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Review Article

Histoplasmosis: Diagnostic and Therapeutic Aspect

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ABSTRACT

Histoplasmosis has been reported since 1932 in various regions in Indonesia. This disease is caused by thermally dimorphic fungus Histoplasma capsulatum var. capsulatum which is experiencing an increasing incidence worldwide. Human infection occurs when spores in soil contaminated with bird and bat droppings are inhaled and change to form yeast in the lungs. The majority of these forms of infection are mild and can heal on their own, but if large numbers of spores/ inoculum are inhaled, or the host is immunosuppressed, serious lung disease and even dissemination may occur with a high mortality rate. The diagnosis can be made by combining clinical symptoms with laboratory test results. Conventional laboratory methods such as direct examination or histopathology and culture are the gold standards for histoplasmosis diagnosis. The weakness of culture is the nature of H. capsulatum as a slow grower fungus that takes 4-6 weeks to grow. In addition, laboratory tests can be carried out with antibody detection or antigen detection. Antigen detection is more beneficial for hosts with immunosuppression or acute form, while antibody detection is more important in the chronic form of the diseases. Molecular-based assays have high specificity but are not yet available commercially and are more widely used for culture identification to confirm the species of H. capsulatum. Histoplasmosis therapy usually begins with the administration of amphotericin B for around two weeks, followed by maintenance with itraconazole for 6 - 9 months duration. A careful history of possible exposure and the appropriate laboratory diagnostic approach is essential to provide appropriate therapy.

Keywords: *Histoplasma capsulatum; pulmonary; dissemination; laboratory diagnosis; antifungal.*

ABSTRAK

Histoplasmosis telah dilaporkan sejak lama di berbagai daerah di Indonesia yakni sejak tahun 1932. Penyakit ini disebabkan oleh jamur dimorfik bergantung suhu Histoplasma capsulatum var. capsulatum. Histoplasmosis saat ini tengah mengalami peningkatan kejadian di berbagai penjuru dunia. Infeksi pada manusia terjadi ketika spora yang terdapat di tanah yang dicemari oleh kotoran burung dan kelelawar terhirup ke saluran napas dan berubah menjadi bentuk ragi di paru-paru. Pada umumnya bentuk infeksi ini bersifat ringan dan dapat sembuh spontan, namun bila spora/ inokulum yang terhirup berjumlah besar atau pejamu dalam kondisi imunosupresi akan dapat terjadi penyakit paru serius bahkan diseminasi ke seluruh tubuh dengan angka kematian yang tinggi. Diagnosis histoplasmosis dapat ditegakkan dengan menggabungkan gejala klinis dan hasil pemeriksaan laboratorium. Metode laboratorium konvensional seperti pemeriksaan langsung atau histopatologi, dan kultur adalah baku emas untuk diagnosis histoplasmosis. Kelemahan kultur terletak pada lamanya waktu yang diperlukan untuk tumbuh sempurna agar dapat di identifikasi secara morfologis yakni mencapai 4-6 minggu. Selain itu, pemeriksaan laboratorium juga dapat dilakukan dengan deteksi antibodi atau deteksi antigen. Deteksi antigen lebih bermanfaat untuk pejamu imunosupresi atau bentuk akut, sementara deteksi antibodi lebih bermanfaat untuk histoplasmosis kronik. Pemeriksaan berbasis molekular memiliki spesifisitas tinggi namun belum tersedia kit komersial untuk penggunaan rutin dan lebih banyak digunakan untuk memastikan spesies. Terapi histoplasmosis biasanya

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dimulai dengan pemberian amfoterisin B selama kurang lebih dua minggu dilanjutkan terapi rumatan dengan itrakonazol selama 6-9 bulan. Anamnesis yang cermat tentang kemungkinan riwayat pajanan dan pendekatan diagnostik laboratorium yang tepat sangat penting untuk menegakkan diagnosis yang akurat sehingag dapat diberikan terapi yang tepat.

Kata kunci: *Histoplasma capsulatum; paru-paru; diseminata; diagnosis laboratorium; antijamur.*

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INTRODUCTION

Histoplasmosis was first found in 1905 by a pathologist named Samuel Taylor Darling, who autopsied an African carpenter's body with irregular fever, weight loss, splenomegaly, leukopenia, and anemia previously. On autopsy, the cause of death initially was suspected due to tuberculosis (TB). Nevertheless, smears from the patient's granulomas in the lung, bone marrow, liver, and spleen revealed no TB bacilli. Then Darling suggested that the microorganism cause the disease was a protozoan and named it *Histoplasma capsulate* (now *Histoplasma capsulatum*).[1] In 1912, Henrique da Rocha-Lima compared the findings of Darling's slides with fungal of *Cryptococcus* and concluded *Histoplasma capsulatum* (Hc) was a species of fungus rather than a protozoan then classified into the kingdom Fungi with phylum Ascomycota until now.[2,3]

The causative species comprised three taxonomic varieties. Two distinct pathogenic varieties for humans are *H. capsulatum* var. *capsulatum* (Hcc) and *H. capsulatum* var. *duboisii* (Hcd), whereas *H. capsulatum* var. *farciminosum* is pathogenic in horses.[4–6] In this review, we will focus on histoplasmosis due to Hcc, which distributed more widely.

The infection due to Hc occurred when spores located in polluted soil contaminate the surrounding air then inhaled and transformed into yeasts in the lungs.[7,8] The fungus' primary habitat is soil contaminated with bird or bat excreta and chicken droppings. Excrement from several avian species has been incriminated in enhancing the fungus' growth due to nitrogen/phosphate-enriched soil.[3,7,9]

The Hc infection can be the source of symptoms in immunocompromised and immunocompetent patients.[10,11] The clinical spectrum of disease can be severe and mortality high due to its ability to disseminate.[12] Hence, histoplasmosis became a significant public health problem since the AIDS pandemic era and more widely known with other immunosuppressed conditions.[13–15] Herein, we review histoplasmosis diagnosis from clinical features and laboratory diagnostic methods, with a therapeutic approach depends on its clinical finding.

EPIDEMIOLOGY

Indonesia's first case of histoplasmosis was first noted by Mueller in East Java, Indonesia, in 1932.[16] Histoplasmin skin test (HST) methods previously suggested for diagnosis of histoplasmosis in immunocompetent individuals. This test can detect if people have been exposed to Hc, which is similar to the tuberculin test that can detect *Mycobacterium tuberculosis* exposure. Nonetheless, HST is currently more widely used in epidemiological studies to determine histoplasmosis's endemicity, not to diagnose histoplasmosis.[17,18] Historically, Indonesia has done the HST in Jakarta, Surabaya, Bali, and Medan in the 1900s with positive results ranging from 12,5-63.6%.[19] Since then, sporadic cases of histoplasmosis have also been reported from various other regions in Indonesia (Java, Sumatera, and Sulawesi).[19–22]

CLINICAL FEATURES

In immunocompetent hosts, most patients are self-limited mild pulmonary infections remarkably never recognized as being histoplasmosis.[23,24] However, in immunocompromised patients or extreme of age or ensuing inhalation, a large inoculum typically presents as a pulmonary disease with diverse manifestations. Those features including acute pulmonary histoplasmosis, chronic cavitary pulmonary histoplasmosis, a complication of pulmonary histoplasmosis, and progressive disseminated histoplasmosis (PDH).[25–27]

Symptomatic acute pulmonary histoplasmosis is a self-limited disease and often presents in children or adolescents when exposed to the environment's organisms. Symptoms of flu-like syndromes consist of fever, malaise, dyspnea, dry cough, and pleuritic chest pain arising at a median of two weeks after exposure. Chest radiographs show diffuse bilateral patchy infiltrates, while chest computed tomography (CT) frequently shows enlarged hilar lymph nodes or mediastinal. A careful history of Hc's possible inhalation is essential to arrive at the appropriate diagnosis due to similarity with community-acquired bacterial and viral pneumonia. Acute severe pulmonary infection occurs when the host is immunocompromised or inhale a large inoculum of Hc conidia. Patients with this condition and who have severe dyspnoea may develop acute respiratory distress syndrome rapidly.[24,27,28] Infection may also be subacute, which evolves slowly over several weeks after exposure to smaller inocula. Subacute manifestations may present with milder symptoms yet more persist with respiratory and constitutional symptoms e.g., cough, fever, and malaise that last several weeks to a month.[26,27]

The manifestation of chronic cavitary pulmonary histoplasmosis occurs primarily in the elderly with underlying structural pulmonary disease or smoking history. The previous history of pulmonary disorders (e.g., emphysema) causing disturbance of Hc clearance, resulting in long-lasting latent inflammation occurs adjacent to preexisting bullae, leading to large cavitary lesions.[23,26,27] Clinical manifestations that can occur include chronic productive cough, hemoptysis, dyspnea, chest pain, nonspecific fever, night sweats, fatigue, and weight loss. These clinical symptoms can take months to years. Chest imaging may demonstrate focal or diffuse infiltrates, nodules, consolidations, and cavitation, commonly in the lung's apical region. In the late phase, we may see interstitial fibrosis and pleural thickening. Clinical and chest imaging features resemble other chronically destructive pneumonia, including TB and other pulmonary fungal infections like chronic pulmonary aspergillosis.[27,29] In Indonesia, where TB is endemic, the differential diagnosis of histoplasmosis should be considered, especially in multidrug-resistant TB. The progression of the chronic form is slow but can be fatal if left untreated.[23,26,27,30]

Sequelae of pulmonary histoplasmosis mostly are asymptomatic calcifications and calcified mediastinal/ peribronchial lymph nodes. Nonetheless, progressive complication leads to obstructive symptomatology, including mediastinal granuloma, mediastinal fibrosis, and broncholithiasis can occur though are rare. Other uncommon manifestations seen in sequelae histoplasmosis patients include: pericarditis, arthralgias, erythema nodosum, and erythema multiforme.[24,27]

The spectrum of PDH more likely to occur in the immunocompromised population. Before the frequent use of immunosuppressive therapy, PDH was seen predominantly in infants. Currently, most cases of PDH were reported in HIV-infected patients, especially with CD4 cells <150/μL.[23] Other immunocompromised patients are at risk of developing PDH, including those with the recipient of organ transplantation, hematologic malignancies, and long-term immunosuppressive therapy.[31] Nonetheless, PDH has also been described in immunocompetent patients, apparently due to extensive inocula exposure.[31,32] A discrete source for disseminated infection often is unclear whether the disease is due to primary infection or reactivation. The clinical syndrome of PDH consists of respiratory symptoms with prolonged fever,

fatigue, weight loss, and night sweats. In patients with disseminated histoplasmosis, an enlarged liver and spleen may be found. In addition, diffuse lymphadenopathy is often found.[23,24,27] The spectrum of this PDH in HIV-infected patients is not specific and hard to distinguish from other infectious diseases, such as disseminated TB, therefore delay the diagnosis.[33–35] Laboratory of a patient with PDH often reveals pancytopenia, elevated liver enzymes, elevated C-reactive protein (CRP), lactate dehydrogenase (LDH), and ferritin.[23,32,36–38] The most common dissemination PDH is the reticuloendothelial system, including liver, spleen, bone marrow, and lymph nodes. The oral mucosa also has been reported as the most affected site of dissemination.[23,27] Meanwhile, the skin is not a common extrapulmonary site of PDH, except in patients with advanced HIV infection.[23,39] The cutaneous involvement lesions vary from papules, pustules, plaques, ulcers, wart-like lesions, and even erythema nodosum.[39] These lesions are usually affected in the face, extremities, and trunk.[40] A nonspecific clinical features of PDH cause history of patients living in endemic areas or probably has recent epidemiologic exposures should be maintained in immunocompromised patients.[23,27]

LABORATORY DIAGNOSTIC METHODS

The European Organization for Research and Treatment of Cancer and the Mycoses Study Group Education and Research Consortium (EORTC/MSGERC) have defined criteria for a proven diagnosis of invasive fungal from dimorphic fungi. A proven (gold standard) criteria for histoplasmosis diagnosis is a positive culture or histopathology or direct microscopy of Hc from clinical specimens (bone marrow, blood, biopsied tissue, sterile fluids, or respiratory specimens). If all proven criteria are not available or showed a negative result, but the patient is immunocompromised with typical clinical features, evidence of environmental exposure to the fungus, and the presence of *Histoplasma* antigen in any body fluid, the diagnosis is considered probable.[41] Laboratory methods for diagnosis histoplasmosis include direct examination, culture, histopathology, antigen/antibody detection, and molecular. These tests' sensitivity is related to several variables, consisting of the patient's clinical form (acute/chronic pulmonary or disseminated), immune status, clinical specimens, and fungal burden.[42]

Direct examination

Direct examination of clinical specimens consists of KOH wet slide examination and histopathology investigation.

KOH wet slide

Examination under microscope using potassium hydroxide (KOH 10%) is a rapid way still have very low sensitivity and specificity for diagnosis.[43,44] Meanwhile, calcofluor white stain examination under the fluorescent microscope may increase Hc's detection; however, the yeast visualization is not pathognomonic.[42] Furthermore, the direct examination requires highly trained professionals to make a proper diagnosis.

Histopathology

Histopathologic examination using specific stains that exhibit Hc's yeast-like structures is a definitive and rapid way for histoplasmosis diagnosis, especially disseminated form. The

Table 1. The sensitivity of laboratory methods based on the patient's clinical form of histoplasmosis[49,50,58]

Methods	Acute pulmonary	Chronic pulmonary	Progressive disseminated
Culture	0 (3), 42 (19)*	66.7 (6)^	74.2 (132)^
Pathology	0 (2), 20 (10)*	75 (4)^	76.3 (76)^
Antigen detection	83.3 (6), 83 (29)*	87.5 (8)^	91.8 (158)^
Antibody detection	66.7 (6), 64 (28)*	83.3 9 (6)^	75 (80)^
Molecular	NA	NA	95 (NA)#

All data showed in percentage (%), The number in parentheses represents the number of patients who were tested ^ cited from:[49], *cited from:[50], #cited from: [58]

samples could be obtained from tissues or body fluids. 41,42,44 The sample-taking procedure of touch biopsy is less invasive and feasible for diagnosis of disseminated histoplasmosis with cutaneous involvement.45 However, a clinical specimen from other sites such as bone marrow aspiration and biopsy is invasive. Furthermore, professional expertise is mandatory to differentiate Hc yeast from other fungal pathogens such as *Blastomyces dermatitis*, *Candida glabrata, Coccidioides* sp, *Cryptococcus* sp, *Emergomyces* sp, *Pneumocystis jirovecii*, *Talaromyces marneffei*, and *Leishmania donovani*.[18,46,47] The sensitivity of the pathology assay varies according to histoplasmosis's clinical manifestation (Table 1).

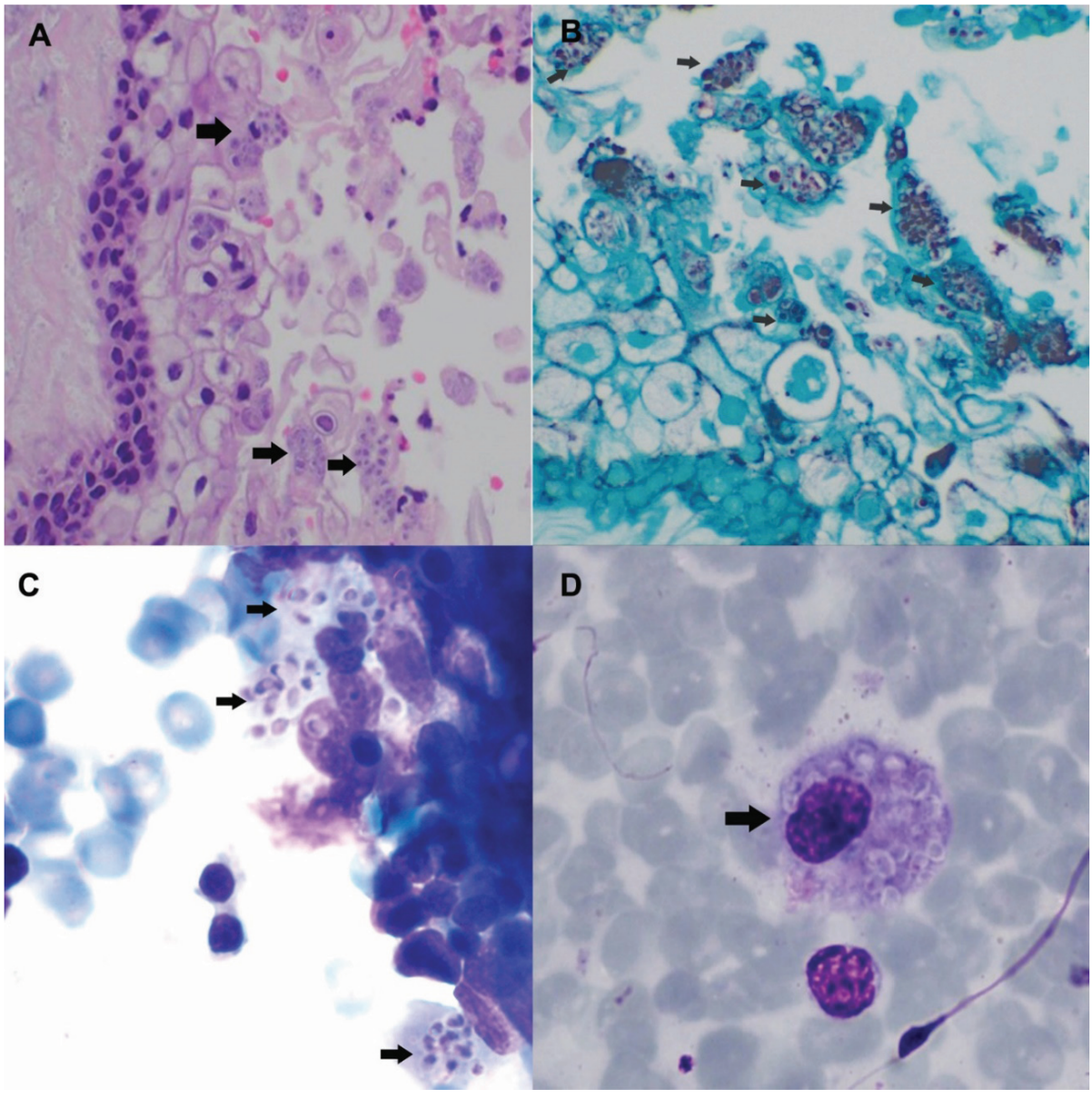

Figure 1. Histopathologic examination of Histoplasma sp. A) Umbilical cord with HE staining, B) Umbilical cord with GMS, C) Bone marrow aspirate smear with Wright - Giemsa, D) Touch biopsy of the skin with Giemsa. The arrows are demonstrating numerous ovoid intracellular yeast cells surrounded by hyaline hallo within macrophage (1000 × magnification). Images A and B courtesy of Dr. Kenneth Chang and Dr. Aw Sze Jet, Department of Pathology and Laboratory Medicine, KK Women's and Children's Hospital; Singapore. Images C and D courtesy of R. Wahyuningsih, Parasitology Laboratory, Faculty of Medicine, Universitas Indonesia.

Histoplasma capsulatum characteristic yeasts are ovoid with a clear halo-like capsule surrounding, divide by narrow-based budding, and predominantly intracellular (within macrophages and giant cells). The yeast diameter measure is around 2-4 µm.[35] Specific pathologic stains for identifying yeast cells of Hc include hematoxylin and eosin (H&E), Gomori methenamine-silver (GMS), or periodic acid-Schiff (PAS). Meanwhile, Wright-Giemsa stains may be used to rapidly discover yeast cells of Hc in peripheral blood or bone marrow aspirate smears (Figure 1).[46,48]

Culture

Histoplasma isolation in culture is still considered the gold standard for diagnosing histoplasmosis. Nevertheless, the process is so time-consuming and requires a biosafety level 3 laboratory. Clinical specimens from patients suspected of histoplasmosis might be inoculated onto an appropriate culture medium, e.g., Sabouraud dextrose agar (SDA) or Brain-Heart infusion (BHI) agar. When culture incubated at 25-30°C, it needs 4 to 6 weeks to be detectable as a mold with cream to brown cottony colonies (Figure 2A). After a colony is identified on medium, a lactophenol cotton blue or lactoglycerol/ lactophenol slide can be performed to establish mold morphology. Microscopic identification of mold morphology will show septated hyphae at first, followed by microconidia based on the maturity of the mycelia phase. The smooth microconidia diameter varies from 2 to 5 µm, followed by tuberculate macroconidia form with 7 to 15 µm in diameter (Figure 2B).[24,42]

Since Hc is dimorphic fungi, if the mold form incubates at 35-37°C, it will transform into yeast phase and commonly occurs within 2 to 4 weeks. Previously conversion method was used as a confirmed diagnosis, but the conversion rate is low, so developed countries have left it behind.[25,42] The sensitivity of the culture-based methods is dependent on the fungal burden. Samples from patients with disseminated histoplasmosis reveal higher sensitivity which is 74%, than in acute pulmonary histoplasmosis is 42% (Table 1).[49,50]

Antigen detection

Antigen detection is a laboratory method that allows a less invasive, rapid, and sensitive diagnosis of acute and disseminated histoplasmosis

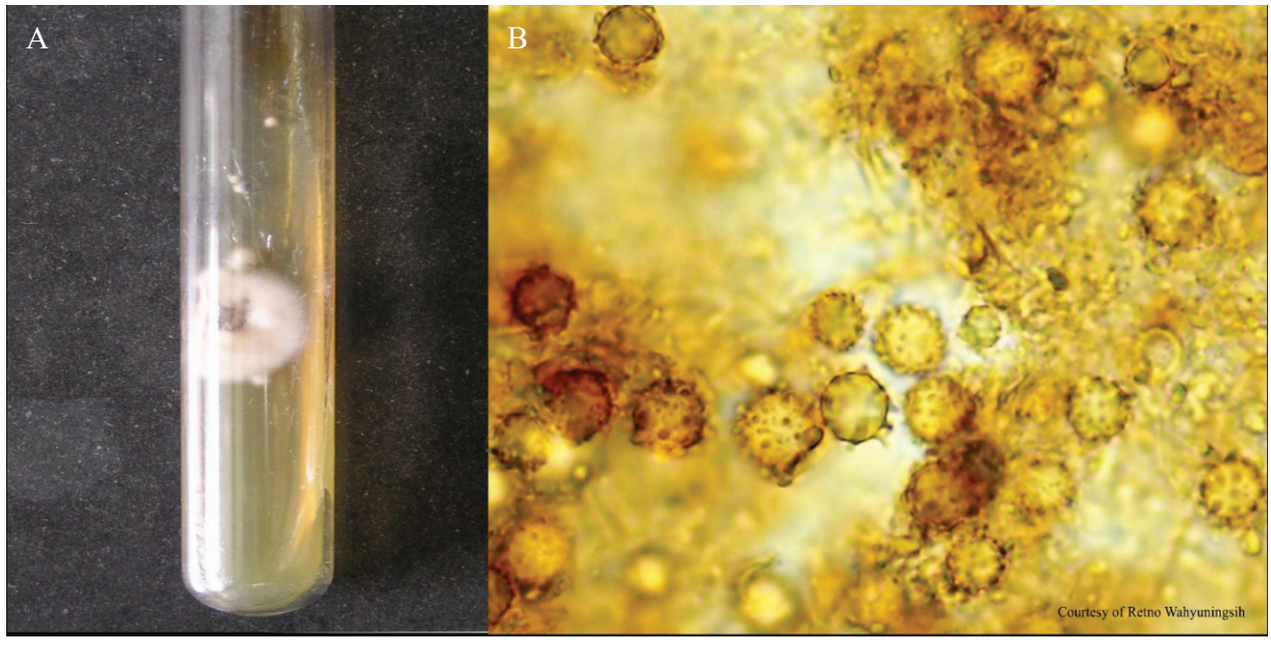

Figure 2. A) Culture of *Histoplasma capsulatum* at 25°C, B) Microscopic of lactophenol/lactoglycerol stained showed tuberculate macroconidia, a characteristic morphological structure of Histoplasma spore, 400× magnification. (Images courtesy of R. Wahyuningsih (Parasitology laboratory, Faculty of Medicine, Universitas Indonesia).

where the burden of infection is high.[18] During infection with Hc, antigens

are released by fungal cells into the tissues and enter body fluids adjacent to the site of infection, such as serum (blood) fluids, bronchoalveolar lavage (BAL), urine, and cerebrospinal fluid (CSF). It allows as a useful method for rapid diagnosis of histoplasmosis and for monitoring the effect of therapy. [17,18,48,51]

Antigen assay for histoplasmosis was first developed in 1986 using a sandwich radioimmunoassay in urine and serum specimens—a radioimmunoassay assay based on detection of polyclonal rabbit antibodies against *Histoplasma* galactomannan. In 1997, the *Histoplasma* antigen detection method was adapted to enzyme immunoassay (EIA). The EIA method was then developed into the second generation in 2004 to prevent false-positive results due to human anti-rabbit antibodies. In 2007, the third generation of *Histoplasma* EIA examination was launched with a quantification test's superiority with higher specificity (MiraVista *H. capsulatum* Galactomannan EIA). This EIA examination can be done with a kit from MiraVista Diagnostics. However, the test can only be done in-house compared to the ALPHA *Histoplasma* EIA test from IMMY commercially available and does not have to be in its laboratory. The use of the kit from IMMY then also received approval from the Food and Drug Administration (FDA) on urine specimens and can be used in local facilities. Besides, the IMMY test was recently modified using monoclonal antibodies, which significantly increased its sensitivity.[42]

Histoplasma antigen tests on urine specimens generally proved slightly more sensitive than serum for diagnosing all forms of histoplasmosis. Moreover, combining both urine and serum testing enhances the sensitivity of antigen detection.[25] In a recent study, specimens from BAL fluid may increase histoplasmosis diagnosis sensitivity.[52] Other specimens such as CSF may be useful too in the diagnosis of *Histoplasma* meningitis.[53] A meta-analysis study in 2016 that evaluated the diagnostic performance of the *Histoplasma* antigen test showed that the overall sensitivity of the test in serum and urine was 81% while the specificity was 99%.[54] While the sensitivity based on clinical manifestations varied (Table 1).

A limitation from the *Histoplasma* antigen assay is the remarkable cross-reactivity with other dimorphic fungal, such as *Blastomyces dermatitidis*, *Paracoccidioides brasiliensis*, *Talaromyces marneffei*, *Coccidioides immitis, and Emergomyces* sp. Another cross-reactivity has also been reported with Platelia *Aspergillus* EIA which the false-positive result is correlated with the concentration of positivity *Histoplasma* antigen EIA.[55] Unfortunately, the antigen detection kit for histoplasmosis not yet available in Indonesia. Thus, meticulously morphological identification is the primary key for laboratory clinicians.

Antibody detection

Antibody detection-based tests may provide a rapid diagnosis; however, unsuitable for an early acute form of infection Hc. The newly formed antibodies can be detected in peripheral blood about 4 to 8 weeks after exposure to Hc and then persist for years.[26,42] Therefore, antibody detection is more suitable for diagnosing subacute and chronic forms of histoplasmosis (Table 1). Besides, this test has significant limitations, particularly in immunocompromised patients, who are unable to enhance the humoral immune response, so false negatives can occur.[56]

The available methods of antibody detection tests against Hc are EIA, complement fixation (CF), immunodiffusion (ID), latex agglutination (LA), and Western blot (WB).[42,44] The most sensitive antibody detection test for histoplasmosis is EIA but has high false-positives results. The low specificity of the EIA test makes it has not been standardized across laboratories.[26] The CF and ID are generally performed in reference laboratories due to their reliability and potential cost-effectiveness.[48] The CF performance is more sensitive than ID but less specific. The ID detects antibodies that bind to H and M fungal antigens of Hc. The H band (20%) is rarely seen as M band (80%). However, when H band is present indicates acute infection. Meanwhile, the M band is more commonly seen but couldn't tell the difference between active from latent infection or resolved histoplasmosis.[42] The ID specificity is 100%, whereas sensitivity ranges from 70 to

95%, depending on histoplasmosis's form.[48] The commercial LA tests, which are commercially available, showed false positives in patients with TB and should be aware by clinicians.[18] Currently, a study to validate the WB assay for diagnosis histoplasmosis showed high sensitivity (94.9%) and specificity (94.1%).[57]

Molecular

Molecular methods that can detect *Histoplasma* DNA for diagnosis are highly specific. Nonetheless, there are no commercial and FDA-approved molecular tests to detect Hc from clinical specimens directly.[44] DNA probes exist commercially but are used for definite identification from positive cultures rather than from direct clinical specimens. Thus, several studies are currently developing direct Hc detection trials from clinical samples.[42] The performance of the molecular tests in the diagnosis varies according to the clinical form of histoplasmosis. A meta-analysis study showed the overall sensitivity of the molecular tests from different types of specimens, e.g., tissue biopsy, respiratory, blood, and bone marrow samples for diagnosing disseminated histoplasmosis was 95%, and the specificity was 99% (Table 1).[58]

TREATMENT

The recommended therapy for histoplasmosis differs according to the patient's clinical spectrum (Table 2). Treatment is indicated in patients with severe or moderately severe acute pulmonary, chronic cavitary pulmonary, disseminated, and central nervous system (CNS) histoplasmosis. The

Table 2. Treatment of histoplasmosis according to the patient's clinical spectrum[44,59,60]

Clinical spectrum of histoplasmosis	Recommendation	Notes
Acute pulmonary (moderately severe or severe)	AmB lipid complex (3-5 mg/kg/day IV) or d-AmB (0.7-1 mg/kg/day IV) for 1-2 weeks or until the patient is clinically stable, then switch to itraconazole 200 mg PO two times a day for ≥12 months	One liter of normal saline (NaCl 0.9%) can be administered before administration of d-AmB to reduce the nephrotoxicity effect. Most available in Indonesia is d-Amb
	Methylprednisolone (0.5–1 mg/kg/day IV) for 1–2 weeks	Combination with steroid is recommended for patients who develop respiratory complications, e.g., hypoxemia/ significant respiratory distress
Acute pulmonary (mild to moderate but with symptoms > 4 weeks)	Itraconazole PO 200 mg two times a day for 6-12 weeks	Absorption of the capsule formulation is affected by gastric pH, which is improved if given with food and carbonated drink
Chronic cavitary pulmonary	Itraconazole PO 200 mg two times a day 12 months	Treatment could be extended to 18–24 months to minimize the risk for relapse
Progressive disseminated	Liposomal AmB (3 mg/kg/day IV) or AmB lipid complex (3-5 mg/kg/day IV) or AmB deoxycholate (0.7-1 mg/kg/day IV) for 1-2 weeks or until the patient is clinically stable then switch to itraconazole PO 200 mg 3 times a day for three days, and then 200 mg two times a day for ≥12 months.	More prolonged treatment may be required in patients with persistent immunosuppression condition
CNS histoplasmosis	Liposomal AmB (5 mg/kg/day IV) for 4–6 weeks, then switch to itraconazole 200 mg PO two/ three times a day for ≥12 months	

Description: AmB: amphotericin B; d-AmB: Amphotericin B deoxycholate; IV: intravenous; PO: peroral

antifungal agent that has been proven to be effective include amphotericin B (liposomal amphotericin B, amphotericin B lipid complex, amphotericin B deoxycholate) and itraconazole.[59]

Amphotericin B deoxycholate (d-AmB) is a polyene antifungal agent administered intravenously by infusion in 2-4 hour intervals. The dosage for histoplasmosis is 0.7-1 mg/kg/day and can be given approximately two weeks. The administration of this drug may cause adverse side effects, divided into acute and chronic reactions. Feasible acute reactions include chills, fever, and tachypnea, which occur 30 to 45 minutes after the first dose. Premedication with paracetamol or corticosteroids can be given to diminish the reaction. Its chronic adverse effect is nephrotoxicity, which is dose and infusion-related. The mechanism of nephrotoxicity due to d-AmB is decreasing glomerulotubular renal flow. Isotonic saline administration before d-AmB may preserve renal function. Clinical features of other kidney effect include hypokalemia, and distal renal tubular acidosis, which can be treated with potassium and bicarbonate.[60]

The primary azole group for histoplasmosis treatment is itraconazole that can be given for 6-9 months. Fluconazole may be utilized as a second-line agent but not as efficacious as itraconazole. Other azole antifungal agents such as voriconazole and posaconazole may be effective for histoplasmosis treatment; however, there are inadequate clinical experience data. While the echinocandins should not be used because they showed limited in vitro activity against Hc.[27,44,59]

SUMMARY

Histoplasmosis is a disease caused by the fungus Hcc, which is distributed worldwide. The infection occurred when the conidia of Hc inhaled and transformed into yeasts in the lungs. This fungal infection can cause symptoms in immunocompromised and immunocompetent patients. The majority of patients are self-limited mild pulmonary infections remarkably never recognized as being histoplasmosis in immunocompetent individuals. However, in immunocompromised patients or extreme of age or following inhalation, a large inoculum typically presents as a pulmonary disease with diverse manifestations. The

Clinical features include acute pulmonary histoplasmosis, chronic cavitary pulmonary histoplasmosis, a complication of pulmonary histoplasmosis, and progressive disseminated histoplasmosis (PDH).

Isolation of Hc from clinical specimens remains the gold standard for the diagnosis of histoplasmosis. However, it takes 4-6 weeks to be identified and needs a high laboratory requirement. Alternately histopathology methods with Wright-Giemsa stains may be used to rapidly detect yeast cells of Hc in peripheral blood or bone marrow aspirate smears.

In recent years, the number of immunocompromised individuals and travelers from and to endemic areas histoplasmosis increases. Also, Indonesia has HST sensitivity above the global scale of histoplasmin sensitivity, which supports an endemic area, e.g., Jakarta, Surabaya, Bali, and Medan in the 1900s. Therefore, physicians need to be aware of this infection because the clinical feature can mimic other pulmonary diseases. A careful history of possible exposure and the appropriate diagnostic approach described above is essential to provide appropriate therapy.

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CONFLICT OF INTEREST

None declared.

REFERENCES

1. Darling ST. A protozoön general infection producing pseudotubercles in the lungs and focal necroses in the liver, spleen and lymphnodes. J Am Med Assoc. Epub ahead of print 1906. DOI: 10.1001/jama.1906.62510440037003.
2. Schwarz J, Baum GL. The history of histoplasmosis, 1906 to 1956. N Engl J Med. 1957;256: 253–258.
3. Bahr NC, Antinori S, Wheat LJ, et al. Histoplasmosis infections worldwide: thinking outside of the Ohio River valley. Curr Trop Med reports. 2015;2:70–80.
4. Kasuga T, White TJ, Koenig G, et al. Phylogeography of the fungal pathogen *Histoplasma capsulatum*. Mol Ecol. 2003;12:3383–401.
5. Teixeira M de M, Patané JSL, Taylor ML, Gómez BL, Theodoro RC, de Hoog S, et al. Worldwide Phylogenetic Distributions and Population Dynamics of the Genus Histoplasma. PLoS Negl Trop Dis. 2016;10(6):e0004732.
6. Dubois A, Janssens PG, Brutsaert P, Vanbreuseghem R. A case of African histoplasmosis; with a mycological note on Histoplasma duboisii n.sp. Ann la Soc belge Med Trop. 1952;32(6):569–84.
7. Edwards JA, Rappleye CA. *Histoplasma* mechanisms of pathogenesis - one portfolio does not fit all. FEMS Microbiology Letters. 2011;324:1–9.
8. Mittal J, Ponce MG, Gendlina I, et al. *Histoplasma capsulatum*: Mechanisms for pathogenesis. In: Curr Top Microbiol Immunol. 2019;422:157-191.
9. Deepe GS. Outbreaks of histoplasmosis: The spores set sail. Sheppard DC, editor. PLOS Pathog. 2018;14(9):e1007213.
10. Mihu MR, Nosanchuk JD. *Histoplasma* virulence and host responses. Int J Microbiol. 2012;2012:268123.
11. Randhawa HS, Gugnan HC. Occurrence of Histoplasmosis in the Indian Sub-Continent: An Overview and Update. J Med Res Pr. 2018;07: 71–83.
12. Boigues BCS, Paniago AMM, Lima GME, et al. Clinical outcomes and risk factors for death from disseminated histoplasmosis in patients with AIDS who visited a high-complexity hospital in campo Grande, MS, Brazil. Rev Soc Bras Med Trop. 2018;51:155–161.
13. Centers for Disease Control. Revision of the CDC surveillance case definition for acquired immunodeficiency syndrome. MMWR Suppl 1987;36(1):1S-15S
14. Chander J. Histoplasmosis. In: Chander J,ed. Textbook of Medical Mycology. 4th ed. New Delhi, India: Jaypee Brothers Medical Publishers Ltd; 2018:311–23.
15. Benedict K, Mody RK. Epidemiology of histoplasmosis outbreaks, United States, 1938-2013. Emerg Infect Dis. 2016;22(3):370–8.
16. Müller H. Histoplasmosis in East Java. Geneeskd Tijdschr voor Ned. 1932;72(14).
17. Wheat LJ. Current diagnosis of histoplasmosis. Trends Microbiol. 2003;11(10):488–94.
18. Guimarães AJ, Nosanchuk JD, Zancopé-Oliveira RM. Diagnosis of Histoplasmosis. Braz J Microbiol. 2006;37(1):1-13
19. Baker J, Setianingrum F, Wahyuningsih R, Denning DW. Mapping histoplasmosis in South East Asia – implications for diagnosis in AIDS. Emerg Microbes Infect. 2019;8(1):1139–45.
20. Anggorowati N, Sulistyaningsih RC, Ghozali A, Subronto YW. Disseminated Histoplasmosis in an Indonesian HIV-Positive Patient: A Case Diagnosed by Fine Needle Aspiration Cytology. Acta Med Indones. 2018 Jan 19;49(4):360.
21. Hartono A, Soeprihatin S. Dua kasus dengan kelainan pada pharynx jang djarang ditemukan. Oto Rhino Laryngol lndon. 1970;2:17–32.
22. Abdulsalam M, Hoedijoko, Gatot D, et al. Histoplasmosis diseminata pada anak. Medika. 1986;12:4–9.
23. Linder KA, Kauffman CA. Histoplasmosis: Epidemiology, Diagnosis, and Clinical Manifestations. Current Fungal Infection Reports. 2019;13(3):120-8.
24. Kauffman CA. Histoplasmosis: A clinical and laboratory update. Clinical Microbiology Reviews. American Society for Microbiology (ASM); 2007;2091):115-32.
25. Hage CA, Azar MM, Bahr N, Loyd J, Wheat LJ. Histoplasmosis: Up-to-Date Evidence-Based Approach to Diagnosis and Management. Semin Respir Crit Care Med. 2015; 36(5):729-45.
26. Azar MM, Hage CA. Clinical Perspectives in the Diagnosis and Management of Histoplasmosis. Clinics in Chest Medicine. W.B. Saunders; 2017;38(3):403-15.
27. Azar MM, Loyd JL, Relich RF, Wheat LJ, Hage CA. Current Concepts in the Epidemiology, Diagnosis, and Management of Histoplasmosis Syndromes. Semin Respir Crit Care Med. 2020;41(1):13–30.
28. Staffolani S, Buonfrate D, Angheben A, et al. Acute histoplasmosis in immunocompetent travelers: A systematic review of literature. BMC Infectious Diseases. 2018;18:673.
29. Baker J, Kosmidis C, Rozaliyani A, Wahyuningsih R, Denning DW. Chronic Pulmonary Histoplasmosis-A Scoping Literature Review. Open Forum Infect Dis. 2020;7(5):ofaa119.
30. Kandi V, Vaish R, Palange P, Bhoomagiri MR. Chronic Pulmonary Histoplasmosis and its Clinical Significance: an Under-reported Systemic Fungal Disease. Cureus. 2016;8(8):e751.
31. Samaddar A, Sharma A, Kumar PH A, et al. Disseminated histoplasmosis in immunocompetent patients from an arid zone in Western India: A case series. Med Mycol Case Rep. 2019;25:49–52.
32. Xiong XF, Fan LL, Kang M, Wei J, Cheng DY. Disseminated histoplasmosis: A rare clinical phenotype

with difficult diagnosis. Respirol Case Reports. 2017;5(3):e002.
33. Jeong HW, Sohn JW, Kim MJ, Choi JW, Kim CH, Choi SH, et al. Disseminated histoplasmosis and tuberculosis in a patient with HIV infection. Yonsei medical journal. 2007;48(3):531-4.
34. Nacher M, Couppié P, Epelboin L, Djossou F, Demar M, Adenis A. Disseminated Histoplasmosis: Fighting a neglected killer of patients with advanced HIV disease in Latin America. PLoS pathogens. 2020 May 14;16(5):e1008449.
35. Murray M, Hine P, Garner P. Guidelines for Diagnosing and Managing Disseminated Histoplasmosis among People Living with HIV[Internet]. PAHO;2020. [cited 25 January 2021]. Available from: https://iris.paho.org/handle/10665.2/5230.
36. Kutkut I, Vater L, Goldman M, Czader M, Swenberg J, Fulkerson Z, et al. Thrombocytopenia and disseminated histoplasmosis in immunocompetent adults. Clin Case Reports. 2017;5(12):1954–60.
37. Choi J, Nikoomanesh K, Uppal J, Wang S. Progressive disseminated histoplasmosis with concomitant disseminated nontuberculous mycobacterial infection in a patient with AIDS from a non-endemic region (California). BMC Pulm Med . 2019;19(1):46.
38. Zarlasht F, Zarlasht F, Ramadan M, Almoadhen M, Lin K, Khaja M, et al. Lactate Dehydrogenase and Ferritin Levels: A Clinical Clue for Early Diagnosis of Disseminated Histoplasmosis in HIV Patients. J Med Cases. 2016;7(3):81–3.
39. Smith JA, Riddell J, Kauffman CA. Cutaneous manifestations of endemic mycoses. Current Infectious Disease Reports. 2013;15: 440–449.
40. Chang P, Rodas C. Skin lesions in histoplasmosis. Clinics in dermatology. 2012;30(6):592-8.
41. Donnelly JP, Chen SC, Kauffman CA, Steinbach WJ, Baddley JW, Verweij PE, et al. Revision and update of the consensus definitions of invasive fungal disease from the European Organization for Research and Treatment of Cancer and the Mycoses Study Group Education and Research Consortium. Clinical Infectious Diseases. 2019.
42. Azar MM, Hage CA. Laboratory diagnostics for histoplasmosis. Journal of Clinical Microbiology. 2017;55(6):1612-20.
43. Nacher M, Blanchet D, Bongomin F, Chakrabarti A, Couppié P, Demar M, et al. Histoplasma capsulatum antigen detection tests as an essential diagnostic tool for patients with advanced HIV disease in low and middle income countries: A systematic review of diagnostic accuracy studies. PLoS Negl Trop Dis. 2018;12(10):e0006802.
44. Almeida-Silva F, Gonçalves D de S, de Abreu Almeida M, Guimarães AJ. Current Aspects of Diagnosis and Therapeutics of Histoplasmosis and Future Trends: Moving onto a New Immune (Diagnosis and Therapeutic) Era?. Current Clinical Microbiology Reports. 2019;15;6(3):98-107.
45. Wahyuningsih R, Adawiyah R, Suriadiredja A, Sjam R, Yunihastuti E, Imran D, et al. Touch Biopsy: A Simple and Rapid Method for the Diagnosis of Systemic Mycoses with Skin Dissemination in HIV-Infected Patients. International Journal of Technology. In Press 2021.
46. Guarner J, Brandt ME. Histopathologic diagnosis of fungal infections in the 21st century. Clinical Microbiology Reviews. 2011;24(2);247-80.
47. Schwartz IS, Govender NP, Sigler L, Jiang Y, Maphanga TG, Toplis B, et al. Emergomyces: The global rise of new dimorphic fungal pathogens. Hogan DA, editor. PLOS Pathog. 2019;15(9):e1007977.
48. Scheel CM, Gómez BL. Diagnostic Methods for Histoplasmosis: Focus on Endemic Countries with Variable Infrastructure Levels. Current Tropical Medicine Reports. 2014;1(2):129-37.
49. Hage CA, Ribes JA, Wengenack NL, Baddour LM, Assi M, McKinsey DS, et al. A multicenter evaluation of tests for diagnosis of histoplasmosis. Clin Infect Dis. 2011;53(5):448-54.
50. Swartzentruber S, Rhodes L, Kurkjian K, Zahn M, Brandt ME, Connolly P, et al. Diagnosis of Acute Pulmonary Histoplasmosis by Antigen Detection. Clin Infect Dis. 2009;49(12):1878–82.
51. Wheat LJ, Garringer T, Brizendine E, et al. Diagnosis of histoplasmosis by antigen detection based upon experience at the histoplasmosis reference laboratory. Diagn Microbiol Infect Dis. 2002;43: 29–37.
52. Hage CA, Davis TE, Fuller D, Egan L, Witt JR, Wheat LJ, et al. Diagnosis of histoplasmosis by antigen detection in BAL fluid. Chest. 2010;137(3):623–8.
53. Bloch KC, Myint T, Raymond-Guillen L, Hage CA, Davis TE, Wright PW, et al. Improvement in Diagnosis of *Histoplasma* Meningitis by Combined Testing for Histoplasma Antigen and Immunoglobulin G and Immunoglobulin M Anti-Histoplasma Antibody in Cerebrospinal Fluid. Clin Infect Dis. 2018;66(1):89–94.
54. Fandiño-Devia E, Rodríguez-Echeverri C, Cardona-Arias J, Gonzalez A. Antigen Detection in the Diagnosis of Histoplasmosis: A Meta-analysis of Diagnostic Performance. Mycopathologia. 2016;181(3–4):197–205.
55. Wheat LJ, Hackett E, Durkin M, Connolly P, Petraitiene R, Walsh TJ, et al. Histoplasmosis-associated cross-reactivity in the Biorad Platelia *Aspergillus* enzyme immunoassay. Clin Vaccine Immunol. 2007;14(5):638–40.
56. Wheat LJ, Azar MM, Bahr NC, Spec A, Relich RF, Hage C. Histoplasmosis. Infect Dis Clin North Am. 2016;30(1):207–27.
57. Almeida M de A, Pizzini CV, Damasceno LS, Muniz M de M, Almeida-Paes R, Peralta RHS, et al. Validation

of western blot for *Histoplasma capsulatum* antibody detection assay. BMC Infect Dis. 2016;16(1):87.
58. Caceres DH, Knuth M, Derado G, Lindsley MD. Diagnosis of progressive disseminated histoplasmosis in advanced HIV: A meta-analysis of assay analytical performance. J Fungi. 2019;5(3):76.
59. Wheat LJ, Freifeld AG, Kleiman MB, Baddley JW, McKinsey DS, Loyd JE, et al. Clinical Practice Guidelines for the Management of Patients with Histoplasmosis: 2007 Update by the Infectious Diseases Society of America. Clin Infect Dis. 2007;45(7):807–25.
60. Stevens DA. Systemic antifungal agents. In: Goldman's Cecil Medicine. WB Saunders; 2012:1971–77.