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Chapter

Treatment of Histoplasmosis

Felix Bongomin, Richard Kwizera, Joseph Baruch Baluku, Lucy Grace Asio and Akaninyene A. Otu

Abstract

Histoplasmosis, caused by the thermally dimorphic fungus *Histoplasma capsulatum,* is an uncommon multisystem disease with a global distribution. The spectrum of clinical manifestations ranges from an asymptomatic or minimally symptomatic acute pulmonary disease following inhalation of a large inoculum of *Histoplasma* microconidia to chronic pulmonary disease in patients with underlying structural lung disease. It also extends to acute progressive disseminated disease in patients with severe immunodeficiency. Generally, antifungal therapy is indicated for patients with progressive acute pulmonary histoplasmosis, chronic pulmonary histoplasmosis and acute progressive disseminated histoplasmosis. In immunocompetent patients, acute pulmonary histoplasmosis may be a self-limiting disease without the need for systemic antifungal therapy. Oral triazole antifungal drugs alone are recommended for less severe disease. However, moderate-to-severe acute pulmonary histoplasmosis requires intravenous amphotericin B therapy for at least 1–2 weeks followed by oral itraconazole for at least 12 weeks. For acute progressive disseminated histoplasmosis, intravenous amphotericin B therapy is given for at least 2 weeks (4–6 weeks if meningeal involvement) or until a patient can tolerate oral therapy, followed by oral itraconazole (or an alternative triazole) for at least 12 months. Chronic cavitary pulmonary histoplasmosis is treated with oral itraconazole for 1–2 years. There is insufficient evidence to support the use of isavuconazole or the echinocandins for the treatment of histoplasmosis.

Keywords: *Histoplasma capsulatum*, histoplasmosis, itraconazole, amphotericin B, HIV

1. Introduction

Histoplasmosis is an uncommon endemic mycosis caused by the fungus *Histoplasma capsulatum* that usually causes an asymptomatic infection but occasionally results in severe multisystem disease [1, 2]. Two main varieties of the saprophytic, thermally dimorphic fungus of the genus *Histoplasma* affect humans; *Histoplasma capsulatum var. capsulatum* and *Histoplasma capsulatum var. duboisii* [3–5]. Histoplasmosis affects over 10,000 people globally; it is neglected, worryingly under-diagnosed, and often misdiagnosed as cancer or tuberculosis with fatal consequences [6–8]. The spectrum of the clinical manifestation of histoplasmosis is very broad, ranging from an asymptomatic or minimally symptomatic acute pulmonary disease following inhalation of a large inoculum of *Histoplasma* microconidia to chronic pulmonary disease in patients with underlying structural lung disease, to acute progressive disseminated disease in patients with severe immunodeficiency [9–13]. In immunocompetent patients, acute histoplasmosis is

typically a self-limiting disease with no need for antifungal therapy [14]. Pneumonia remains the most common disease presentation but extrapulmonary dissemination can occur, especially in immunocompromised patients [12]. A definite diagnosis of histoplasmosis is based on the isolation of the organisms in fungal culture [15]. Rapid detection of the *H. capsulatum* polysaccharide antigen using enzyme immunoassay (EIA) in urine, blood or bronchoalveolar lavage fluid is also available and very useful especially among immunocompromised patients with disseminated or acute pulmonary disease [13, 16]. Serologic testing for antibodies can be achieved by EIA, immunodiffusion, and complement fixation [13, 16, 17]. These antibody tests may be falsely negative in immunosuppressed patients and are most valuable when combined with a compatible clinical presentation and epidemiologic risk factors.

This chapter provides an overview of the currently available treatment options for the different manifestations of histoplasmosis.

2. Antifungal agents used in the treatment of histoplasmosis

Histoplasmosis is primarily treated with 2 distinct classes of antifungal agents: The triazoles and the polyenes. Data is lacking on the use of the echinocandins for the treatment of histoplasmosis.

2.1 Triazole

The triazole class of antifungals examples of which includes drug like fluconazole, itraconazole, voriconazole, posaconazole and isavuconazole [18, 19]. Of these, itraconazole is the drug of choice for the treatment of the various forms of histoplasmosis as a sole therapy or as a step-down therapy following amphotericin B infusion [13, 14, 20].

Triazole antifungals inhibit the cytochrome P450-dependent enzyme 14-alpha-lanosterol demethylase (CYP51) encoded by the *ERG11* gene that converts lanosterol to ergosterol in the cell membrane, inhibiting fungal growth and replication (fungistatic) [18, 19]. Drug-drug and drug-food interactions, as well as side effects are major issues associated with itraconazole therapy. Common side effects of itraconazole include drug-induced hepatitis, gastrointestinal discomfort, heart failure, ankle edema, alopecia, erectile dysfunction, gynaecomastia, peripheral neuropathy, visual disturbance and headaches [21]. Itraconazole interacts with agents used in the treatment of HIV (especially, nevirapine) and tuberculosis (especially, rifampicin) leading to decreased or increased exposures to itraconazole and therefore increased risk of hepatotoxicity. With the exception of fluconazole, voriconazole and posaconazole are used as alternative agents for the treatment of histoplasmosis if there is a contraindication to the use of itraconazole [13, 14, 20]. However, to the best of our knowledge, there is no data to support the use of isavuconazole for the treatment of histoplasmosis.

2.2 Polyene

The polyene antibiotic, amphotericin B derived from the fermentation product of the filamentous bacteria, *Streptomyces nodosus* is a broad-spectrum antifungal agent administered as deoxycholate (conventional amphotericin B) or liposomal formulation [18, 19].

In its mechanism of action, amphotericin B preferentially binds ergosterol in the fungal cell membrane (and to a lesser extent, cholesterol in cell membrane of humans) to form channels through which small molecules leak from the inside of the fungal cell to the outside, resulting in death of the fungal cell (fungicidal) [18, 19].

Common side effects of amphotericin B include, acute infusion-related reactions characterised by nausea, vomiting, rigors, fever, hyper or hypotension, and hypoxia mainly driven by the effects of amphotericin B on pro-inflammatory cytokine production. Nephrotoxicity is another very important side effect of amphotericin B occurring in about 34–60% of patients. Blood disorders, especially anaemia and electrolyte disturbances, especially hypomagnesaemia and hypokalemia are common but can be part of the rare Fanconi syndrome. Other side effects include infusion site phlebitis, and acute kidney injury [21].

3. Overview of antifungal treatment of histoplasmosis

It is important to understand the indications and the choices of antifungal agents in the treatment of histoplasmosis. Manifestations of histoplasmosis that are a typically treated include moderate to severe acute pulmonary histoplasmosis, symptomatic chronic cavitary pulmonary histoplasmosis, acute progressive disseminated disease, and histoplasmosis in immunocompromised individuals [12, 13], (**Table 1**). Treatment is also indicated for complications of histoplasmosis such as mediastinal granulomas and adenitis [14], (**Table 1**). Itraconazole can be used for the treatment of symptomatic immunocompetent patients with indolent non-meningeal infection, including chronic cavitary pulmonary histoplasmosis [12, 13]. Itraconazole is also used as a step-down oral agent following initial treatment of severe disease with amphotericin B [12, 13]. Itraconazole is administered at a dose 200 mg 3 times daily for 3 days, as loading dose and then 200 mg once or twice daily, for maintenance therapy [12, 13]. Duration of itraconazole therapy depends on the histoplasmosis syndrome being managed (**Table 1**).

Amphotericin by intravenous infusion is the drug of choice for the initial treatment of fulminant or moderate to severe infections, followed by a course of oral. Following successful treatment, itraconazole can be used for secondary prophylaxis against relapse until immune reconstitution is realised [12, 13]. The deoxycholate formulation of amphotericin B is administered at a dose of 0.7–1.0 mg/kg daily by intravenous infusion, meanwhile the lipid formulation of amphotericin B can be administered at a higher dose of 3.0–5.0 mg/kg daily. Liposomal formulation is preferred to the deoxycholate due to its superior side effect profile, better response rate and survival benefit [14, 20].

3.1 Central nervous system histoplasmosis

There are no known prospective studies that have evaluated treatment of central nervous system (CNS) histoplasmosis. Treatment recommendations are guided by several case reports, retrospective case series and expert opinion [12, 13].

Liposomal amphotericin B achieves higher CNS concentrations than deoxycholate formulations and together with triazoles, is the recommended therapy for CNS histoplasmosis [22]. While the choice of the optimal triazole is in doubt, there is evidence from an animal model to suggest that fluconazole may be antagonistic when combined with amphotericin B [23]. Voriconazole could have a role among patients with good performance status as monotherapy or in combination with amphotericin B, but the evidence is limited and the occurrence of hepatotoxicity and hypersensitivity may limit its use [24–26]. One case series of 11 cases reported a morbidity free survival of 54.5% when patients were treated with intravenous amphotericin B deoxycholate for 8 weeks followed by maintenance therapy with fluconazole or itraconazole for 12–18 months [27].

Histoplasmosis syndrome or complication	Risk factor	Clinical time-course	Indication for treatment	Treatment		Antifungal therapy duration
Acute progressive disseminated histoplasmosis	Immunosuppression such as advanced HIV disease	1–2 weeks	Always	Mild disease	Itraconazole	12 months followed by maintenance antifungal suppression until immune recovery
				Moderate to severe disease	Amphotericin B for 1–2 weeks in non-meningeal and 4–6 weeks in meningeal disease followed by itraconazole as step-down therapy	
Acute pulmonary histoplasmosis	High inoculum exposure to *Histoplasma* conidia	1–2 weeks	Moderate or severe disease or immunosuppressed patient	Mild disease	Itraconazole	12 weeks
				Severe disease	Amphotericin B for 1–2 weeks followed by itraconazole as step-down therapy	
Subacute pulmonary histoplasmosis	Low inoculum exposure to *Histoplasma* conidia	Weeks to months	If symptoms last >1 months or immunosuppressed patient	Itraconazole		6–12 weeks
Chronic cavitary pulmonary histoplasmosis	Chronic obstructive pulmonary disease and other lung diseases Smoking	Months to years	Always	Itraconazole		1–2 years and until radiologic resolution or stabilisation
Mediastinal adenitis	Reactive and enlarged mediastinal lymph nodes	Early complication	If compressive symptoms present or adenitis last >1 months	Itraconazole and steroids		6–12 weeks
Mediastinal granuloma	Coalesced necrotic mediastinal lymph nodes	Early or late complication	If compressive symptoms present	Surgery and itraconazole		6–12 weeks
Mediastinal fibrosis	Fibrosis of mediastinal structures	Late complication	If compressive symptoms present	Stenting, arterial embolization or surgery		Not applicable

Table 1.
Treatment of histoplasmosis syndromes and their complications [13, 14].

The Infectious Diseases Society of America (IDSA) recommends treating CNS disease with liposomal amphotericin B (3.0–5.0 mg/kg daily for a total of 175 mg/kg given over 4–6 weeks), followed by a maintenance phase with itraconazole for at least a year at a dose of 200 mg, given 2–3 times a day [14]. Resolution of CSF abnormalities, including a negative antigen test is the recommended treatment target. Specific recommendations for CSF monitoring are: (a) worsening disease in the initial 2 weeks of therapy or lack of improvement by 1 month of therapy, in order to re-evaluate the diagnosis, (b) when amphotericin B is being replaced by a triazole, (c) if relapse is suspected and (d) after 1 year of therapy, to make the decision of treatment continuation or stoppage. Therapeutic drug monitoring for itraconazole is recommended during treatment to ensure adequate drug exposure. Treatment recommendations for histoplasmosis meningitis or CNS masses are the same. Also, for patients with concurrent pulmonary disease, chronic suppressive therapy with 200 mg of itraconazole, given once a day, is indicated until the patient's immune system is reconstituted [13, 14, 28].

The role of steroids is not well described, although case reports indicate they can be successfully used [14] . Similarly, routine brain or spinal cord surgery is not recommended by IDSA but is chronicled in case reports [14, 28]. Hydrocephalus complicating CNS histoplasmosis may be managed with shunt placement when the patient has received at least 2 weeks of amphotericin B therapy [22]. The management of increased intracranial pressure and the long-term sequelae that require rehabilitation is similar to what is done for stroke and brain tumours [14, 28].

In a sizable cohort of patients, the one-year survival of patients with CNS histoplasmosis was reported to be 75% among patients who were initially treated with liposomal or deoxycholate formulations of amphotericin [28].

3.2 Histoplasmosis in pregnancy

All presenting clinical syndromes of histoplasmosis in pregnancy require antifungal therapy due to the increased risk of trans-placental transmission of the infection to the developing fetus [29]. Preferably, pregnant women can be treated with amphotericin B preparations for 4–6 weeks. Lipid formulation of amphotericin B is given at a dose of 3–5 mg/kg/day. For pregnant women with low risk for nephrotoxicity, amphotericin B deoxycholate (0.7–1.0 mg/kg/day) may be offered as a substitute [14, 30]. Coupled with this, post-partum monitoring of the child for any evidence of the infection is vital. In any case of the newborn showing signs of histoplasmosis infection, it is recommended that treatment of amphotericin B deoxycholate (1 mg/kg/day) is given for 4 weeks [14, 30].

Itraconazole is generally considered teratogenic to the growing fetus and is therefore best avoided in pregnancy. However, itraconazole may be considered for treatment in pregnant women with systemic histoplasmosis, but only after the first trimester [31, 32]. Amphotericin B therefore remains the drug of choice in managing histoplasmosis in pregnancy, as azole antifungals should generally be avoided.

3.3 Histoplasmosis-associated immune reconstitution inflammatory syndrome in the context of human immunodeficiency virus disease

Immune reconstitution inflammatory syndrome (IRIS) is a spectrum of inflammatory disorders linked with paradoxical worsening of pre-existing infectious diseases (previously diagnosed or subclinical) in HIV-infected patients. It typically follows, the initiation of antiretroviral therapy (ART): whereby the ART improves the patient's immune system enough to mount an inflammatory response tends to unmask the underlying infectious processes, such as histoplasmosis [33–36].

In studies done among HIV patients, histoplasmosis-associated - IRIS was associated with histoplasmosis; IRIS was reported to be uncommon with incidence rates of 0.74 cases per 1000 HIV-infected person-years 0.5% [37–39]. However according to another study among 271 patients, the emergence of IRIS tended to be quite common in people with HIV and disseminated histoplasmosis; whether the IRIS is triggered by the Histoplasma or other co-infections, is still unclear [40].

For HIV patients with histoplasmosis to be considered to have histoplasmosis - associated IRIS, they should fulfil most or all of the following criteria: AIDS with low pretreatment CD4 count (≤100 cells/μL), a positive immunological and virological response to ART, clinical manifestations of an inflammatory condition, association between ART initiation and appearance of clinical features of the inflammatory condition and; absence of evidence of ART resistance, patient non-compliance, drug allergy or adverse reactions, a concomitant non- fungal infection, or decreased drug levels due to malabsorption or drug-drug interactions [36, 38, 41–43].

The clinical manifestations vary from case to case, and they commonly include fever, lymphadenopathy, mucocutaneous lesions, and disseminated disease. The timeline of occurrence from initiation of ART is also varied from a few days to months, and symptoms can set in when the patient is already on the ART course or when the ART is just introduced [39, 44, 45]. Histoplasmosis-associated IRIS in HIV patients may have a predilection for females over males, with one study showing that it was four times more frequent in females than males [39].

If the symptoms of IRIS are mild, the patient is managed symptomatically. The role of steroids in treating histoplasmosis-IRIS is yet unclear [39].

However if the presentation is severe, corticosteroids may be used as they have been seen to be of benefit in TB-associated IRIS, though they should be used with caution [46].

Once a patient exhibits features of IRIS while already on effective ART, the ART should be continued and the patient should be initiated on histoplasmosis treatment immediately. However if the patient is not receiving ART, a two-week delay is encouraged before starting ART while the patient is on antifungal therapy (amphotericin B or itraconazole) as per the guidelines [14].

4. Conclusions

Itraconazole alone is used for the treatment of mild forms of histoplasmosis and as a step-down therapy in severe disease and for secondary prophylaxis to prevent relapse in the immunocompromised after induction therapy with amphotericin B. Moderate-to-severe acute pulmonary histoplasmosis as well as acute progressive disseminated histoplasmosis require intravenous amphotericin B therapy for at least 2 weeks (4–6 weeks if meningeal involvement) or until a patient can tolerate oral therapy, then oral itraconazole (or an alternative triazole) for at least 12 weeks (for acute pulmonary) or 12 months (for acute progressive disseminated histoplasmosis). Chronic cavitary pulmonary histoplasmosis is treated with itraconazole for 12–24 months. There is insufficient evidence to support the use of isavuconazole and the echinocandins for the treatment of histoplasmosis.

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