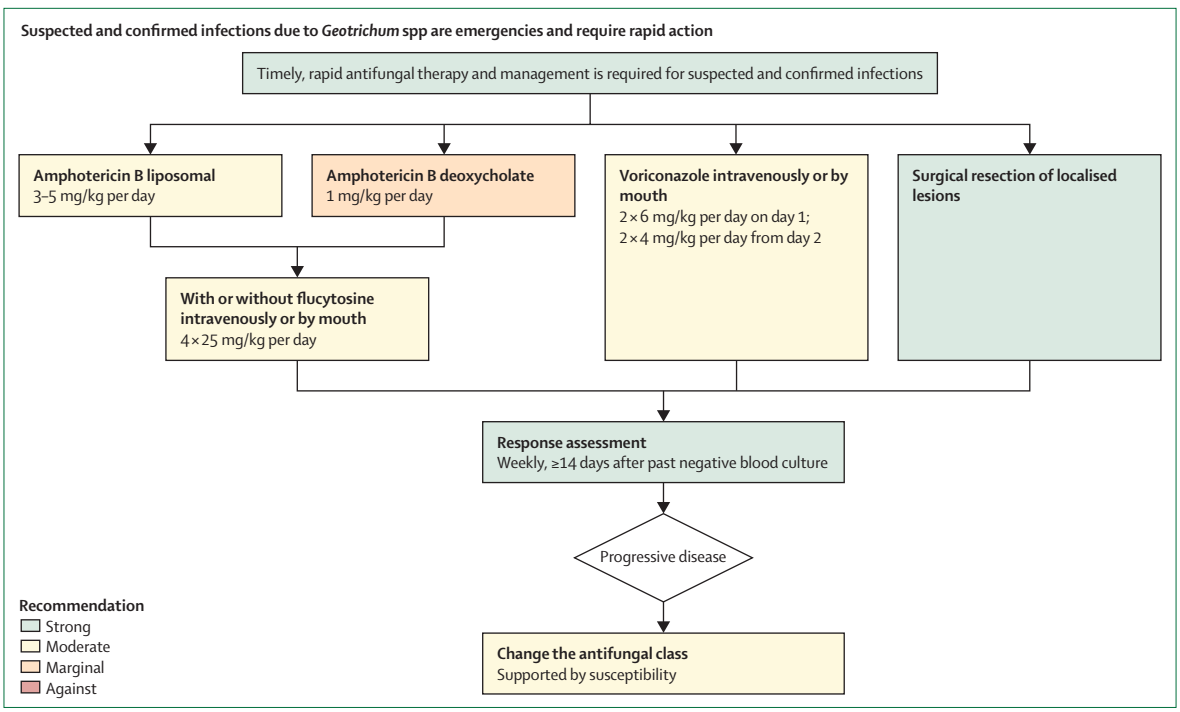

Figure 2: **Evidence-based treatment pathway for first-line antifungal therapy and management of patients with invasive geotrichosis**

produce hyphae, pseudohyphae, and several conidia types. Identification by biochemical methods is possible for *S clavata* (but not *M capitatus*), which can grow with cellobiose and salicin as carbon sources.[30] With large databases, the use of MALDI-TOF MS has become more reliable than for small databases.[35] Molecular tests can prove definitive in identification.[45,46] *M capitatus* has MICs to itraconazole, posaconazole, voriconazole, and isavuconazole of less than or equal to 1 mg/L. Isavuconazole MICs for *S clavata* can be as high as 4 mg/L. Fluconazole MICs are typically 16–32 mg/L for *M capitatus* although some strains have lower MICs. This species is also intrinsically resistant to echinocandin (appendix pp 32–50, 144–50).

In patients who are neutropenic, disease can radiographically resemble hepatosplenic candidiasis and imaging is moderately supported. We strongly recommend culture for epidemiology and antifungal susceptibility. Species identification by molecular approaches is strongly supported to assist treatment; phenotypic and MALDI-TOF MS identification methods are moderately supported. Because of inter-strain variability of azole susceptibility, it is reasonable to obtain MICs to guide clinical care. We strongly recommend finding MIC by use of a reference method for epidemiological knowledge.

Antifungal treatment and other management

There are no comparative antifungal treatment trials for *M capitatus* infection. Susceptibility results can be considered together with clinical presentation, where clinical presentation should primarily guide treatment.[38,43,47] Recommendations are to use an amphotericin B formulation with or without flucytosine, or with voriconazole for initial therapy, on the basis of clinical data. Breakthrough infections have occurred in patients who are immunocompromised and given echinocandin prophylaxis[48] and in patients who are given posaconazole, amphotericin B formulations, and fluconazole. Echinocandins should not be used as monotherapy[45,48,49] due to increased mortality but combination with voriconazole has been reported.[50,51] Despite antifungal treatment, outcomes can be poor.[42]

There are insufficient data to direct management of central venous access devices (CVADs) in patients with *M capitatus* infections, but early catheter removal has had positive effects on survival.[40] Adjunctive growth factors or interferon-gamma and neutrophil transfusions can be helpful.[51] Splenectomy for splenic abscesses might be beneficial in antifungal drug-refractory cases (appendix p 151).

The use of an amphotericin B formulation with or without flucytosine or with voriconazole as initial antifungal therapy is moderately supported. We strongly recommend control of underlying neutropenia and CVAD removal is strongly recommended (figure 3**).**

Trichosporonosis

Epidemiology

Trichosporon spp yeasts are distributed worldwide in soil, decomposing wood, water, foods (eg, cheese), beetles,

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See **Online** for appendix

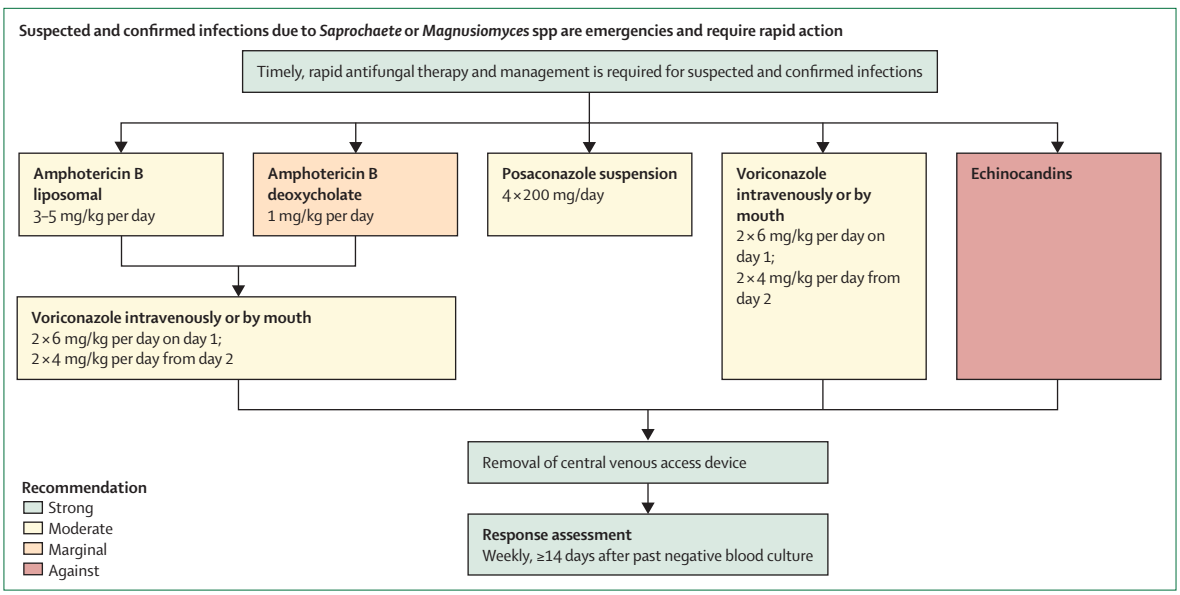

Figure 3: **Evidence-based treatment pathway for first-line antifungal therapy and management of patients with *Saprochaete* or *Magnusiomyces* spp infections**

bird droppings, bats, and cattle. They can form part of the normal microbiota of human skin, the gastrointestinal tract, and the respiratory tract.[52,53]

Of 12 species, *Trichosporon asahii* is the most common, followed by *Trichosporon inkin*, *Trichosporon faecale*, and *Trichosporon asteroides*. Prevalence rates of non-*T asahii* species and *T asahii* genotypes vary with geography (see appendix pp 162–63 for details and the worldwide distribution of invasive trichosporonosis).

The most common clinical manifestation is fungaemia, but endocarditis, CNS infections, and other infections are described.[53] Invasive disease most often affects haematology patients who are immunocompromised with neutropenia, CVADs, and exposure to antifungals.[25,54–56] Haematology patients with fungaemia often present with metastatic skin lesions (ie, 18–43%), pneumonia (ie, 18–53%), and hepatosplenic abscesses.[55,56] Other patients who are at risk include patients who are critically ill and undergoing medical procedures. Mortality ranges from 30–90%.[55,57]

Diagnosis

Evidence for imaging is given in the appendix (p 164).[53,55] We moderately recommend imaging to diagnose or to exclude disease. Chest CT is preferred over chest x-ray for pulmonary lesions. Echocardiography is moderately supported for suspected endocarditis. We strongly recommend follow-up imaging. Abdominal CT scanning in patients with acute leukaemia and fungaemia is strongly supported.

Histopathology examination of lung and skin biopsies with fungal stains has been helpful for diagnosis; arthroconidia are rarely reported.[53,55] Inferring species or genus from histopathology is not possible.

Panfungal PCR methods on fresh and formalin-fixed paraffin-embedded sections have enabled diagnosis,[28,58] as has genus-specific nested PCR[59] and hybridisation with *Trichosporon* spp-specific probes.[60] Direct identification of *Trichosporon* spp from blood has been reported.[61] Few data are available regarding use of other molecular techniques.[52,62]

We strongly recommend examination of tissue by fungal stains. Direct detection and identification of *Trichosporon* spp in clinical specimens by *ITS*-directed panfungal PCR is moderately recommended, with weak support for use of other molecular methods.

Gram stain of blood cultures and other specimens showing hyphae, blastoconidia, and arthroconidia provides useful diagnostic information.[53] Culture is the mainstay of diagnosis (appendix pp 165–66). For isolates, presence of blastoconidia and arthroconidia in a urease-positive yeast enables presumptive identification of *Trichosporon* spp.[53,55]

Commercial biochemical methods usually provide species identification for *T asahii*. However, non-*T asahii* isolates can be misidentified as *T asahii* or are simply not identified (appendix p 167).[53] MALDI-TOF MS equipped with extended in-house libraries can identify at least ten species.[55,63] *IGS1* region sequencing has provided species identification with good results.[64–66]

We strongly recommend direct microscopy of clinical specimens and culture to yield an isolate for susceptibility testing and species identification of isolates. However, the usefulness of species identification in guidance of therapy is uncertain. Identification by phenotypic methods (for *T asahii*) and by MALDI-TOF MS are both moderately supported, with strong support for molecular-based identification. Figure 4 shows the diagnostic pathway.

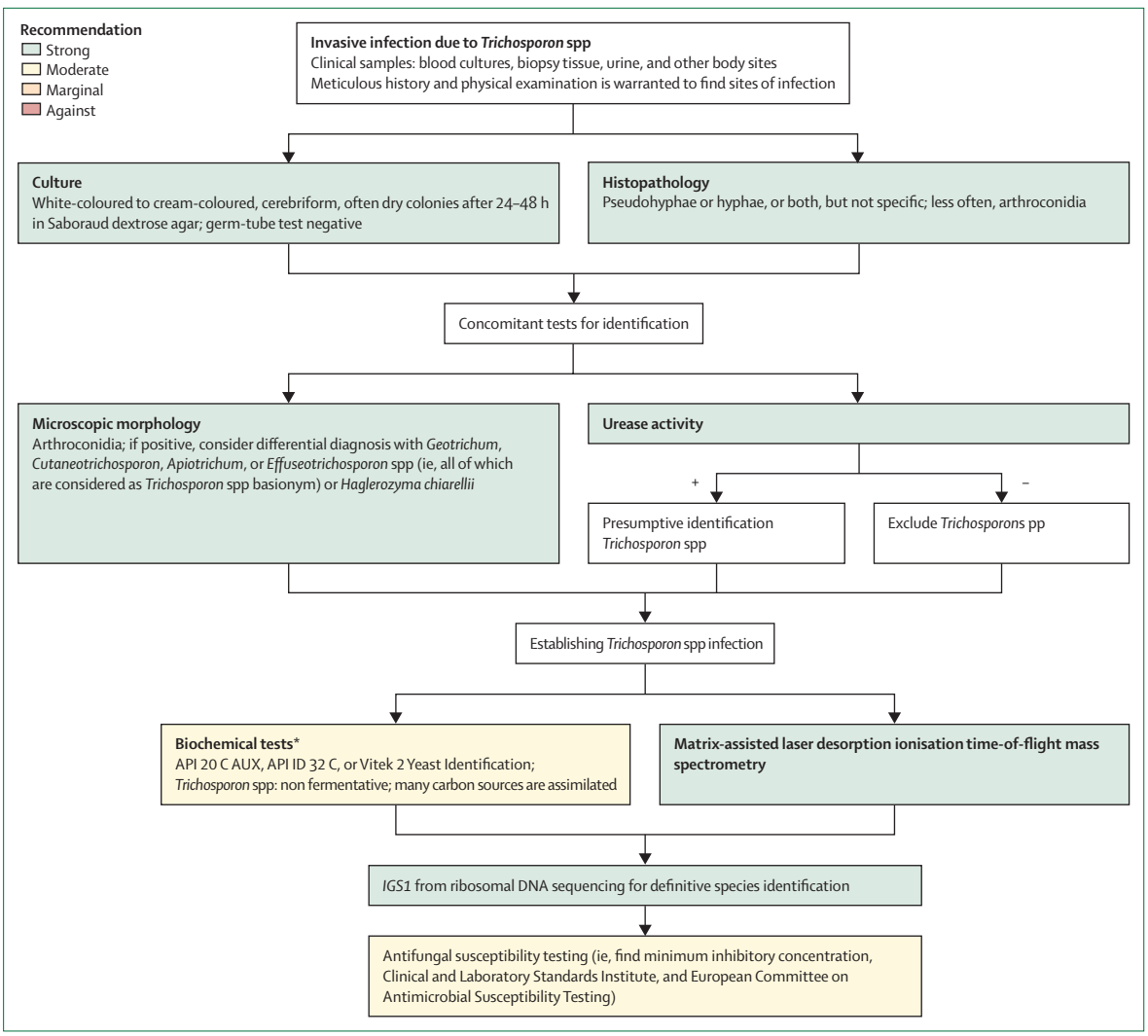

Figure 4: **Evidence-based diagnostic pathway for patients with suspected systemic *Trichosporon* spp infections**
*Commercial biochemical tests are being discontinued.

For susceptibility testing, *Trichosporon* spp-specific clinical breakpoints and epidemiological cutoff values for all antifungal drugs are scarce.[53,64] Details are in the appendix (p 173).

Trichosporon spp are intrinsically resistant to echinocandins (MICs >8 mg/L).[67] Most species have low voriconazole and posaconazole MICs (MIC_{90} 0·25–0·50 mg/L)[57,68–70] and the geometric mean MIC of isavuconazole is 0·09 mg/L.[71] Fluconazole has exhibited species-dependent and strain-dependent activity (appendix pp 24–27). MIC_{90} values of amphotericin B are typically less than or equal to 1 mg/L. From the few data that are available, *T faecale* have tested resistant to most antifungals.[72,73]

There are few data to support susceptibility-driven antifungal therapy. We strongly recommend susceptibility testing by reference methods for epidemiological knowledge.

Management

Owing to a scarcity of randomised clinical trials, recommendations for antifungal treatment are derived from data from animal studies,[74] in-vitro studies,[65] and case series from predominantly haemato-oncological patients.

Voriconazole or fluconazole-based regimens are superior to those based on amphotericin B preparations for all forms of infection, with some data supporting efficacy for use of posaconazole.[38,55,74,75] Early evidence for isavuconazole supports its use.[71] Azole-polyene combinations have not offered advantages as initial therapy;[53,55,75] therefore, we recommend reserving these drugs for salvage therapy. Combined echinocandin–triazole therapy has not conferred benefit.[53,55] Breakthrough infections while receiving echinocandins or polyenes can be successfully treated with voriconazole.[53,55,68,76] On the basis of outcome data, for

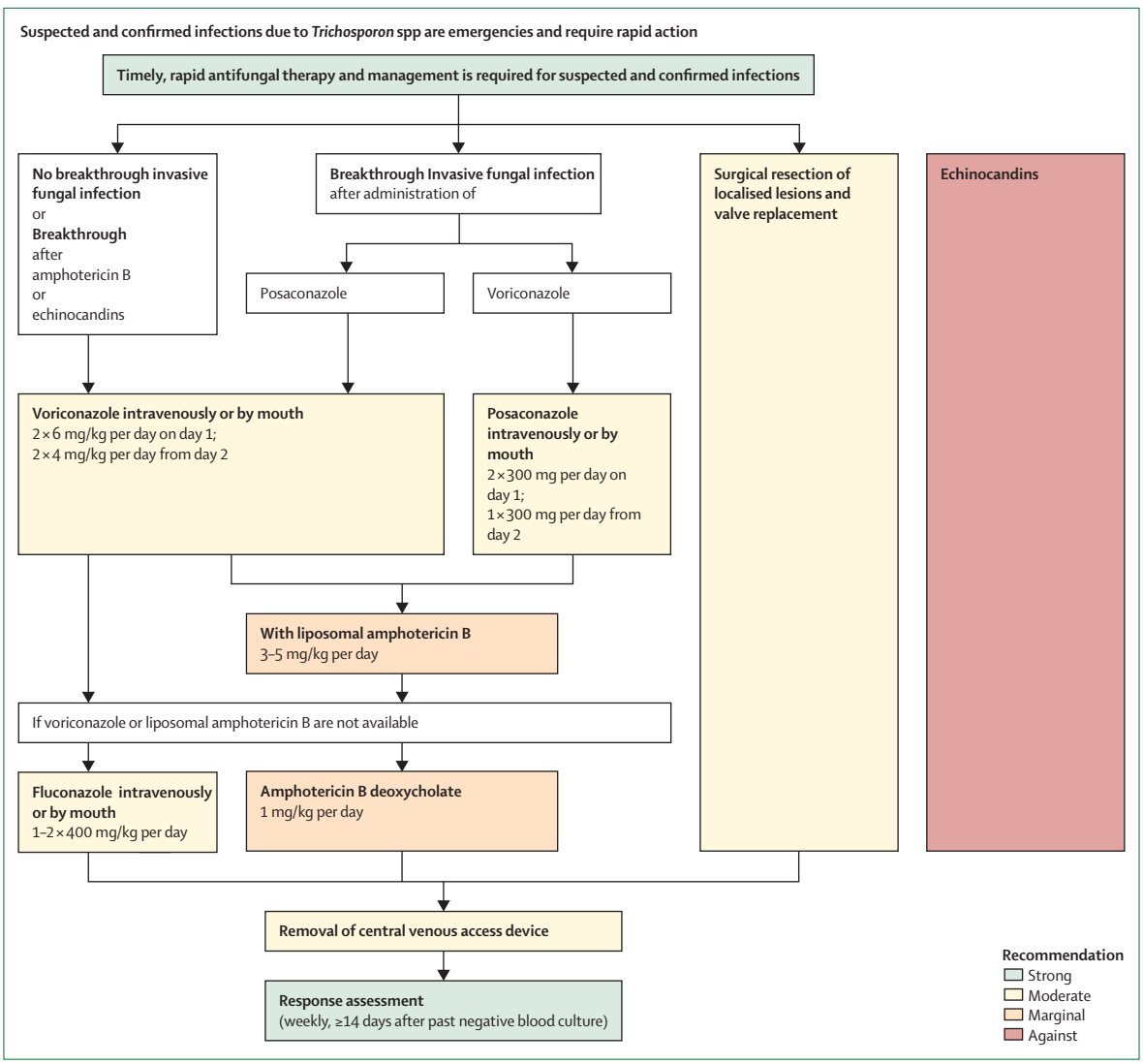

Figure 5: **Evidence-based treatment pathway for antifungal therapy and management of patients with systemic trichosporonosis**

patients with CVAD-related infections or endocarditis, CVAD removal and valve replacement might be required for source control (appendix p 177). Expert consensus favours treatment for 2 weeks in the absence of deep-seated infection and 4–6 weeks, or until radiological resolution, for patients with organ involvement.[53,55,75]

We moderately recommend voriconazole for initial antifungal therapy. Fluconazole is also moderately supported, contingent on the MIC. Weak support exists for combination antifungal therapy. Echinocandins are not recommended. CVAD removal and cardiac valve surgery is moderately supported (figure 5). We moderately recommend a long duration of therapy if there is organ involvement, and 2 weeks for only fungaemia.

Antigen biomarkers and other rare yeast infections

Specific serological markers to detect rare yeast pathogens are not available and there are no recommendations. Insufficient data exist for recommendations on the diagnostic use of the serum 1,3-β-D-glucan test; the test is weakly supported as a screening test as it might assist with the detection of some rare yeasts (appendix pp 179–80).

This guideline also covers *Kodamaea ohmeri*, *Malassezia*, *Pseudozyma*, *Rhodotorula*, *Saccharomyces*, and *Sporobolomyces* species infections. A summary of the antifungal recommendations is shown in the table. Details of epidemiology, evidence from the literature, and recommendations for diagnosis are within the appendix (*Kodamaea ohmeri* spp pp 63–81, *Malassezia*

	First-line therapy	First-line alternative	Second-line therapy	Avoid	Central venous access device removal
Geotrichum spp	Liposomal amphotericin B with or without flucytosine (moderately recommended)	Voriconazole (moderately recommended)	Drug class that was not used as first-line therapy (marginally recommended)	Echinocandins (recommended against)	No specific data (moderately recommended)
Saprochaete or *Magnusiomyces* spp	Liposomal amphotericin B with or without flucytosine (moderately recommended)	Voriconazole (moderately recommended)	NA	Echinocandins (recommended against)	Yes (strongly recommended)
Trichosporon spp	Voriconazole or posaconazole (moderately recommended)	Fluconazole (moderately recommended)	Liposomal amphotericin B or amphotericin B deoxycholate (marginally recommended)	Echinocandins (recommended against)	Yes (moderately recommended)
Kodamaea ohmeri	Liposomal amphotericin B or amphotericin B deoxycholate (moderately recommended)	Echinocandins (moderately recommended)	Voriconazole, fluconazole, other azoles, or different formulation of amphotericin B to that used as first-line therapy (marginally recommended)	NA	Yes (moderately recommended)
Malassezia spp*	Liposomal amphotericin B (moderately recommended)	Amphotericin B deoxycholate (moderately recommended)	NA	NA	Yes (strongly recommended)
Pseudozyma (*Moesziomyces* or *Dirkmeia*) spp	Liposomal amphotericin B (moderately recommended)	Voriconazole (moderately recommended)	Amphotericin B lipid complex (marginally recommended)	Fluconazole and echinocandins (recommended against)	Yes (strongly recommended)
Rhodotorula spp	Liposomal amphotericin B with or without flucytosine (moderately recommended)	Amphotericin B deoxycholate with or without flucytosine (marginally recommended)	NA	Triazoles and echinocandins (recommended against)	Yes (strongly recommended)
Saccharomyces spp	Liposomal amphotericin B or amphotericin B deoxycholate (moderately recommended)	Fluconazole or echinocandin (ie, caspofungin or micafungin) (moderately recommended)	Drug class that was not used as first-line therapy (marginally recommended)	NA	Yes (strongly recommended)
Sporobolomyces spp	Liposomal amphotericin B (moderately recommended)	Voriconazole (moderately recommended)	..	Fluconazole and echinocandins (recommended against)	Yes (moderately recommended)

Detailed recommendations regarding doses can be found in the appendix. Selection of salvage therapy is dependent on the drug class that the patient has already been treated with. NA=not applicable.
*Amphotericin B lock therapy is only weakly supported.

Table 1: **Recommended systemic antifungal therapy and other management in adults with rare yeast infections inclusive also of *Kodamaea ohmeri*, *Pseudozyma*, *Rhodotorula*, *Saccharomyces*, and *Sporobolomyces* spp infections**

pp 81–94, *Pseudozyma* spp pp 94–101, *Rhodotorula* spp pp 101–28, *Saccharomyces* spp pp 129–42, *Sporobolomyces* spp pp 155–62)

Children, neonates, and management constraints

Generally, recommendations for management of rare yeast infections in children and neonates are similar to those for adults with respect to diagnostic modalities and choice of antifungal therapy but need to take into account paediatric-specific dosing regimens, tolerability, and safety. These principles are described in the appendix (pp 181–87).

Realisation of early cross-consultation between specialists can be challenging as patients present to diverse first contacts of care. Further, no simple, bedside rapid antigen tests exist for direct pathogen detection from clinical samples. In the laboratory, these pathogens can be difficult to culture (eg, *Malassezia* spp), unfamiliar to laboratory personnel, and misidentified, hence access MALDI-TOF MS systems or molecular-based approaches that are up to date is a priority. Management pathways are reliant on multicentre epidemiological surveys involving reliable diagnostics to improve characterisation of these infections.

Finally, a small armamentarium of antifungal agents (eg, if essential medicines are restricted to fluconazole and amphotericin B deoxycholate) means that potent agents might be unavailable. Open-label clinical studies to obtain experience in treating rare yeast infections is worthy of discussion.

Conclusions

In conclusion, knowledge of local epidemiological patterns of rare yeast infections is important to inform diagnostic and management priorities. As exemplified by *G candidum*, *Saprochaete* or *Magnusiomyces* spp, and *Trichosporon* spp infections, fungaemia is common but clinical characteristics of all rare yeast infections are protean. We strongly recommend susceptibility testing by use of reference methods for epidemiological study but also as a useful tool to guide antifungal therapy. Although the guideline recommends particular antifungal and surgical treatments, the management of many rare

yeast infections requires considered and individualised approaches.

Contributors

SC-AC, JP, ALC, NPG, and OAC coordinated the work of the authors and guided the development of the guideline. SC-AC, ALC, JP, NPG, OAC, KA, JNdAJ, GG-E, JS-G, NG, AHG, CL-F, LO-Z, LP, TP, RR-R, DS, AS, and JS wrote the initial Review draft. All authors contributed to the literature review, compilation of data tables, and interpretation and assessment of recommendations. All authors participated in review and revisions, approved the final manuscript, and are responsible for all aspects of the work.

Declaration of interests

KA, DEA, JC, LD-G, CG, P-RH, MI, SSK, OL, LP, TP, RR-R, MR, JS-G, ES, DS, AS, IS, RS, JS, ET, LT, AMT, MH, and FFT declare no competing interests. SA-A reports speaker honoraria from Gilead Sciences and travel grants from Astellas and Pfizer, outside the submitted work. TB reports grants from Gilead Sciences and personal fees from Gilead Sciences and Pfizer, outside the submitted work. SC-AC reports untied educational grants from Merck Sharp and Dohme Australia and F2G and is on the antifungal advisory boards of Merck Sharp and Dohme Australia, Gilead Sciences, and F2G, outside the submitted work. ALC reports grants from Astellas and Pfizer; personal fees from Astellas, Pfizer, Eurofarma, Merck Sharp and Dohme, Gilead Sciences, and Biotoscana-United Medical; and non-financial support from Eurofarma, Gilead Sciences, and Biotoscana-United Medical, outside the submitted work. OAC is supported by the German Federal Ministry of Research and Education; is funded by the Deutsche Forschungsgemeinschaft under Germany's Excellence Strategy (Cologne Cluster of Excellence on Cellular Stress Responses in Aging-associated Diseases, EXC 2030—390661388); has received research grants from Actelion, Amplyx, Astellas, Basilea, Cidara, Da Volterra, F2G, Gilead Sciences, Janssen, Medicines Company, Melinta, Merck/Merck Sharp and Dohme, Octapharma, Pfizer, and Scynexis; is a consultant to Actelion, Allecra, Amplyx, Astellas, Basilea, Biosys, Cidara, Da Volterra, Entasis, F2G, Gilead Sciences, Matinas, MedPace, Menarini, Merck/Merck Sharp and Dohme, Mylan, Nabriva, Noxxon, Octapharma, Paratek, Pfizer, PSI, Roche Diagnostics, Scynexis, and Shionogi; and has received lecture honoraria from Al-Jazeera Pharmaceuticals, Astellas, Basilea, Gilead Sciences, Grupo Biotoscana, Merck/Merck Sharp and Dohme, and Pfizer, outside the submitted work. JNdAJ reports grants from Fundação de Amparo à Pesquisa do Estado de São Paulo, outside the submitted work. TF reports grants from Ministry of Health, Czech Republic, outside the submitted work. GG-E reports grants from Gador SA Laboratory (Argentina) and travel grants from Pfizer and Grupo Biotoscana, outside the submitted work. NG reports honoraria from Merck Sharp and Dohme, Australia, in 2019 and has participated in educational activities under the auspices of the Australia–New Zealand Mycology Interest Group. The Australia–New Zealand Mycology Interest Group workshops and meetings receive pharmaceutical sponsorship (from Pfizer, Gilead Sciences, Merck Sharp and Dohme, and Mayne Pharma), outside the submitted work. NPG reports grants from the National Institutes of Health, US Center for Disease Control and Prevention, Bill & Melinda Gates Foundation, UK Medical Research Council, and National Health Laboratory Service Research Trust and non-financial support from Gilead Sciences, outside the submitted work. AHG reports grants from Gilead Sciences, Merck Sharp and Dohme, and Pfizer and personal fees from Amplyx, Astellas, Basilea, Gilead Sciences, Merck Sharp and Dohme, Pfizer, F2G, and Synexis, outside the submitted work. CL-F reports grants from Gilead Sciences and Astellas and personal fees from Gilead Sciences, Astellas, Merck Sharp and Dohme, Basilea, and Angelini, outside the submitted work. JM reports grants from Astellas, Gilead Sciences, Merck Sharp and Dohme, and Pfizer, outside the submitted work. PM reports personal fees from Angelini, Basilea, Gilead Sciences, Merck Sharp and Dohme, Nabriva, Pfizer, and Fundación Ciencias de la Salud, outside the submitted work. LO-Z reports grants from Cidara, Scynexis, Amplyx, Pfizer, and Astellas and personal fees from Cidara, Scynexis, F2G, Pfizer, Astellas, Merck, and Gilead Sciences, outside the submitted work. JP reports grants from Merck, Astellas, Pfizer, Amplyx, and Minnetronix and personal fees from Merck, F2G, Scynexis, Amplyx, and Ampili, outside the submitted work. AV reports research grants from Procter and Gamble, L'Oréal Paris, Pfizer, and Astellas and honorarium from Merck Sharp and Dohme, outside the submitted work. NW reports grants from Astellas, bioMerieux, Cepheid, Cidara, Covance, F2G, and Viamet and personal fees from Gilead Sciences and Mayne Pharma, outside the submitted work. Y-CC reports personal fees for lectures from Pfizer, Merck Sharp and Dohme, and Gilead Sciences, outside the submitted work.

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