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Global guideline for the diagnosis and management of the endemic mycoses: an initiative of the European Confederation of Medical Mycology in cooperation with the International Society for Human and Animal Mycology

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GRT, TL, AC, and ACP served as guideline coordinators and served as the chair for each subsection working group. All authors contributed to the writing and editing of the manuscript.

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See Online for appendix

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Abstract

The global burden of the endemic mycoses (blastomycosis, coccidioidomycosis, emergomycosis, histoplasmosis, paracoccidioidomycosis, sporotrichosis, and talaromycosis) continues to rise yearly and these infectious diseases remain a leading cause of patient morbidity and mortality worldwide. Management of the associated pathogens requires a thorough understanding of the epidemiology, risk factors, diagnostic methods and performance characteristics in different patient populations, and treatment options unique to each infection. Guidance on the management of these infections has the potential to improve prognosis. The recommendations outlined in this Review are part of the “One World, One Guideline” initiative of the European Confederation of Medical Mycology. Experts from 23 countries contributed to the development of these guidelines. The aim of this Review is to provide an up-to-date consensus and practical guidance in clinical decision making, by engaging physicians and scientists involved in various aspects of clinical management.

Introduction

The endemic mycoses are caused by a diverse group of fungi that share characteristics: each fungus occupies a specific ecological niche in the environment and is able to cause disease in healthy and immunocompromised hosts. There are numerous species of dimorphic fungi; however, *Blastomyces, Coccidioides, Emergomyces, Histoplasma, Paracoccidioides, Sporothrix* spp, and *Talaromyces marneffei* (formerly *Penicillium marneffei*) represent the most commonly encountered causes of infections in clinical care. Biosafety is an important consideration when handling these organisms, and laboratories should incorporate national guidance and regulations into their processes and practices to ensure the safety of laboratory staff. There are substantial differences in the geographical distribution, clinical presentation, radiographic manifestations, diagnostic approach, and therapeutic interventions among these mycoses. Management requires recognition of risk factors (eg, environmental exposure in an endemic region) and appropriate use of diagnostic and therapeutic interventions. Readily available guidance is important to ensure efficient diagnosis and treatment, and to optimise patient outcomes.

This Review contains comprehensive guidance to facilitate clinical decision making and to provide an overview of the areas of uncertainty in the field. We aim to address limitations of previous recommendations, by engaging physicians and scientists involved in various aspects of the endemic mycoses, representing the fields of dermatology, haematology, infectious diseases, intensive care, microbiology, paediatrics, pathology, pharmacology, radiology, and surgery. Additionally, the guideline group, which comprises experts from all parts of the world, updates current knowledge in the field via a strict methodology

consistent with a previous guideline document.[1] The evidence and a full description of the methodology and literature supporting each recommendation can be found in the appendix (pp 1–150). The general approach applied in the European Confederation of Medical Mycology guideline programme has been described previously.[1] We invited experts to participate in this specific guideline in February, 2018. Our selection of experts was determined by their publication activity in the field of the endemic mycoses, their personal involvement in patient management, and their distribution over the world regions defined by the UN as previously described.[1] Further information on guideline development, systematic approach, authors, and work flow is provided in the panel. 37 scientific societies focusing on infectious diseases reviewed and endorsed this guidance document (appendix p 149).

Blastomycosis

Epidemiology

Blastomyces spp have been isolated in soils near freshwater drainage systems, although wind probably has a role in dispersal.[2] *Blastomyces dermatitidis* and *Blastomyces gilchristii* are seen primarily in southeastern and southcentral regions of the USA bordering the Mississippi and Ohio River basins, the northcentral states bordering the Great Lakes, and areas surrounding the St Lawrence Seaway, extending from Quebec into Saskatchewan in Canada (figure 1A). Other species are found in western parts of Canada and the USA (*Blastomyces helicus*),[3] in Africa and the Middle East (*Blastomyces percursus*), and in South Africa (*Blastomyces emzantsi*).

Diagnosis

The typical appearance of *Blastomyces* spp on microscopic examination of patient samples is a round-to-oval multinucleate yeast cell, 8–15 μm in size, with a single broad-based bud (figure 2A). Septate hyphae with a diameter of 1–2 μm and oval single-cell conidia at the tip of conidiophores (lollipop-like shape) are characteristic but not specific.[4] Serological methods do not have the specificity necessary for diagnosis. An antigen detection assay (MiraVista, Indianapolis, IN, USA) is available with a reported sensitivity of 85–93% and a specificity of 79–99%, although this assay has not been validated for less common *Blastomyces* spp. Urine testing is more sensitive than serum or bronchoalveolar lavage.[5]

Treatment

Antifungal therapy is recommended for all forms of blastomycosis. The severity of patient illness and the underlying level of immunosuppression guide these treatment choices. For patients with severe disease, liposomal amphotericin B (L-AmB; 5 mg/kg per day) or an alternative amphotericin B (AmB) formulation is generally recommended. The availability of the triazole agents has shortened the required duration of AmB therapy to 1–2 weeks for many patients. After clinical improvement with AmB, stepdown to a triazole is recommended. The triazole component is most often continued for 6–12 months depending on the site of disease, with more prolonged courses recommended for CNS or bone involvement, based on relapses in case series.[6]

The most used triazole-based treatment is itraconazole (200–400 mg/day), which is recommended as the first-line triazole, based on success rates of 90–95% in a prospective phase 2 study.[7] A small trial with fluconazole of 23 patients was less successful than previous reports of itraconazole,[8] but efficacy with a higher dose of fluconazole (400–800 mg/day) therapy was moderately successful (87%) and can be used in patients who are intolerant to other triazoles.[9] A case series where voriconazole was used has shown outcomes similar to itraconazole, including favourable efficacy in disease of the CNS.[10] Case reports with posaconazole and, more recently, isavuconazole suggest efficacy, although there is little experience with these agents.[11,12] The management of blastomycosis-associated acute respiratory distress syndrome is difficult and guided by data from case reports and small series of fewer than 50 cases. L-AmB is the mainstay of management. Corticosteroids have been used regularly for this indication in some centres, but there is little evidence for efficacy and expert consensus is absent.[13]

Recommendations

Clinical specimens should be examined microscopically with an optical brightener or fungal stains, or both. Fungal culture on Sabouraud dextrose agar or potato dextrose agar with and without cycloheximide should be incubated for up to 6 weeks at 25–30°C. In the USA and Canada, a *Blastomyces* antigen assay showing an acceptable sensitivity and specificity (>80%) is available. Testing of urine is preferred over other sample types. All patients with blastomycosis should have a chest radiograph done. Additional imaging is based on symptoms, to ascertain if complications of the disease have occurred and to determine a response to therapy.

All patients with blastomycosis should be treated. Patients with severe disease should receive L-AmB induction therapy in most cases. Alternative AmB formulations are acceptable if L-AmB is not available. After clinical improvement with AmB, stepdown to itraconazole is recommended for 6–12 months. Longer courses of therapy are recommended for individuals with CNS or bone involvement. Alternative triazoles can be used in cases of itraconazole intolerance, although higher doses of fluconazole are required and evidence with other triazoles is scarce.

Coccidioidomycosis

Epidemiology

Coccidioidomycosis is caused by *Coccidioides immitis* and *Coccidioides posadasii*. These fungi survive well in areas of low precipitation (12–50 cm of rainfall per year), with few winter freezes and alkaline soil.[14] The inoculum needed for infection is small and can be as low as a single arthroconidium. *C immitis* is primarily found in California and Washington in the USA and in northwest Mexico, whereas *C posadasii* is found in the southwestern region of the USA, in Mexico, and in arid regions of South America (figure 1B).[15] Within the USA, the number of coccidioidomycosis cases continues to increase yearly.

Diagnosis

The diagnosis of coccidioidomycosis is proven by culture of *Coccidioides* spp from any clinical site. Histopathology can show spherules or endospores (figure 2B). *Coccidioides* spp grow on routine blood agar and Sabouraud dextrose agar, incubated at 25–30°C. Mycelial growth can be seen as early as 4–5 days after incubation, although cultures should be held for up to 6 weeks. Most patients are diagnosed with coccidioidomycosis via serological testing. EIA, immunodiffusion, and complement fixation (CF) testing are commercially available and exhibit differing sensitivity and specificity.[16] A typical coccidioidal infection results in serum IgM production within 1–3 weeks of symptoms onset, followed thereafter (4–8 weeks) by IgG production.[17] Coccidioidal antigen testing is also available with an EIA and might be helpful in patients who are highly immunocompromised. Meningitis remains a particularly morbid form of the disease and should be considered with sustained headache or other CNS symptoms.[18]

Patients with primary pulmonary disease usually have a dense infiltrate, often in the upper lobe, with associated hilar or mediastinal adenopathy. Severe manifestations of acute pulmonary coccidioidomycosis are uncommon and are most frequently observed after a high inoculum exposure or substantial underlying immunodeficiency.

Treatment

Many clinicians support a period of observation rather than antifungal therapy for individuals with primary pulmonary coccidioidomycosis because most patients will control their infection without long-term sequelae. Two observational studies have shown antifungal therapy does not appear to affect the risk of extrapulmonary dissemination.[19,20] Treatment with fluconazole or itraconazole should be given to all patients with underlying immunosuppression, substantial cardiopulmonary comorbidities, or those with prolonged infection or CF titres of 1/32 or higher. Patients exhibiting weight loss of more than 10%, night sweats for more than 3 weeks, and infiltrates exceeding 50% of one lung or bilateral disease should be treated as well, particularly if these individuals have CF titres of 1/32 or higher.[21] Severe disease should be treated with an AmB formulation, followed by a triazole. Disease refractory to fluconazole is treated with itraconazole, voriconazole, posaconazole, or AmB, depending on disease severity.[21,22]

Recommendations

We recommend that clinical specimens be examined microscopically with standard fungal stains for the presence of *Coccidioides* spp. Identification of spherules in a clinical specimen is considered proven disease, even in the absence of positive culture results. We recommend serological testing of blood in all patients with suspected coccidioidomycosis, with repeat quantitative serological testing (CF) approximately every 12 weeks during care to evaluate a response to therapy. A CSF sample should be obtained from all patients suspected of meningitis. All patients with coccidioidomycosis should have a chest radiograph. Pulmonary infiltrates from *Coccidioides* spp should be followed up to resolution, with repeat imaging after the initial infection. Treatment for pulmonary disease should start with fluconazole or itraconazole, whereas meningitis should be treated with fluconazole as the first-line agent.

Emergomycosis

Epidemiology

There are currently five species of *Emergomyces* reported to cause human disease. Nearly all cases of emergomycosis have involved patients who were immunocompromised. Disease caused by *Emergomyces pasteurianus* has been reported in patients from Europe, Asia, India, and Africa. *Emergomyces africanus* has been reported only from southern Africa (figure 1C). Emergomycosis is the most frequently diagnosed endemic mycosis in South Africa.[23] Emergomycosis caused by *Emergomyces canadensis* has been infrequently reported in central and western regions of North America, whereas *Emergomyces orientalis* and *Emergomyces europaeus* have been reported from only a single patient each.[24,25]

Diagnosis

The diagnosis of emergomycosis is proven by culture of *Emergomyces* spp from blood or tissue.[26,27] Clinical samples inoculated onto standard fungal media (eg, Sabouraud agar, malt extract agar, or potato dextrose agar) are incubated at 24–30°C and typically grow after 7–30 days. The identification of *Emergomyces* spp in culture can be confirmed by DNA sequencing.[26] Skin lesions are present at the time of diagnosis in 95% of patients and biopsy is essential for diagnosis.[26] Histopathology is suggestive, but *Emergomyces* spp yeast cells are morphologically indistinguishable from those of *Histoplasma* spp. Antigen testing specific for emergomycosis is not available.

Treatment

There have been no trials regarding the treatment of emergomycosis, and all data are observational. Minimum inhibitory concentrations for fluconazole of 64 μg/mL or more have been reported for most isolates tested, including isolates of *E africanus*, *E canadensis*, *E orientalis*, and *E pasteurianus*.[28] AmB and mould-active triazoles have been consistently active in vitro. The optimal dose and duration of antifungal therapy for emergomycosis is not yet established. Most patients reported in the literature have been treated either with AmB followed by itraconazole or itraconazole alone.[29]

Recommendations

Culture of *Emergomyces* spp from a patient with compatible symptoms should be considered diagnostic of disease. When skin lesions are present, punch or incisional biopsies are strongly recommended; blood cultures should be done in aerobic bottles and, where available, lysis-centrifugation tubes. Patients who are immunocompromised with disseminated disease should be treated with L-AmB (3–5 mg/kg per day) for 10–14 days or with an alternative AmB formulation. Maintenance treatment with itraconazole (200 mg orally twice daily) is recommended for 12 months pending immune reconstitution.

Histoplasmosis

Epidemiology

Histoplasma spp are commonly present in soil contaminated with bat guano and bird excreta. Studies of skin testing with histoplasmin have shown that millions of people living

in Latin America and the Caribbean have been exposed to the fungus.[30] In North America, histoplasmosis is highly endemic along the St Lawrence, Mississippi, and Ohio River basins, and microfoci exist in the mid-eastern states (figure 1D). Although histoplasmosis is most frequently documented in the Americas, this condition is a true global disease. In a 5-year European study, 118 cases of histoplasmosis were reported,[31] with autochthonous cases reported in Germany, Italy, and Turkey. In Africa, over 400 cases of histoplasmosis have been reported,[32] with most cases secondary to *Histoplasma capsulatum* var *duboisii* in west Africa.

Diagnosis

All biopsied tissues should be submitted for either periodic acid–Schiff or Grocott methenamine silver staining (figure 2C). The sensitivity of tissue examination varies by the burden of disease and is highly dependent on the degree of host immunosuppression.[33] Conventional blood cultures have low sensitivity (around 50%) in patients with advanced HIV,[34] although improved sensitivity is seen with the lysis-centrifugation method. Serological testing is most useful for patients with chronic pulmonary histoplasmosis and might not be useful in patients with severe immunosuppression. The detection of *Histoplasma* spp antigen in urine or serum is useful in making a rapid diagnosis of probable histoplasmosis and, if positive, is useful for longitudinal assessment. Chest, abdominal, and CNS imaging should be done according to the clinical scenario.

Treatment

In a randomised clinical trial, L-AmB at 3 mg/kg daily was shown to provide a survival benefit, compared with AmB-deoxycholate (AmB-d), in patients with advanced HIV and disseminated histoplasmosis.[35] After successful induction therapy during the treatment of disseminated infection, itraconazole (200 mg twice daily) is usually given for at least 1 year.[36] In individuals with less severe disease, fluconazole has a lower success rate than itraconazole,[35,37] and emergence of fluconazole resistance has been reported in patients receiving fluconazole therapy.[38] Voriconazole is not routinely recommended.[39] Histoplasmosis secondary to tumour necrosis factor-α inhibitor therapy requires discontinuation of the tumour necrosis factor-α blocker during antifungal therapy. After a clinical response to treatment, pharmacological immunosuppression might be reinstituted if antifungal treatment is administered for around 12 months and the test results for the individuals are negative for *Histoplasma* spp antigen.[40]

Recommendations

Whenever possible, tissue should be obtained for the histopathological diagnosis of histoplasmosis, using fungal stains (ie, Grocott methenamine silver staining) and fungal culture. Most clinical laboratories identify isolates using a DNA probe, although in some locations the conversion from mycelial phase to yeast is still done. L-AmB is the drug of choice for induction therapy for patients with advanced HIV and moderate-to-severe histoplasmosis. Other AmB formulations are acceptable alternatives when L-AmB is not available. Itraconazole is an alternative induction therapy for patients with less severe infection. Antifungal treatment in non-immunosuppressed patients is suggested for at least 6

months, although the severity and site of disease need to be considered before determining the duration of therapy.

Paracoccidioidomycosis

Epidemiology

Paracoccidioides spp are soil-inhabiting fungi, although the current understanding of their precise environmental habitat is limited. The primary infection usually occurs during the first two decades of life in individuals who live within the endemic regions of Latin America and who have diverse activities related to the management of soil or soil products. Paracoccidioidomycosis occurs in the subtropical humid areas of most of the countries in Latin America (figure 1E). The prevalence of this infection is known to vary greatly between different endemic regions. However, skin testing has shown up to 50–75% of individuals within an endemic region have been infected.[41] The acute or subacute clinical forms, representing 10% of the clinical cases, are prevalent in children and adolescents (younger than 16 years), affecting both sexes equally. The chronic form is prevalent in adults (older than 16 years), with a male to female ratio of 20:1, and this difference might be secondary to inhibition of mycelial-to-yeast conversion by oestrogens.[42]

Diagnosis

Microscopy enables a proven diagnosis of paracoccidioidomycosis to be made. Rounded, thick-walled yeast cells (typically 15–30 μm in diameter, and up to 60 μm in some cases) with multiple buds (ship wheel-like, pilot wheel-like, or Mickey Mouse ear-like cells; figure 2D) are diagnostic features and are frequently observed in aspirates but are uncommon in sputum samples. Cultures should be inoculated and incubated at 25–30°C for 4–8 weeks, although these cultures might be negative depending on the site and burden of infection. Most patients are diagnosed using non-invasive testing, such as serological testing. Immunodiffusion assays (IMMY, Norman, OK, USA) are the most widely used reference assay.[43–45] This assay is inexpensive and has a high specificity (>95%) and sensitivity (around 80%), although the assay might not be widely available in all countries. Quantitative antibody titres are higher in patients with acute and more severe disease forms than in patients with less severe disease. The guidelines for the use of antibody detection in the diagnosis of paracoccidioidomycosis have been summarised in the appendix (p 72). Serological testing can also be used to assess the response to treatment, with a decrease in titre considered as a favourable sign.[43] Antigen detection assays are not yet commercially available.

Treatment

Itraconazole has largely been used for patients with mild-to-moderate clinical forms of the disease (appendix pp 77–78).[46–48] In a single-centre noncomparative study, itraconazole has been shown to exhibit an efficacy rate of 91% (median of 6 months for the duration of treatment).[47] Comparison of itraconazole with co-trimoxazole (trimethoprim–sulfamethoxazole) has shown itraconazole to be superior (86·4% success rate *vs* 51·3% success rate).[49] Another study showed a significantly shorter time to serological cure in the itraconazole group compared with the co-trimoxazole group (105 days *vs* 159 days;

p=0.001).[48] Voriconazole (6 mg/kg per day for 6–12 months) is similarly efficacious in paracoccidioidomycosis and is useful in cases with CNS involvement.[46] AmB is recommended for patients who are immunocompromised (ie, patients with advanced HIV disease). After induction therapy with an AmB formulation, maintenance treatment with an azole derivative or co-trimoxazole is required.

Recommendations

Due to the characteristic appearances of *Paracoccidioides* spp in clinical samples, microscopy has an important role in the diagnosis of paracoccidioidomycosis. Microscopy should preferably be done using optical brighteners. Paracoccidioidomycosis is mainly a chronic condition, and antibodies can be detected in most infected patients. However, the accuracy of serological assays for the diagnosis of paracoccidioidomycosis is dependent on the quality as well as the sensitivity and specificity of the antigen preparation used. It is recommended that serological testing only be done by reference laboratories, using reagents with known and published performance characteristics. Itraconazole (200 mg daily for 9–12 months) is the therapy of choice for patients with mild-to-moderate forms of paracoccidioidomycosis, with co-trimoxazole (for 18–24 months) being the main therapeutic alternative to itraconazole. A short (2–4 weeks) induction therapy with AmB is reserved for severe cases, or for patients who are immunocompromised. Induction therapy with AmB should be followed by 200–400 mg of itraconazole.

Sporotrichosis

Epidemiology

Sporotrichosis is a subacute-to-chronic infection caused by the dimorphic saprotrophic fungal genus *Sporothrix*, of which only a few species are known to infect humans and animals.[50] The estimated prevalence of sporotrichosis is between 0·1–0·5%, although the number of cases is rapidly increasing in Brazil, which specifically relates to *Sporothrix brasiliensis* zoonotic transmission (figure 1F). Previously, it was believed that only members of the pathogenic clade of *Sporothrix schenckii* were able to cause disease, but a taxonomic revision has shown the presence of novel medically relevant species: *S brasiliensis*, *Sporothrix globosa, Sporothrix mexicana*, and *Sporothrix pallida*.[51,52] The clinical presentation of *S schenckii* infection is typically a chronic subcutaneous mycosis. *S globosa* most commonly causes a fixed or lymphocutaneous infection, whereas infections caused by *S brasiliensis* are often more severe. Infections caused by *S mexicana* or *S pallida* typically present with subcutaneous nodules or draining lesions.[50]

Diagnosis

The standard and most sensitive method for diagnosis of invasive sporotrichosis is culture, although cultures might be negative.[53] Material obtained via lesion aspiration, biopsy, sputum, or body fluids should be inoculated on Sabouraud dextrose agar and incubated at room temperature (figure 2E). Histopathology is often negative, even with the use of fungal specific stains, which is largely due to the small number of organisms that are needed to cause disease. The ovoid yeast cells are 3–5 μm in diameter, oval-shaped to cigar-shaped, and eosinophilic projections from the yeast can be present, representing the asteroid body

associated with *Sporothrix* spp. A latex agglutination assay has been used in the past to assist in the diagnosis of meningeal sporotrichosis,[54] but this assay is no longer available, and serological testing has little use in anything other than meningitis. Other assays have been developed and have exhibited excellent sensitivity (89–90%) and specificity (100%) but are currently limited by availability.[53–55]

Treatment

For cutaneous and lymphocutaneous sporotrichosis, therapy with itraconazole is associated with response rates of 80–100% (appendix pp 87–89).[56–58] A variety of different itraconazole doses have been studied, with no clear difference observed among doses prescribed.[56] In a cohort study comparing terbinafine (250 mg daily) and itraconazole (100 mg daily), there was no marked difference in outcomes and no marked difference in adverse events between groups.[58] Saturated solution of potassium iodide has long been used for the treatment of cutaneous sporotrichosis, with response rates between 70% and 89%.[59,60] Although this option is efficacious and cost-effective, alternative agents are preferred due to the difficulty of this regimen for patients (eg, dysgeusia, gastrointestinal intolerance, and acneiform eruptions).[59] Insufficient data are available for newer azole agents used in single or combination salvage therapy, and high minimum inhibitory concentrations have been observed in vitro with voriconazole and isavuconazole, suggesting these agents are not effective.[61]

Recommendations

We recommend culture and histopathological evaluation of skin or tissue aspirates or biopsies when the diagnosis of sporotrichosis is considered. Skin and soft tissue sporotrichosis rarely warrants imaging and, in these cases, only if concern exists for spread to contiguous bone or deeper structures. For cutaneous and lymphocutaneous sporotrichosis, itraconazole (200 mg orally daily) is recommended for 2–4 weeks after resolution of lesions, usually for a 3-month to 6-month duration of therapy. Alternative therapies include terbinafine (500 mg orally twice daily), or increasing the oral itraconazole dose to 200 mg twice daily. We recommend against using voriconazole or isavuconazole. For disseminated or severe pulmonary sporotrichosis, L-AmB (3–5 mg/kg daily) is recommended or, alternatively, AmB-d (0·7–1·0 mg/kg daily). After the patient has shown a favourable response to treatment, therapy can be changed to itraconazole (200 mg orally twice daily) for at least 12 months.

Talaromycosis

Epidemiology

Talaromycosis is an invasive fungal infection caused by the thermally dimorphic fungus *T marneffei* and is endemic throughout southeast Asia and is highly endemic in northern Thailand, Vietnam, Myanmar, Hong Kong, Taiwan, southern China, and northeastern India (figure 1G).[62] HIV is a major risk factor for talaromycosis. In just over two decades, the HIV epidemic has transformed talaromycosis from a rare infection to a leading HIV-associated opportunistic infection in southeast Asia, accounting for up to 16% of HIV-associated hospital admissions.[63–65] Furthermore, the fungus is the second leading cause

of HIV-associated bloodstream infections and death in Vietnam and southern China, with a mortality of up to 28%.[66]

Diagnosis

A presumptive diagnosis of talaromycosis is made based on the microscopic examination of skin lesion scrapings, lymph node or bone marrow aspirates, or based on the histopathological examination of tissue sections. Occasionally, *T marneffei* can be observed on the peripheral blood smear of patients with fungaemia. Characteristics of *T marneffei* include identification of a transverse septum in a dividing yeast cell (figure 2F), 3–6 μm in diameter, round-to-oval in shape, extracellular, and present within macrophages. Antigen detection (Mp1p) is highly accurate, inexpensive, does not require sophisticated equipment, and is particularly well suited for patients with advanced HIV disease and high fungal burden in the blood. A commercial antigen detection assay was approved in 2018 in China for clinical use and other assays are in development. A number of qPCR assays, based on specific *T marneffei* regions, have been developed. These assays have high specificities (100%) in whole blood or plasma samples, but sensitivity ranges from 70% to 86%.[67,68]

Treatment

Disseminated talaromycosis is fatal if untreated, and the mortality rate approaches 30% even with antifungal therapy.[62,65,66] Treatment should be given promptly to all patients who are immunocompromised. Similar to the approach in cryptococcosis, antifungal therapy is divided into induction, consolidation, and maintenance phases. In a multicentre, randomised controlled trial in Vietnam, induction therapy with AmB-d was shown to be superior to itraconazole with respect to mortality, blood fungal clearance, disease relapse, and immune reconstitution inflammatory syndrome.[69] A double-blind, placebo-controlled trial in Thailand showed that maintenance therapy with itraconazole (200 mg daily) in patients with advanced HIV disease decreased the relapse rate from 57% to 0% ($p<0{\cdot}001$).[70] Primary prophylaxis with itraconazole (200 mg orally daily) has been shown to reduce the incidence of invasive fungal infections (ie, talaromycosis, cryptococcosis, and oesophageal candidiasis) in HIV-infected patients with a CD4 count of less than 200 cells per μL in a randomised controlled trial in Thailand.[71]

Recommendations

In patients with a clinical suspicion of talaromycosis, we strongly recommend that patient specimens, including skin smears or biopsy, blood, sputum, and aspiration samples of lymph nodes, pus, bone marrow, pleural fluid, ascites, and CSF, should be sent for direct microscopy and fungal cultures. Identification of a transverse septum on microscopy establishes a presumptive diagnosis. Culture is the gold standard for diagnosis of talaromycosis and should be observed for up to 14 days. In settings where the Mp1p test is not available but there is a high clinical suspicion in patients without typical skin lesions, we recommend qPCR testing of whole blood or plasma with a validated in-house assay as a rapid diagnostic. We strongly recommend induction therapy with AmB. Specifically, L-AmB is preferred over AmB-d where available. L-AmB is given at 3–5 mg/kg per day intravenously, and AmB-d is given at 0·7 mg/kg per day intravenously, both for 10–14 days,

followed by consolidation therapy with itraconazole (200 mg orally twice daily) for 10 weeks, followed by maintenance therapy with itraconazole (200 mg orally daily).

Future directions and unmet needs

Important questions persist in the field of the endemic mycoses. The fungal kingdom has undergone substantial taxonomic revision and new species have recently been proposed. The importance of these cryptic species has yet to be determined, although emerging data suggest antifungal susceptibility and host differences. In addition to cryptic species (which are distinguished only by genetic but not phenotypic differences), several morphologically and clinically distinct fungi, such as *S brasiliensis*, several new species of *Blastomyces*, and the new genus *Emergomyces* have been recognised. New diagnostics focused on non-invasive methods (eg, serological testing, antigen capture, breath testing, and imaging) are also under active investigation and merit further study. Invitro susceptiblity testing and its correlation to clinical response will also need to be further evaluated. Because many diagnostics require the expertise of specialised reference laboratories, improvements in this area would be a welcome advance and might reduce the time to diagnosis and initiation of treatment. A number of novel antifungal agents are in various stages of development, and several have substantial activity in the treatment of endemic mycoses and might be able to alter the time course of disease.[72,73] Improvements in our understanding of these diverse mycoses require the input and collaboration of a wide range of investigators, and through collaborative efforts advanced the field of endemic mycoses can continue.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Key messages

- The endemic mycoses cause disease in both immunocompetent and immunocompromised hosts.
- The geographical range of the endemic mycoses continues to expand, following their recognition in non-traditional regions.
- Several novel species have been recently described in the endemic mycoses.
- Advances in laboratory techniques and non-invasive testing have improved diagnostic test specificity and sensitivity.
- Radiographic imaging is generally warranted only if concern for infection at a particular site exists—routine radiography is not typically indicated.
- Treatment options continue to expand, and our understanding of agent selection as well as dose and duration of therapy continues to evolve.

Panel: How the guideline group worked

In January, 2018, experts were identified based on their publication activity in the field of the endemic mycoses in the previous 5 years, their involvement in patient management, and their distribution over world regions defined by the UN. Experts were invited to develop this guideline in February, 2018.

This guideline follows the structure and definitions of previous guidelines on invasive fungal infections, which are in accordance with the Grading of Recommendations Assessment, Development and Evaluation (GRADE) and Appraisal of Guidelines for Research & Evaluation (AGREE) systems. The PICO (population, intervention, comparison, and outcome) approach is reflected by the tables listed in the appendix (p 7).

Both, diagnostic assays and treatment strategies might alter patient course, and are thus regarded as interventions. First, a population is defined; then the intention or objective is stated, followed by the intervention. For such logical sequence, strength of recommendation (SOR) and quality of evidence (QOE) are provided, followed by the references on which the recommendation is based. SOR and QOE are results of two independent evaluations, thus allowing a strong recommendation even in the absence of the highest quality evidence.

Search strings used were (“endemic mycoses” OR “endemic fungal infect*” OR Blastomyc* OR Coccidioid* OR Emmonsi* OR Emergomyc* OR Histoplasm* OR Paracoccidioid* OR Penicilliosis OR “Penicillium marneffei” OR Sporotrichosis OR Sporothr* OR Talaromyc* [All Fields]) AND (epidemiology OR outbreak OR treatment OR therapy OR diagnosis OR diagnostics) OR (case*[Title/Abstract] OR patient*[Title/Abstract] OR report[Title/Abstract]) AND (“2013/01/01”[Pratt]:“2017/12/31”[PDat])”.

From March to May, 2018, video conferences on the methodology were held, and a video tutorial was added in March, 2018. Assistance and supervision to the group were provided by the coordinators (GRT, TL, AC, ACP). Documents were shared among the authors on a password-protected OneDrive (Microsoft Corp, Redmond, WA, USA) repository, and were updated several times per day. Updates on PICO tables were written in red font; after spellcheck and formatting font colour was changed to blue for consideration by the group. Contents discussed and agreed on were changed to black font. Once all tables were finalised, a writing group, including all authors, contributed the first draft, which was circulated to all participants in February, 2020. Recommendations were consensus-based. If no consensus was found, majority vote was used.

In June, 2020, a 4-week public consultation phase ensued. Comments received were evaluated, and either dismissed or used to change the manuscript, resulting in a final author review in December, 2020. 37 scientific societies reviewed and endorsed the guidance document.

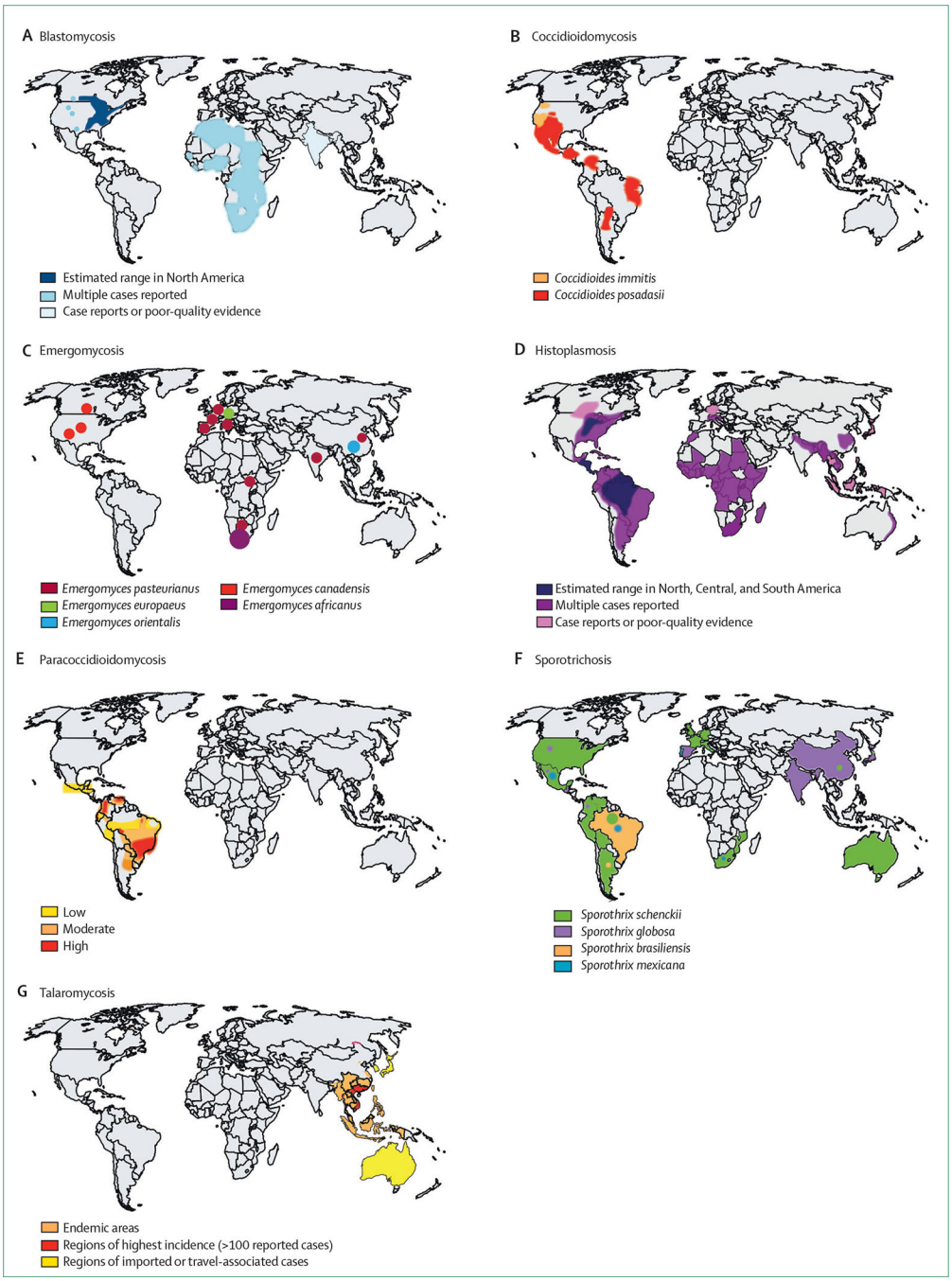

Figure 1: Geographical regions of the endemic mycoses (A–G)

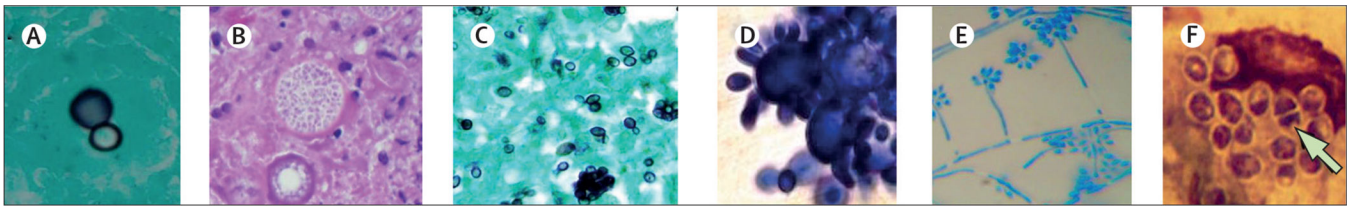

Figure 2: Microscopic findings of endemic mycoses

(A) Grocott methenamine silver staining of *Blastomyces* spp yeast from a tissue sample with broad-based budding apparent in centre (400× magnification; courtesy of Dr Carol Kauffman). (B) Hematoxylin and eosin staining of *Coccidioides* spp spherule containing numerous endospores (40× magnification; courtesy of Dr Bridget Barker). (C) Silver staining shows yeast forms of *Histoplasma* spp (40× magnification; courtesy of Dr John Baddley). (D) Lactophenol cotton blue staining of a smear paracoccidioidomycosis (400× magnification; courtesy of Dr Flavio Telles). (E) Lactophenol cotton blue stain shows rosette-like clusters at the tips of the conidiophores, which are characteristic of *Sporothrix* spp (40× magnification; courtesy of Dr Flavio Telles). (F) Giemsa stain shows transverse septum (arrow) in a dividing yeast cell, which is characteristic of *Talaromyces marneffei* (60× magnification; courtesy of Dr Thuy Le).