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Review

Endemic mycoses: a treatment update

Olivier Lortholary[a]*, David W. Denning[b] and Bertrand Dupont[c]

[a]Service de Médecine Interne, Centre de Recherche en Pathologie Infectieuse et Tropicale, Hôpital Avicenne, Université Paris Nord, 125 route de Stalingrad, 93009 Bobigny, France; [b]Department of Infectious Diseases and Tropical Medicine (Monsall Unit), North Manchester General Hospital, Delaunays Road, University of Manchester, Manchester M8 6RB, UK; [c]Unité de Mycologie et Centre National de Référence des Mycoses et des Antifongiques, Institut Pasteur, 25 rue du Dr Roux, 75724 Paris Cedex 15, France

Endemic mycoses remain a major public health problem in several countries and they are becoming increasingly frequent with the spread of HIV infection. Amphotericin B remains the drug of choice during the acute stage of life-threatening endemic mycoses occurring in both immunocompetent and immunocompromised hosts. Ketoconazole is effective in non-AIDS patients with non-life-threatening histoplasmosis, blastomycosis, or paracoccidioidomycosis. Itraconazole is the treatment of choice for non-life-threatening *Histoplasma capsulatum* or *Blastomyces dermatitidis* infections occurring in immunocompetent individuals and is the most efficient secondary prophylaxis of histoplasmosis in AIDS patients. Itraconazole is also effective in lymphocutaneous and visceral sporotrichosis, in paracoccidioidomycosis, for *Penicillum marneffei* infection, and is an alternative to amphotericin B for *Histoplasma duboisii* infection. Coccidioidomycosis may be effectively treated with prolonged and sometimes life-long itraconazole or fluconazole therapy. Fluconazole has relatively poor efficacy against histoplasmosis, blastomycosis and sporotrichosis. New antifungal agents have been tested *in vitro* or in animal models and may soon be evaluated in clinical trials.

Introduction

Endemic mycoses remain a major public health problem in several countries. They are most often acquired through contact with nature and rarely with infected humans or animals. Most of the cases are observed in rural areas and particularly in low socioeconomic groups. Most systemic endemic mycoses occur after inhalation of conidia, while subcutaneous mycoses are caused by the inoculation of vegetable matter or soil. The frequency of AIDS-associated histoplasmosis and coccidioidomycosis is now increasing with the spread of HIV infection, usually presenting as disseminated disease;[1] other endemic mycoses are less frequently associated with HIV infection.[2,3]

Although there have been no studies directly comparing azoles and amphotericin B in the treatment of endemic mycoses, the availability of oral azoles has ensured better tolerated treatments. This seems particularly useful for fungal diseases that need lengthy therapeutic courses, such as coccidioidomycosis, or for endemic mycoses occurring during AIDS, which require lifelong suppressive therapies.

This update will focus on the treatment of endemic mycoses and review recent papers on this topic. Recommendations are summarized in the Table.

Histoplasmosis due to *Histoplasma capsulatum*

Immunocompetent individuals

In immunocompetent patients treatment of histoplasmosis is indicated for disseminated disease and in cases with endovascular or nervous system involvement. Treatment is also indicated for chronic pulmonary disease and for symptomatic mediastinitis. Amphotericin B is the most active drug presently available, followed by itraconazole and ketoconazole. Fluconazole is less active, even at higher doses, but is useful in patients who cannot tolerate itraconazole or ketoconazole or who are receiving interacting

*Corresponding address. Unité de Mycologie et Centre National de Référence des Mycoses et des Antifongiques, Institut Pasteur, 25 rue du Dr Roux, 75724 Paris Cedex 15, France. Tel: +33-1-45-68-83-54; Fax: +33-1-45-68-84-20; E-mail: olortho@pasteur.fr

Table. Summary of the therapeutic recommendations for endemic mycoses

	First choice	Alternative regimen
H. capsulatum		
non-AIDS		
life-threatening	AmB (1 mg/kg per day)	–
mild or moderate	Itra (≥200 mg/day; >6 months[a])	Keto or Fluco
AIDS		
induction		
life-threatening	AmB (1 mg/kg per day; <2 weeks)	–
mild or moderate	Itra (400 mg/day)	Fluco (800 mg/day)
suppressive therapy	Itra (400 mg/day)	Fluco (400 mg/day)
H. duboisii	Itra (100–400 mg/day; >6 months)	Keto or AmB
Coccidioidomycosis		
non-AIDS		
non-meningeal	Itra (400 mg/day; >1 year)	Fluco (400 mg/day; >1 year)
meningeal	Fluco (≥400 mg/day; lifelong)	
AIDS		
induction		
life-threatening	AmB (1–1.25 mg/kg per day)	Fluco (>400 mg/day)
mild or moderate	Itra (400 mg/day)	Fluco (400 mg/day)
suppressive therapy	Itra (400 mg/day)	Fluco (400 mg/day)
Blastomycosis		
life-threatening or CNS	AmB (1 mg/kg per day)	–
mild or moderate	Itra (≥200 mg/day)	Keto or Fluco
Paracoccidioidomycosis	Itra (≥200 mg/day)	Keto
Penicilliosis (in AIDS)	AmB(≥0.6 mg/kg per day) then Itra (≥200 mg/day)	Itra (400 mg/day)
Sporotrichosis		
lymphocutaneous	Itra (200 mg/day; >3 months)	SSKI
visceral	Itra (400 mg/day; >1 year)	AmB or Fluco
severe disseminated or CNS	AmB (1 mg/kg per day)	–
Chromoblastomycosis	Itra (100–200 mg per day) ± 5-FC	–
Lobomycosis	Surgery	–
Mycetoma	Keto (>3 months) ± surgery	Itra

[a]Patients with chronic cavitary pulmonary histoplasmosis require >1 year of therapy.
Abbreviations: SSKI, saturated solution of potassium iodide; AmB, amphotericin B; Itra, itraconazole; Fluco, fluconazole; Keto, ketoconazole; 5-FC, flucytosine.

drugs. 5-Flucytosine has no place in the treatment of histoplasmosis because *H. capsulatum* is naturally resistant.

Primary infection. Treatment of primary infection is rarely required in adults unless the patient is symptomatic for more than 8 days or hospitalization is necessary.[4–6] However, treatment should always be given in children less than 1 year old, because of the potential speed of disease progression. Ketoconazole may be administered (200–400 mg/day) for the first 2 months or iv amphotericin B (0.3–0.5 mg/kg per day) for 2–4 weeks. Itraconazole (200 mg/day) may also be used. Fluconazole has been successfully used for acute non-life-threatening pulmonary disease in two patients.[7] Corticosteroid therapy is sometimes administered to patients with hypoxia, but no definitive recommendations can be made.

Chronic pulmonary histoplasmosis. In previous studies, response rates to amphotericin B treatment for 6 weeks to 4 months have been up to 75%.[4–6] However, relapse is a problem and respiratory tract cultures must be obtained for up to 1 year after the end of treatment to define cure.

Azoles are now the first-line treatment of chronic pulmonary histoplasmosis. Ketoconazole (400 mg/day for 6–12 months) is still a first-line treatment, with 84% efficacy reported in a Mycoses Study Group trial.[8,9] More recently, itraconazole has been successfully used for this indication.[4–6,10] In an open non-comparative trial, itraconazole (200–400 mg/day for a median of 9 months) was successful in 13 of 20 patients (65%) with pulmonary cavitary lesions.[11] Itraconazole was also successful in all patients with mediastinal or nodular pulmonary lesions. A long duration of therapy is needed in patients with incomplete responses and/or extensive disease. Recently, McKinsey *et al*.[7] described 11 patients with chronic pulmonary histoplasmosis who received fluconazole (usually 400 mg/day) for a median of 7 months. Five (46%) of them responded to therapy (three cured, two improved) without any significant toxicity.[7] Fluconazole has also been reported effective in histoplasmic mediastinal granuloma,[12] although alopecia has been recently recognized as a complication of long-term treatment with this drug.[13] This lower response rate of fluconazole compared with ketoconazole and itraconazole is consistent with previous data.

Surgery may be indicated for relapsing or refractory/pulmonary cavitary lesions or for mediastinal mass lesions although it has not been demonstrated that this helps prevent mediastinal fibrosis. Other indications for surgery are less frequent (e.g. cases of endocarditis, despite some rare observations demonstrating the efficacy of antifungals alone, or pericarditis causing tamponade).

Disseminated histoplasmosis. The mortality rate of disseminated disease is 83–93% in non-immunocompromised patients,[6] but is reduced with the use of amphotericin to 7–23%.[4–6] Relapses are observed in 5–23% of cases, more often in patients with endocarditis, infected prostheses, mycotic aneurysms, or adrenal gland involvement. Liposomal amphotericin B was found effective in murine histoplasmosis and in at least one human case.[14,15]

Ketoconazole (400 mg/day for at least 6 months) may be given as a first-line treatment in patients without central nervous system (CNS) involvement.[4–6] The response rates were up to 100% in one Mycoses Study Group trial.[8] A daily dosage of 800 mg can no longer be recommended, since it is less well tolerated (causing digestive tract disturbances and endocrine abnormalities) and was found to be associated with a decreased efficacy (57%) compared with the 400 mg dose (100%).[8] Initial studies of itraconazole[4–6,10] tested low dosages (100 mg/day) of the drug, which controlled the disease in up to 70% of cases (of which ⩾31% of cases were cured). In another Mycoses Study Group trial,[11] itraconazole (200–400 mg/day for a median of 8 months) was effective and safe in all ten treated patients. One recent study documented the efficacy of itraconazole (a mean of 7.2 mg/kg per day for 3–12 months) in seven children with disseminated histoplasmosis.[16] Finally, in another recent trial of the Mycoses Study Group,[7] fluconazole (200–800 mg/day for a median of 11 months) was associated with cure or improvement in 10 of 14 disseminated cases (71%). The only patient who received 800 mg/day relapsed with histoplasmal meningitis.[7]

For *H. capsulatum* meningitis[4] a cumulative dose of 30 mg/kg of iv amphotericin B has been proposed, but there have been no studies to indicate that higher cumulative doses are any more effective. Relapses are observed in nearly 50% of the cases and cerebrospinal fluid (CSF) must be sampled up to 1 year after treatment has been stopped. Intrathecal amphotericin B should be reserved for patients who have already experienced one relapse, since it carries substantial morbidity. Ketoconazole is not effective for CNS disease, since it diffuses poorly into the CSF. Few patients with *H. capsulatum* meningitis have received itraconazole or fluconazole, and no definitive conclusions can be given on their respective efficacies.

Patients with AIDS

Histoplasmosis is described in HIV-infected individuals chiefly as a disseminated disease in endemic areas.[17,18] Histoplasmosis has also recently been described as an imported disease in 56 French HIV-infected individuals, occurring sometimes several years after their return from endemic areas.[19]

Induction therapy. Amphotericin B, at a dose of 1 mg/kg per day for 3–14 days, followed by itraconazole remains the treatment of choice for AIDS patients with severe or moderately severe forms of histoplasmosis. Amphotericin B induces remissions in 80% of AIDS patients with disseminated histoplasmosis, mainly during the first week of treatment. Most of the failures occur in patients with late stages of the disease or those with CNS involvement. Severe forms are classically defined by hypotension (<90 mm Hg), hypoxia (PaO_2 <60 mm Hg), neuropsychiatric disorders, myositis, or disseminated intravascular coagulation.[17] Moderately severe forms are defined by fever >39.5°C, Karnofsky score <60, albumin <30 g/L, liver enzymes >5 times normal, neutrophil count <500/mm^3, platelet count <50,000/mm^3, or creatinine serum level ⩾5 times normal. Corticosteroid therapy is not beneficial, even in very ill patients.[17]

Since the response rate is <20%,[17] ketoconazole should not be used in AIDS patients with disseminated histoplasmosis. The low response rate may be explained by its low absorption, poor compliance owing to digestive tract dysfunction, or its low intrinsic activity in the context of immunosuppression.[17] Itraconazole (300 mg bd for 3 days then 200 mg bd for 3 months) was effective in 59 patients with moderate forms of histoplasmosis (excluding CNS involvement) and gave a remission rate of 85%.[20] In the latter study, blood cultures became negative within a median of 1 week and response rates were lower in patients who

were severely ill. Therefore, amphotericin B remains the drug of choice for life-threatening disseminated histoplasmosis in AIDS whereas itraconazole is effective in patients who are not so ill. The place of itraconazole has not yet been defined for AIDS patients with meningitis. Because of its poor absorption during the late stage of AIDS, serum concentrations should be measured after 1 week's therapy.

Fluconazole[4–6] was initially evaluated in ten patients (five who received 100 mg/day and five who received 400–800 mg/day) and was associated with six failures.[21] A recent study with 50 patients demonstrated that initial treatment with fluconazole (1600 mg on day 1, then 800 mg/day for 12 weeks) was successful in 74%.[22] These data suggest that fluconazole is moderately effective during the induction phase of disseminated histoplasmosis during AIDS. Its role in patients with histoplasmal meningitis has not yet been determined. It is also important to note that relapses due to resistant strains (MIC increasing from 0.625 to 20 mg/L) have recently been reported.[23]

Primary prophylaxis.[17] Recently, itraconazole (200 mg/day) was compared with placebo as primary prophylaxis of histoplasmosis in AIDS patients in endemic cities in the USA (Indianapolis, IN, Kansas City, KS, Memphis, TN, Nashville, TN) and proved highly effective.[24] In a retrospective study, fluconazole (100 mg/day) did not lower the incidence of histoplasmosis in AIDS patients in Dallas, TX, USA.[25] One patient receiving fluconazole (50 mg/day) developed histoplasmosis[21] and another patient under maintenance therapy for cryptococcosis developed histoplasmosis.[26] In a recent evaluation of fluconazole (200 mg/day) prophylaxis during HIV infection, no protective effect against histoplasmosis was observed.[27] We also observed, in France, several HIV-infected patients who developed histoplasmosis while receiving low doses of fluconazole.[19]

Secondary prophylaxis.[17] Relapses occur in 35–80% of AIDS patients with histoplasmosis. Thus, lifelong suppressive therapy (secondary prophylaxis) is indicated. Administration of amphotericin B every week or every other week is more effective than ketoconazole (80–97% vs 50%) in the prevention of relapses, with a median survival time of 13–17 months. Neither amphotericin B nor ketoconazole is indicated as maintenance therapy in patients with CNS involvement. Bacteraemia, catheter infections and thrombophlebitis often occur during amphotericin B secondary prophylaxis. Thus, itraconazole (200 mg bd) was tested and shown to be well tolerated and highly effective (95%) as maintenance therapy in 42 patients who had received amphotericin B induction therapy (15 mg/kg total).[28] The median survival time was 109 weeks. Indeed, itraconazole represents the maintenance therapy of choice in patients who are able to absorb it and are not taking another medication that could interfere with it. Itraconazole has also been effective as maintenance therapy for especially severe forms of disease, such as endocarditis (personal data), or CNS involvement. In contrast, in a retrospective study, relapses were noted in 12% of 76 patients receiving 100–400 mg/day of fluconazole, after induction therapy with amphotericin B, itraconazole, or fluconazole.[29] The relapse rate was higher in those receiving fluconazole 100 mg/day, but these data were insufficient to establish the optimal dosage of fluconazole in this indication. Survival was prolonged in those patients who had initially received 1 g of amphotericin B. Survival time was shorter (94 weeks) with fluconazole than that observed in the study evaluating the efficacy of itraconazole. In another study, the relapse rate at a dose of 400 mg/day was 32% for patients who had received fluconazole as induction therapy.[22] Thus, in most instances, fluconazole ($\geqslant$200 mg/day) should be reserved for patients who cannot tolerate itraconazole or have drug-interaction problems.

Histoplasma duboisii infections

The standard treatment for *H. duboisii* infections is amphotericin B (1 mg/kg per day) with a minimum cumulative dose of 2 g. Relapses may be observed up to several years after antifungal treatment has been stopped. Ketoconazole may also be given as a first-line treatment at 600–800 mg/day for 3 months followed by 400 mg/day for 6–12 months, and sometimes longer.[4] Indeed, short-term treatment (2–3 months) increases the risk of relapse. The efficacy of itraconazole has been demonstrated in a few cases at various dosages (100–400 mg/day) for $\geqslant$6 months. In a few cases, histoplasmosis continued to worsen for several years while patients received amphotericin B or ketoconazole.[4] Fluconazole was reported to be effective in one case, but there was no prolonged follow-up.[30] Surgery may be used in cases of bone/joint involvement, lymph node involvement, or subcutaneous abscesses. We recently reported a large series of *H. duboisii* infections.[31] Among 21 patients who had a histologically or mycologically confirmed infection, 15 received amphotericin B as a primary treatment: seven were cured (mean total dose 2.8 g); four received ketoconazole (400–800 mg/day) for 4.5–6 months: two initially responded but relapsed 1–12 months after stopping treatment; one was stable and one was still receiving the drug at the time of analysis. As the disease is very difficult to cure, the term 'remission' may be more appropriate than 'cure' unless protracted follow-up is available.

Coccidioidomycosis

Immunocompetent hosts

Uncomplicated primary infection.[32] The clinical utility of treating uncomplicated primary coccidioidomycosis remains controversial, since most patients recover sponta-

neously. Some workers believe the risk of meningeal or bone and joint involvement argues for treating all cases with an azole, but the precise duration of treatment remains unknown. A few characteristics predict worse disease and, therefore, treatment may be justified: male gender; pregnancy; the elderly and infants; a high concentration of specific antibodies; laboratory-acquired infection (high inoculum); persistance of symptoms after 6 weeks; negativity of specific skin tests; non-Caucasian patients; and pre-existing immunosuppression.

Other forms.[4,32] The best therapeutic strategy for other forms of coccidioidomycosis remains unknown, since no comparison has been performed between amphotericin B and azoles or between azoles. Flucytosine is useless for coccidioidomycosis, since the fungus is naturally resistant.

Disseminated coccidioidomycosis occuring during pregnancy should be treated with amphotericin B. At a dose of 1–3 g, amphotericin B gives a remission rate of 50–75% in non-meningeal disease. In CNS involvement, amphotericin B is ineffective by the parenteral route, which necessitates intrathecal (it) administration (preferably), or insertion of an Ommaya reservoir. Intrathecal amphotericin B carries substantial risk of neurotoxicity and an Ommaya reservoir may become superinfected. In the case of encephalitis or cerebral vasculitis, for which mortality may be as high as 30–50%, both iv and it therapies may be used in association with steroids for at least 1 year.[32] After treatment has been stopped, the CSF should be analysed every 6 weeks for 2 years.

At a dosage of 200–400 mg/day for a mean of 26 weeks, ketoconazole gave 13% complete remissions and 70% improvement in 85 patients.[33] In another study of various clinical manifestations of coccidioidomycosis the response rate was comparable, with objective results in 81–94% of cases.[34] In a more recent trial, using strict criteria of remission, ketoconazole (400–800 mg/day) gave 23.2–32.1% success whatever the clinical presentation.[35] Side-effects were reported in 38% (400 mg/day) or 66% (800 mg/day) of cases. In chronic pulmonary disease, ketoconazole needs to be administered for $\geqslant$6 months after apparent control of the disease. Relapse rates vary according to the organs involved (11% in cutaneous forms, up to 33% in pulmonary or bone lesions) and the dosage used (11% at 400 mg/day vs. 52% at $\geqslant$800 mg/day). The high rate of side-effects observed at 800–1200 mg/day makes ketoconazole unsuitable for meningitis.

Relapses are frequent in chronic pulmonary coccidioidomycosis if low dosages of fluconazole (50–100 mg/day) or short durations of treatment are used. In a study evaluating fluconazole 200–400 mg/day for a mean duration of 13 weeks, a significant clinical improvement was noted in four of five disseminated forms, six of six pulmonary forms, and 12 of 16 (75%) neurological forms in previously treated patients.[36] In a multicentre study, fluconazole (typically 400–600 mg/day for 11–24 months) was effective in 14 of 16 cases and relapses were observed in three of 14 cases.[37] In another recent study, fluconazole (200–400 mg/day) was evaluated in 78 patients without neurological involvement and was effective in 86% of patients with bone lesions, 55% of those with chronic pulmonary disease and 76% of those with soft tissue diseases.[38] Among 41 patients whose treatment was interrupted, 15 (37%) experienced a relapse. Fluconazole (50–400 mg/day for a mean of 10 months) was effective in ten of 15 patients with coccidioidal meningitis.[39] Results of a larger study showed a response in 37 of 47 (79%) of patients, some of whom had failed prior therapy.[40] The relapse rate is high (75%) after treatment has been stopped, suggesting that lifelong treatment is appropriate.[41] In one recent study, conversion from it amphotericin B to fluconazole was associated with a stable disease course of meningitis for up to 19 months.[42] Recently, three patients with brain abscesses remained in remission while receiving fluconazole therapy[43] and a single case with ocular dissemination was also successfully treated with fluconazole.[44]

Similar results were obtained when itraconazole was given to 37 patients with various forms of coccidioidal disease: 63% of patients responded over a mean duration of treatment of 7 months.[45] In another study of itraconazole, 100–400 mg/day, efficacy was noted in 25 of 44 cases (57%) with several manifestations of disease; failures were observed in 43% and relapses in 16%.[46] Another paper reported mycological sterilization in 15 of 16 patients with pulmonary infection who received itraconazole (400 mg/day).[47] Higher dosages have also been proposed for refractory coccidioidomycosis. During meningitis, an objective response was observed in four of five patients (300–400 mg/day for a median of 10 months) with refractory meningitis.[48] The NIAID Mycoses Study Group is currently comparing itraconazole and fluconazole for the treatment of coccidioidomycosis.[49] Surgery may be indicated in refractory pulmonary cavitary lesions, for severe haemoptysis or relapsing bacterial superinfection, and in severe osteoarticular lesions or arthritis.[50] In patients with meningitis, communicating hydrocephalus is common and ventricular shunting is useful to manage this.

Immunocompromised hosts

Among immunocompromised hosts, coccidioidomycosis is mostly observed in HIV-infected individuals. Its incidence may be as high as 25% in endemic areas.

Induction phase.[4,17] Amphotericin B is the first therapeutic choice for patients with diffuse interstitial coccidioidal pneumonia[51], in which mortality may be as high as 70%. In those who respond a minimum cumulative dose of 1 g is recommended before switching to azoles. At a dose of 400 mg/day, ketoconazole is not effective in HIV-infected patients. Fluconazole (400–800 mg/day) is an alternative to amphotericin B in moderately severe forms. It has also

been reported to be effective in patients with meningitis, with survival times >2 years. The role of itraconazole for the management of coccidioidomycosis in HIV-infected patients has not yet been established.

Primary prophylaxis.[4,17] No study has proven the utility of primary prophylaxis against coccidioidomycosis during HIV infection and some patients have developed coccidioidomycosis while receiving ketoconazole for another indication. Prophylactic administration of fluconazole (200 mg/day) is currently being evaluated in endemic regions in the USA. HIV-infected patients whose coccidioidal serology is positive are probably good candidates for such prophylaxis. Skin tests should not be done in these patients and are, therefore, not a suitable means of identifying patients at risk.

Secondary prophylaxis.[4,17] Lifelong maintenance therapy is indicated.[52] However, the optimum regimen is not yet established. Daily fluconazole (200–400 mg/day) or weekly amphotericin B are reasonable alternatives. Ketoconazole is ineffective and itraconazole has not been tested for this indication.

Blastomycosis

Blastomyces dermatitidis is a dimorphic fungus occasionally responsible for acute pneumonia, cutaneous or bone lesions, and, rarely, disseminated disease. Blastomycosis is endemic in certain parts of North America and also in Africa.

Amphotericin B is the treatment of choice for life-threatening blastomycosis including acute respiratory distress syndrome and CNS disease.[5] Patients with cavitary pulmonary lesions or with persistently positive respiratory cultures may require a longer duration of treatment. Choroidal blastomycosis has recently been successfully treated with amphotericin B.[53] Amphotericin B remains the drug of choice in children with blastomycosis.[54] Ketoconazole (400 mg/day for ⩾6 months) was also effective in 80% of cases (without CNS disease), and no relapses occurred during a 17 month follow-up period.[55] Another study (65 patients treated for ⩾6 months) demonstrated that 800 mg/day ketoconazole gave a cure rate of 100% vs. 70% in the group receiving 400 mg/day.[56] Patients with prostatitis are particularly prone to relapse, as the urinary (and prostatic) penetration of ketoconazole is low. Fluconazole (200–400 mg/day) is less effective, with response rates of 60–70%, with no relapse during a follow-up of 7 months.[57]

Itraconazole (200–400 mg/day) was evaluated in 48 patients with pulmonary or disseminated blastomycosis without CNS involvement and was successful in 90–95% of cases.[58] Itraconazole is now the drug of choice for non-meningeal, non-life-threatening blastomycosis in immunocompetent individuals. There are insufficient data to recommend itraconazole for blastomycosis of the CNS.[5]

The azole SCH 56592 has recently been successful in an experimental model of blastomycosis but no clinical trials have yet been performed.[59] Adult respiratory distress syndrome is a recently recognized complication of blastomycosis for which continuous positive airway pressure has recently been successfully used.[60] Surgery may be indicated for cavitary pulmonary lesions not responding to the antifungal therapy, for soft tissue infection,[61] or for patients with CNS masses or abscesses.[62]

Blastomycosis in AIDS

Blastomycosis has rarely been reported in AIDS. Therapeutic recommendations include amphotericin B for life-threatening forms and itraconazole in other cases. Although, no definitive recommendation can be given, itraconazole is probably the best secondary prophylaxis for AIDS patients with blastomycosis.

Paracoccidioidomycosis

Paracoccidioides brasiliensis is a dimorphic fungus found in Central and South America and responsible for pulmonary infections, cutaneous and/or mucosal lesions, and, sometimes, disseminated disease. All patients from whom it is isolated should be treated and pulmonary fibrosis is still the major sequela despite the availability of new antifungal drug therapy.

Immunocompetent hosts

Amphotericin B is generally used in disseminated cases, those in whom other therapies have failed, or in cases intolerant to sulphonamides or sulphones. Remission occurs in up to 60% of cases, but in 20–30% of cases treated with amphotericin B there are relapses.[63] Prolonged treatment with azoles may be given after amphotericin B has been stopped. Ketoconazole (200–400 mg/day for 6–12 months) yields a response rate as high as 80–90%.[64] Its efficacy for pulmonary disease is more difficult to analyse, since sequelae are frequent. The relapse rate has been estimated as 10%. Itraconazole was first evaluated at 50 mg/day with an improvement of cutaneous lesions within 15 days.[65]

The largest study evaluated the drug (mostly 100 mg/day for a mean duration of 6 months) in 47 patients predominantly with multifocal disease.[66] All the patients showed a marked clinical improvement. Persistent chest X-ray abnormalities were found in 13% and mycological cure was observed in 87% within the first month of treatment. No relapse was observed in 15 patients who were followed for ⩾6 months.[66] In other studies of itraconazole, relapse rates have been estimated as 3–5%. Such results suggest that itraconazole is the treatment of choice for paracocci-

dioidomycosis. In contrast, clinical experience of fluconazole in this disease is still limited, but 27 of 28 treated patients showed objective responses in one study.[67] Relapse rates were not reported. Other treatments have also been tried. Dapsone (a sulphone; 100 mg/day for ⩾2 years) is effective in mild forms or after amphotericin B has been stopped. Careful follow-up is required because of potential side-effects. The less expensive compounds sulphadiazine and co-trimoxazole may also be used, but they have to be given for prolonged periods and relapses may occur in up to 30% of treated patients.[68] Such treatments were, however, recently reported to be effective in a small number of cases of osteoarticular paracoccidioidomycosis.[69]

Immunocompromised hosts

Paracoccidioidomycosis has recently been reported among patients with AIDS in Latin America.[70] No definitive therapeutic recommendation can presently been given. Itraconazole is probably the drug of choice in this setting but co-trimoxazole has also been suggested as a curative treatment.[71]

Penicillium marneffei infection in AIDS

Two recent reviews summarized current knowledge about *P. marneffei* infection.[72,73] Disseminated *P. marneffei* infection during AIDS is best treated with amphotericin B for 2 weeks, followed by itraconazole, or with itraconazole alone if the patient is not systemically unwell. The frequency of relapse is high after cessation of such therapy and maintenance therapy with itraconazole (200 mg/day) is indicated. Fluconazole and ketoconazole, even at a high doses, are less effective than itraconazole. In immunocompetent individuals, itraconazole is an appropriate first-line therapy.

Sporotrichosis

Sporotrichosis is caused by the dimorphic fungus *Sporothrix schenckii*, which is chiefly responsible for cutaneous or lymphocutaneous disease, particularly in the upper limbs. Disseminated disease is increasingly observed in immunocompromised hosts, such as HIV-infected individuals or alcohol abusers. The organism occurs worldwide, but most cases are observed in the Americas.

Cutaneous or lymphocutaneous sporotrichosis

In cutaneous or lymphocutaneous sporotrichosis, an oral saturated solution of potassium iodide remains useful (five drops tds initially in adults, progressively increasing up to 40–50 drops tds, mixed in milk, juice, or water after meals) for 3–6 months. It is still the first-line treatment in developing countries, but because of intolerance is now the second-line treatment in the USA. Side-effects (particularly gastrointestinal disturbances) are responsible for poor compliance.[74] Initial studies evaluated itraconazole at a low dosage (100 mg/day for 3–6 months) and reported a cure rate of 100% without relapse in 17 patients with cutaneous or lymphocutaneous sporotrichosis.[75] Although an initial evaluation of fluconazole proved encouraging in three patients,[76] more recent data from 14 patients with lymphocutaneous sporotrichosis reported that only ten were cured despite four patients receiving 400 mg/day.[77] Other suggested therapeutic modalities include local hyperthermia treatment to the lesions each day for several weeks (particularly applicable during pregnancy when systemic antifungal therapy cannot be given[74]), liquid nitrogen,[78] and, more recently, terbinafine.[79]

Other forms

Pulmonary, osteoarticular, and disseminated forms of sporotrichosis should always be treated with antifungal agents rather than potassium iodide. Amphotericin B remains indicated for neurological and life-threatening forms.[74] Ketoconazole (400–800 mg/day) has poor efficacy against localized or pulmonary, osteoarticular, and disseminated sporotrichosis,[74] such that it should no longer be prescribed. Of 15 patients with osteoarticular sporotrichosis who received itraconazole (200–600 mg/day) during a Mycoses Study Group trial,[80] 11 (83%) responded, but four of these patients later relapsed. Long-term suppressive therapy with itraconazole (200 mg/day) was successfully used for sporotrichosis involving a prosthetic knee joint.[81] Two recently reported patients with multifocal osteoarticular sporotrichosis who received itraconazole (200 mg/day) for 24 months had not relapsed within 41 and 68 months after discontinuing treatment.[82] Itraconazole is, therefore, a first-line treatment for non-meningeal, non-life-threatening sporotrichosis. The pulmonary forms remain difficult to treat, even with itraconazole, and may require surgery in addition. Sixteen patients with osteoarticular or visceral sporotrichosis who were given fluconazole (400 mg daily for 9 months) were recently reported.[77] Only five patients responded to therapy (two partially), while 11 failed. Thus, fluconazole should be considered a second-line therapy for sporotrichosis.

Sporotrichosis in AIDS

Results with amphotericin B have been disappointing, with clinical progression observed during therapy.[74] Therefore, itraconazole is probably appropriate as first-line treatment. Lifelong suppressive therapy with itraconazole then has to be given and was reported as effective in a case of sinus infection.[83]

Chromoblastomycosis (chromomycosis)

This subcutaneous disease may be caused by nearly 30 different fungal species, the most frequent being *Fonsecaea*, *Phialophora*, *Wangiella*, and *Cladosporium* spp. First-line treatment often requires surgery (excision, cryosurgery), eventually followed by a graft. Carbon dioxide laser and local heat therapies have also been successfully used. Medical treatment is often only moderately effective, depending on the species of infecting fungus. Flucytosine for several months, alone or in association with amphotericin B or ketoconazole, is effective in up to 80% of cases. Ketoconazole, alone at 200–800 mg/day for 2–29 weeks, produced improvement in 32% of cases, but relapse was common after treatment was stopped. Itraconazole at doses of 100–200 mg/day is more effective than ketoconazole, particularly against *Cladosporium* spp.[84] and might be used with flucytosine or cryotherapy for infections caused by *Fonsecaea pedrosoi*.[85] Longer doses of itraconazole may be more effective but have been incompletely studied.

Lobomycosis

Lobomycosis is caused by a non-cultivatable fungus *Loboa loboi*, chiefly found in Brazil and French Guiana. Surgical excision is the only useful therapy and all antifungal drugs tried have given disappointing results.

Eumycetoma

Fungal mycetoma[86,87] is a chronic disease caused by several different fungi which mainly affects the lower extremities. Therapy is based on a combination of antifungals and surgery. Small fungal mycetoma are easily removed surgically. Ketoconazole (400 mg/day for 3–36 months) has been shown to be effective against *Madurella mycetomatis* infection, but is of poor efficacy against *Pseudallescheria boydii* or *Acremonium* spp. infections. The therapeutic efficacy of itraconazole remains controversial but efficacy was observed against *Madurella grisea* infections. A recent report also documented its efficacy against *Acremonium falciforme*.[88] Additional data are required before clear-cut recommendations can be given.

Conclusions

In conclusion, amphotericin B remains the drug of choice during the acute stage of life-threatening endemic mycoses occurring in both immunocompetent and immunocompromised hosts, although better tolerance and availability in oral forms allows azoles to be used in the outpatient setting for most patients with endemic mycoses. When well absorbed, ketoconazole is effective in non-AIDS patients with non-life-threatening histoplasmosis, blastomycosis, or paracoccidioidomycosis, but is never indicated for the treatment of systemic mycoses in patients with AIDS. Itraconazole (200–400 mg/day for $\geqslant$6 months) is the treatment of choice for non-life-threatening *H. capsulatum* or *B. dermatitidis* infections occurring in immunocompetent individuals and is the optimal agent for secondary prophylaxis of histoplasmosis during AIDS. Itraconazole is also effective in lymphocutaneous and visceral sporotrichosis, for *P. marneffei* infection and as an alternative to amphotericin B for *H. duboisii* infection. All forms of coccidioidomycosis may be effectively treated with itraconazole or fluconazole (probably requiring a higher dosage for chronic pulmonary forms and especially for coccidioidal meningitis). Fluconazole has relatively poor efficacy against histoplasmosis, blastomycosis and sporotrichosis and should be reserved for patients with non-life-threatening forms of these diseases who are unable to take itraconazole. The cost of new triazoles may represent a problem in developing countries where these diseases are endemic. New antifungal agents, recently tested *in vitro* or in animal models, will probably soon be evaluated by clinical trials in humans.

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