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Endemic mycoses-are we making progress in management?

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Abstract

Purpose of the review: The endemic fungi are a significant cause of morbidity and mortality in effected patients. The range of endemicity for these are expanding with infections observed outside of traditional locations. Enhanced diagnostic and treatment practices may significantly alter patient outcomes.

Recent Findings: Recently completed clinical trials have focused on an assessment of improving efficacy while minimizing patient toxicity. Practice changing trials have been completed in histoplasmosis showing the utility of a single up-front liposomal amphotericin B dose followed by standard itraconazole dosing. The recent evaluation of several antifungal options including isauvconazole in the treatment of coccidioidomycosis also show promise for additional therapeutic agents. A recently conducted trial has also shown the superiority of amphotericin B therapy over itraconazole in the treatment of talaromycosis.

Summary: The increased range of endemic mycoses coupled with the growing immunocompromised patient population mandates continued investigation of improved diagnostic and therapeutic options. Advances in these areas have led to more rapid diagnosis and more efficacious antifungal therapy.

Keywords

histoplasmosis; coccidioidomycosis; blastomycosis; sporotrichosis; talaromycosis

Introduction

The endemic mycoses are a diverse group of fungal pathogens that share several key characteristics. Each occupies a specific ecological niche in the environment and is able to cause disease in otherwise healthy hosts. The agents in this review, *Blastomyces*,

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Coccidioides, *Histoplasma*, *Sporothrix*, and *Talaromyces marneffei* are each increasingly recognized, and climatic events have been associated with geographic expansion and a higher number of cases per year for many of these organisms. Changes in the *in vitro* susceptibility profiles of these agents have also been recently reported [1], necessitating the search for alternative or new antifungal agents in an attempt to optimize patient outcomes.

Severe disease caused by the endemic mycoses is treated with an amphotericin B formulation (lipid agents are preferred) followed by triazole agents. Each of these agents possess unique pharmacokinetic and toxicity profiles that require a thorough understanding by the prescribing practitioner. The triazoles are teratogens and should not be used in the first trimester, while each also exhibits variable effects on the CYP450 system resulting in potential hepatotoxicity and/or drug-drug interactions. Fluconazole causes dose-dependent alopecia, xerosis and cheilitis [2]. Itraconazole may cause gastritis, peripheral edema and is a negative inotrope potentially resulting in heart failure. Voriconazole may cause photosensitivity, photopsia, fluorosis, or encephalopathy [3, 4], while posaconazole may cause hypertension or electrolyte disturbance [5]. Isavuconazole may similarly cause electrolyte disturbance or infusion reactions. The fungistatic nature of currently available oral antifungals mandates long courses of therapy for most of the endemic mycoses, and these durations allow cumulative toxicities which may contribute to less than desirable treatment tolerability and outcomes. Additionally, the diagnosis is often delayed and only considered after several courses of antibacterial therapy have been (wrongly) prescribed [6, 7]. Despite the geographic expansion of these pathogens they are not required to be reported in most states further complicating our understanding of the burden of these agents.

Histoplasmosis

The typical treatments for histoplasmosis treatment have not changed in over two decades, but that stability may be challenged in the coming years. Many persons with mild acute pulmonary disease or evidence of previous or dormant histoplasmosis do not require treatment.[8–11] The standard treatment for moderate to severe acute pulmonary histoplasmosis remains liposomal amphotericin B (LAmb, 3–5 mg/kg/daily intravenously) for one to two weeks followed by itraconazole 200mg three times daily for three days then twice daily for 12 weeks and adjunct corticosteroids are used in some cases.[8] This is primarily based on case reports.[8, 12] More mild disease can treated with itraconazole only at the same dose, if necessary.[13, 14] Therapeutic drug monitoring is advised due to difficulty with absorption.[15] In severe acute disease corticosteroids are sometimes used to improve hypoxemia.[15]

Disseminated histoplasmosis is treated similarly (LAmb followed by itraconazole) but treatment is always required.[8] Johnson and colleagues conducted a randomized double-blind trial comparing LAmb with amphotericin B deoxycholate(AmBD) and found lower mortality (2% vs. 13%) in those that received liposomal amphotericin B, establishing LAmb as the preferred initial agent.[16] Recently, Pasqualotto and colleagues conducted an open-label randomized trial and found that among 118 participants, a single dose of LAmb (10mg/kg) on day one appeared to be non-inferior to standard LAmb treatment – both arms were followed by standard itraconazole dosing.[17] A larger, phase three trial is planned

to confirm these findings and further evaluate efficacy and toxicity. Mild disseminated disease can be treated with itraconazole alone and all disseminated disease requires at least 12 months of itraconazole and ideally documentation of resolution of antigenuria and/or antigenemia (when available).[8, 18–20]

Histoplasmosis includes a number of other syndromes where the same principles of treatment involving itraconazole for more mild disease requiring treatment and LAmb up-front for more severe (including CNS) or chronic disease apply.[8] Although often used as 'step-down' therapy for CNS disease, itraconazole's CNS penetration is poor. Thus, an alternative azole could theoretically be preferable, though evidence is limited. The most compelling candidate is isavuconazole which has low *in vitro* minimum inhibitory concentrations(MICs) in *Histoplasma* isolates from patients who failed treatment with fluconazole as opposed to voriconazole which had high MICs – both have good CNS penetration.[21–26] In a 2023 systematic review of CNS histoplasmosis, mortality was 12% (9/73) in those treated with itraconazole and 20% (3/15) in those treated with voriconazole.[27] Although the *P* value for the comparison was 0.43, it's difficult to say whether or not there is a true difference in efficacy based on this data, particularly given the sample size and lack of correction for potential confounders.

Posaconazole has low MICs in the same isolates mentioned in relation to isavuconazole above from persons with CNS histoplasmosis and clinical success has been reported, although CNS penetration is low.[22, 28, 29] Ultimately, evidence is scant and itraconazole is typically used as step-down therapy in most CNS histoplasmosis cases. Of note, super bioavailability (SUBA)-itraconazole is now FDA approved for histoplasmosis but neither formulation is approved for CNS disease where it has not been prospectively studied.[30]

Alternatives to standard treatment: Fluconazole was less effective than itraconazole in an open-label non-randomized trial, is prone to the development of resistance on therapy and is less efficacious in clearing *Histoplasma* antigen than itraconazole and its use is therefore not recommended if other options exist.[21, 31–33] Voriconazole demonstrates *in vitro* activity against *H. capsulatum* but with higher MICs against isolates from persons who failed treatment with fluconazole, suggesting development of resistance on voriconazole is possible.[22] Although there are reports of clinical success with voriconazole in histoplasmosis, a relatively large single center study showed higher rates of death at 42 days in 19 patients who received voriconazole compared to 175 who received itraconazole.[34, 35] Whether this truly indicates inferiority is unclear but this is the most robust data to date and so in most situations, voriconazole use should be avoided.[36] Isavuconazole and posaconazole are active *in vitro*, including in isolates from those who failed fluconazole therapy.[22, 23] The lack of MIC rise in isavuconazole is notable as its structure is closer to fluconazole and voriconazole than posaconazole and itraconazole.[34] Both agents have also been effective as alternative agents for histoplasmosis but robust evidence of efficacy is not available and they should be used only as alternative agents.[25, 28] A number of antifungal agents, including fosmanogepix and olorofim, are currently in development and have excellent *in vitro* activity against *Histoplasma* spp. Clinical studies evaluating these agents are currently ongoing and may help to refine their use as antifungal agents.

Echinocandins are not recommended for use in the treatment of histoplasmosis. Although *H. capsulatum* does contain 1,3-β-D glucan in the cell wall there is evidence that micafungin is not effective *in vitro* and the single clinical report available is a case where micafungin was used unsuccessfully to treat sepsis empirically and histoplasmosis was diagnosed at autopsy.[37–39]

To truly make progress in management of histoplasmosis we need better evidence related to newer azoles and novel antifungals as well as the single high-dose liposomal amphotericin strategy for disseminated histoplasmosis. Ideally this data would come from prospective randomized controlled trials. But largescale registry or multi-center collaborative data should be leveraged as well. Additionally, tumor necrosis factor-alpha inhibitors and transplant-related immunosuppression, while clearly necessary and effective, put patients at high-risk for reactivation if they have had a prior infection. Screening these individuals for prior infection might be a useful approach but no such data exists. One candidate test could be an interferon-gamma release assay that assesses T-cell responses to *H. capsulatum* antigens, whether or not this would be effective isn't clear[40]. Antigen testing would likely miss many at-risk cases.

Coccidioidomycosis

Significant differences in treatment practices exist in the treatment of primary pulmonary coccidioidomycosis. Many clinicians support a period of observation as opposed to antifungal therapy as most patients clear their infection without the need for antifungal therapy. However, others offer antifungal treatment to all patients with primary pulmonary coccidioidomycosis in an attempt to expedite symptom resolution. No placebo-controlled study has been successfully performed to determine the optimal approach, however two observational studies have shown treatment does not appear to impact the rate of extrapulmonary dissemination.[41, 42]

All patients with underlying immunosuppression, significant cardiopulmonary comorbidities, or those with prolonged infection, or ongoing symptoms should be treated with fluconazole 400–800 mg/day or itraconazole 200mg twice daily. Treatment is often given to groups at high risk of complications (those of Oceanic or African genomic ancestry).

Severe pulmonary infection is treated with an amphotericin B formulation followed by a triazole (fluconazole/itraconazole). In coccidioidal-associated ARDS some prescribe a 21-day tapering course of corticosteroids although there is scant data reporting the efficacy of this approach. The duration of therapy is highly dependent on the extent and site(s) of original infection, the rapidity of improvement, and resolution of radiologic and clinical manifestations. Typically, 3–6 months is preferred for primary pulmonary disease with clinical follow-up for a year or longer after initial infection.[43] In contrast, chronic pulmonary disease (chronic pneumonia and chronic cavitary disease) often requires life-long therapy for disease control. Meningitis requires life-long antifungal therapy, while other disseminated forms may have treatment discontinued after 2–3 years of antifungals provided close clinical and serologic follow-up is available after stopping antifungals.

Disease refractory to fluconazole is treated with an alternative triazole (itraconazole, voriconazole, posaconazole) or amphotericin B depending on disease severity [44, 45]. Itraconazole is preferred in cases of skeletal disease. Posaconazole, voriconazole, and isavuconazole are alternative agents and are more frequently required in patients refractory or intolerant to other antifungals.[25, 46–48]

Pregnancy is a significant risk factor for severe coccidioidomycosis particular those newly infected in the second or third trimester. All triazoles are considered teratogenic and cannot be used in the first trimester, with an assessment of the potential risk-benefit profile when used in the 2nd or 3rd trimester. Reviews detailing the approach to therapy during pregnancy have been published.[49]

Future advances are needed in the evaluation of patients anticipating immunosuppression. Patients in the pre-transplant setting, or those prescribed immunosuppressive agents are at risk for the development of severe coccidioidomycosis or for latent disease to recur. Skin testing, T-cell assays, or sequential metabolomic analyses may all allow for a reduction in the number of severe cases and establishment of primary and secondary prophylaxis protocols reducing the burden of infection. Advances in our understanding of patient immunogenomics may also identify those at the highest risk of developing severe or disseminated disease and provide prognostic information early in the course of infection after diagnosis.

Blastomycosis

Blastomycosis treatment relies on amphotericin B formulations and itraconazole in most situations. Moderate to severe pulmonary or extrapulmonary disseminated blastomycosis should be treated initially with LAmB (3–5mg/kg/day) or AmBD (0.7–1mg/kg/day) for 1–2 weeks or until clinical improvement, followed by itraconazole for 6–12 months.[50] Initial reports reported high efficacy with AmBD, however LAmB is now preferred due to the decreased toxicity with similar efficacy.[26, 51, 52] Corticosteroids are sometimes used in severe cases with acute respiratory distress syndrome (ARDS) although whether or not they are beneficial is unclear.[53]

Mild disease can be treated with itraconazole alone for the same duration.[14, 50] Itraconazole is used as the primary oral agent based on high rates of efficacy reported in prospective, non-randomized studies.[14, 51] Lifelong suppression may be needed in persons who cannot have their immune suppression reversed.[50] CNS disease should be treated with liposomal AmB for 4–6 weeks followed by azole therapy.[50, 54] Voriconazole has been clinically effective and is preferred over itraconazole as the ‘step-down’ agent in CNS disease due to the poor CNS penetration of itraconazole (in contrast to current recommendations for CNS histoplasmosis).[8, 54–58] Isavuconazole is another agent with reports of clinical success in CNS disease.[59]

Alternatives to standard treatment: Voriconazole is preferred as a ‘step-down’ agent in CNS disease but, although effective in some cases, should be seen as an alternative to itraconazole if no CNS involvement is present due to less robust evidence of efficacy in non-CNS disease. [35, 54, 60]

Fluconazole has been used but its efficacy is less than that of itraconazole and may be less than other azoles as well.[26, 35, 60–62] Fluconazole does have excellent CNS penetration. Thus, fluconazole should be seen as alternative for use only when itraconazole cannot be used in non-life threatening blastomycosis, particularly when CNS involvement occurs and voriconazole is not a viable option. If used, a dose of 400–800mg daily is preferable.[62]

Isavuconazole MICs are low *in vitro* and there are multiple clinical reports of favorable outcomes, including those with CNS disease.[25, 59] Although *in vitro* activity is excellent, there are relatively few cases that have reported the use of posaconazole for non-severe disease with mixed results.[60, 63–67] Thus, isavuconazole and posaconazole can be considered alternative agents for blastomycosis. Lastly, echinocandins should not be used due to poor in vitro activity and rare reported use with mixed results resulting in clinical failure.[35, 68, 69]

Sporotrichosis

Itraconazole is the treatment of choice for cutaneous and lymphocutaneous sporotrichosis with response rates of 80–100%.[70–72] A variety of different itraconazole doses have been studied with no clear difference observed between doses prescribed.[70] Lymphocutaneous disease requires longer courses of therapy. Alternative agents/doses include, terbinafine 500 mg twice daily, saturated solution potassium iodide (SSKI), or fluconazole 400–800 mg daily. SSKI was the standard treatment until the 1990s and in areas where other antifungals are not available it is still used, although not preferred. Osteoarticular infections respond less well (approximately 70%) to itraconazole and may require initial therapy with amphotericin B and require itraconazole treatment for at least 12 months. Ongoing widescale outbreaks in Brazil following the adaptation of *Sporothrix* spp to higher host temperatures have also seen coincident increases in antifungal MICs. Alternative agents are thus needed given the high MICs for voriconazole and isavuconazole, and little data for posaconazole. In some cases, combination antifungal therapy may be required to optimize outcomes.[73]

Sporotrichosis diagnostics are insufficient and cultures and biopsy results are not always positive for the etiologic agent. Alternative approaches including serology, metabolomics, or radiographic detection are thus needed in an attempt to establish the diagnosis.

Talaromycosis

Disseminated talaromycosis is also primarily treated with itraconazole and/or amphotericin B. Where available, LAmB (3–5mg/kg/day) is preferred over AmBD for 10–14 day initially, followed by itraconazole for itraconazole consolidation therapy (200mg twice daily) for 10 weeks and then maintenance itraconazole at 200mg daily.[74] Induction therapy with amphotericin is based on a randomized controlled trial in Vietnam showing lower mortality for AmBD compared to itraconazole.[75] Itraconazole maintenance therapy drastically reduced relapse in a placebo controlled randomized controlled trial in Thailand (57% vs 0%, $p<0.001$).[76]

There have been reports using voriconazole or fluconazole for treatment with success although higher MIC values have been reported and seem to correlate with delayed blood culture clearance with these agents.[77, 78] Further, in a open label, non-randomized trial

comparing AmBD and voriconazole among 410 patients with disseminated talaromycosis (n=269 AmBD, n=141 voriconazole), although there was no difference in mortality, there was improved clinical resolution and fungal clearance among those who received AmB.[79] The same outcome pattern was seen in logistic regression of matched cohorts (n=122 each arm).[79] The use of posaconazole and isavuconazole have each been reported in one case.[80] These agents should only be used when preferred therapies are not possible.

Conclusion:

Although this group of pathogens shares a tendency for higher risk in certain geographic regions and basic treatment approaches (amphotericin for initially therapy for severe disease and itraconazole for more mild disease) there are numerous key differences as well as areas that remain uncertain. Evidence for the use of azoles outside of itraconazole remains largely inadequate for each condition and whether or not novel antifungals such as olorofim or fosmanogepix will be options is unclear. Further, we need better evidence regarding potential options for screening prior to use of immune suppressing medications in some cases. As a group, these fungi have not received research funding commensurate with their burden – to more rapidly improve outcomes increased funding and collaborative research approaches will be needed.

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Key points:

1. Amphotericin B remains the key initial therapy for serious infections due to endemic fungi.
2. Itraconazole is most often the preferred agent for less serious disease requiring treatment.
3. mild-to-moderate coccidioidomycosis may be treated with fluconazole or itraconazole.
4. Although commonly used, evidence for other triazoles is inadequate in most cases and limited to retrospective series.
5. The use of itraconazole in CNS disease is an area where clarity is needed for each pathogen.