Chapter

Introductory Chapter: The Global Distribution of Human Histoplasmosis - An Overview

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1. Introduction

Between 1906 and 1909, Dr. Samuel T. Darling described human histoplasmosis (of Darling or Darling's disease) among three patients in the Canal Zone, Panama who had presented with severe emaciation, pancytopenia, intermittent fevers and splenomegaly – resembling kala-azar and disseminated tuberculosis, clinically [1]. Dr. Darling demonstrated numerous small, intracellular encapsulated micro-organisms in tissue specimens of his patients and named the organism, *Histoplasma capsulatum* [2].

H. capsulatum is a thermally dimorphic fungus, existing as a mould in the environment and as a small narrow-based budding yeast in the host at 37°C. Environmental isolations of the fungus have been made from soil enriched with excreta from chicken, starlings, and bats [3, 4]. *H. capsulatum* species complex comprises of two distinct varieties, that is, *H. capsulatum var. capsulatum* (hereafter referred to as *H. capsulatum*) and *H. capsulatum var. duboisii* (hereafter referred to as *H. duboisii*) [5]. Epidemiologically, *H. capsulatum* is patchily distributed around the world, whereas *H. duboisii* is almost restricted to Sub-Saharan Africa [6]. Histologically, the yeast form of *H. capsulatum* is smaller, about 1–5 μm compared to the larger *H. duboisii*, which is about 5–20 μm [7]. Clinically, *H. capsulatum* is associated with protean manifestations; meanwhile *H. duboisii* mainly causes musculoskeletal and cutaneous manifestations [8, 9]. Both species complex are associated with pulmonary diseases; however, the absence of pulmonary lesions does not exclude the diagnosis of other forms of histoplasmosis [8].

Humans acquire histoplasmosis through inhalation of *Histoplasma* microconidia (spores) from abiotic environment. Majority of the immunocompetent individuals are asymptomatic, some develop self-limiting influenza-like syndromes and a vast minority develop disseminated disease, especially those with severe immunosuppression such as those with HIV/AIDS and those on biologic therapy [10, 11]. Subclinical infections can be demonstrated through histoplasmin skin testing while clinical disease through conventional culture and microscopy or histopathological analysis of the appropriate clinical specimen [12–14]. In this chapter, we aimed to overview the global epidemiology of histoplasmosis and also we touched briefly on its clinical manifestations, diagnosis, and treatment.

2. Global epidemiology

The global distribution of histoplasmosis and *Histoplasma* is incompletely understood [15]. The true burden of histoplasmosis in many areas of the world

remains unknown due to lack of diagnostics, awareness among clinicians, and in histoplasmosis not being a notifiable disease. *Histoplasma* inhabits soils enriched with bird and bat excreta, high nitrogen content with a neutral PH [16]. Occupational exposures among excavators and those at construction sites resulting into disruption of soil and inhalation of large inoculum of *Histoplasma* spores have been described [17].

Despite the global report of histoplasmosis, majority of the cases are reported from North and Latin America [6, 15, 18]. In North America, the Ohio and Mississippi river valleys and the Atlantic coastal states of Florida and New York have high rates of prior sub-clinical histoplasmosis based on histoplasmin skin tests [6, 15, 18]. Histoplasmosis in South and Central America is heavily driven by the HIV pandemic, and AIDS-associated histoplasmosis remains as common as tuberculosis in this region [19–21]. Imported and autochthonous cases of histoplasmosis have been described in Europe. Likewise in Africa, microfoci of histoplasmosis exist with reported large and small outbreaks have been attributed to histoplasmosis, but most infections are sporadic and imported cases from endemic areas have also been described [15, 22]. In review of literature of recently published data, chronic cavitary histoplasmosis is described as a common entity in endemic areas and commonly misdiagnosed as smear-negative tuberculosis [23].

In HIV population, globally, about half a million people get infected with *Histoplasma* infection every year. However, approximately 100,000 people develop disseminated disease [24, 25], with mortality rates if treated ranging between 30 to 50% and 100% if not [20, 21, 26–29]. Accordingly, WHO has recognised as a killer of patients with advanced HIV and has currently recognised histoplasmosis as a neglected tropical diseases and has included *Histoplasma* antigen tests on the WHO essential diagnostic list [30].

Histoplasmosis is a major killer of HIV-infected patients in South and Central America [29, 31]. In 2012, about 6710–15, 657 cases of symptomatic HIV-associated histoplasmosis were estimated in Latin America, with areas such as Central America, the northernmost part of South America, and Argentina having a prevalence above 30% and incidence >15 cases per 100 people living with HIV, resulting to about 671–9394 deaths related to histoplasmosis, compared with 5062 deaths related to tuberculosis reported in the region [32]. In Brazil, AIDS-associated disseminated histoplasmosis had a mortality as high as 33.1% [27]. In Guatemala, 31.2% of patients with advanced HIV had histoplasmosis [33].

Excluding the Indian sub-continent, 407 cases of histoplasmosis in South East Asia have been reported [34]. Most cases (255 (63%)) were disseminated histoplasmosis and 177 (43%) cases were HIV associated [34]. A similar study was reported from Bangladesh were 22 of the 26 cases had disseminated histoplasmosis, 4 had HIV, and 9 patients were misdiagnosed for tuberculosis [35]. In a more recent study, around 1692 cases of histoplasmosis were reported from Asian countries; India (623 cases), China (611 cases), and Thailand (234 cases) [36].

Oladele and colleagues described 470 cases of histoplasmosis in Africa between 1952 and 2017 [9]. In Nigeria, 4.4% of 750 subjects from across the country tested positive for histoplasmin skin test [13]. In the East African region, a study from Northern Tanzania retrospectively identified 0.9% cases of probable histoplasmosis among febrile inpatients, ~66.7% of whom were HIV-infected and ~77.8% were clinically misdiagnosed as tuberculosis or bacterial pneumonia [37]. In Uganda, 1.3% (2/151) of HIV-infected persons with suspected meningitis were serum *Histoplasma* IgG positive [38].

3. Syndromes of histoplasmosis

3.1 Pathogenesis

Following inhalation of *Histoplasma* microconidia, it rapidly transforms from the mycelial into the yeast form [17, 39]. Innate response involves early migration of the neutrophils toward the yeast; however, they are unable to destroy it. Alveolar macrophages then engulf the fungi but can't destroy it either, but instead the yeast multiplies inside it [17, 39]. In immunocompetent individuals, T-cell-mediated immunity is activated, and the T-cells release pro-inflammatory cytokines which activate mononuclear phagocytes, hence producing tumour necrotic factor α (TNF-α) and more cytokines [17, 39]. Well-defined granulomas are formed. *H. capsulatum* may disseminate to other organs but on activation of cellular immunity, it is quickly controlled, and individuals have a quick recovery or develop latency. Therefore, most infections go unnoticed [17, 40].

However in immunosuppressed individuals or individuals exposed to large inoculum, T-cell-mediated immunity may not contain the infection, as poorly circumscribed granulomas are usually formed, and progressive dissemination may occur [5, 41]. Patients become symptomatic and may require hospitalisation for antifungal treatment and supportive care occur [5, 41]. The most common cause of disseminated progressive disease is reactivation of latent pulmonary infection [17, 40].

3.2 Clinical manifestation

Histoplasmosis has varied presentation depending on the host immune status and the inoculum size. In immunocompetent individuals exposed to a low infectious inoculum, individuals are usually asymptomatic or experience a mild flu-like respiratory illness [41]. In most cases, these cases go unnoticed unless patients are being investigated for a suspected outbreak. Among immunocomptent travellers exposed to highly infectious (large inocula) of *Histoplasma*, acute episodes of pneumonia occurring either immediately or a few weeks later have been described [42].

Individuals whose cellular immunity is compromised for number of reasons for example HIV infection, organ transplant, immunosuppressive therapy or biological therapy, i.e., anti-TNF-α drugs usually present with a disseminated form of histoplasmosis [10, 11, 43]. Disseminated histoplasmosis presents with fever, fatigue, malaise, anorexia, weight loss, and respiratory symptoms [1, 5]. Lymphadenopathy, hepato-spenomegaly, mulluscum contagiosum like skin lesions, and oral lesions are common. Shock with multi-organ failure and coagulopathy are terminal events and are commonly misdiagnosed for bacterial sepsis [1, 5].

In acute pulmonary histoplasmosis, almost all patients are asymptomatic or experience a self-limiting infection that often goes undetected. Symptoms appear in about 10% of patients, last for less than 2 weeks and are often misdiagnosed. Such patients are usually at extremes of age, having underlying co-morbidities or immunocompromised. Common symptoms suggestive of acute pulmonary histoplasmosis include non-productive cough, dyspnoea, headache, malaise, fever, chills, and chest pain that are due to mediastinal lymph node enlargement [40]. Less common symptoms include rheumatologic complaints arthralgia, arthritis, *erythema nodosum*, *erythema multiforme*, especially in females [40]. Chest radiographs typically show diffuse pneumonitis, hilar and/or mediastinal lymphadenopathy.

Chronic pulmonary histoplasmosis includes chronic cavitary pulmonary histoplasmosis and *Histoplasma* nodule (histoplasmoma) [23]. It is a progressive disease occurring over a period of months to years. Chronic pulmonary histoplasmosis

occurs in patients with structural lung diseases. Haemoptysis is common among patients with chronic pulmonary histoplasmosis, noted in up to a third of the cases. Chest radiography reveals calcified mediastinal and hilar lymph nodes of normal size along with infiltrates that evolve over time, first from focal or diffuse infiltrated to consolidations, cavitations, interstitial fibrosis, and pleural thickening, similar to patients chronic pulmonary aspergillosis and pulmonary tuberculosis [23]. Uncommon complication of pulmonary histoplasmosis includes mediastinitis, manifesting as adenitis, granulomatosis, and fibrosing [5].

Acute progressive disseminated histoplasmosis is rare except in extremes of age (less than 1 year old and more than 50 years old) and those with significant immunocompromise, for example, HIV patient with CD4 count <200 μ/l [11, 29, 32]. Acute progressive disseminated histoplasmosis may proceed after acute pulmonary histoplasmosis or re-activation of latent pulmonary lesion after a long period of latency. Patients with acute progressive disseminated histoplasmosis present with systemic (constitutional-fevers, weight loss, and weakness) and pulmonary symptoms. Focal or diffuse multi-organ is typical, with predilection for the reticuloendothelial system and the central nervous system. Physical examinations may reveal painful oropharyngeal ulceration, hepato-splenomegaly, and diffuse lymphadenopathy [5, 10, 17, 44].

4. Diagnosis

A high index of clinical suspicion is required for timely diagnosis, given the non-specific nature of presentation of histoplasmosis. A robust history, physical examination, and tailored investigation are needed simultaneously for a definitive diagnosis. Although histopathology and culture remain the gold standard for diagnosis of histoplasmosis, advancements in technology have provided *Histoplasma* antigen detection which is reliable, non-invasive, and highly sensitive [14, 41]. Misdiagnosis of acute progressive disseminated histoplasmosis has been linked to high mortality rates. Up to 42% mortality if initiation of treatment is delayed and as high as 100% if antifungal therapy is not given at all [21].

H. capsulatum can be cultured from sputum, blood, bone marrow, tissue biopsy or brochoalveolar lavage (BAL). Culture needs a period of 4–6 weeks to be appreciable as white-fluffy mould. The culture is most sensitive in patients with chronic pulmonary histoplasmosis (sputum) or progressive disseminated histoplasmosis (bone marrow) [45, 46]. Cultures have limitations such as long-turn around time, suboptimal sensitivity and require Biosafety level 3 facilities [14, 41]. Sensitivity of culture is about 70–85% [10].

Histopathology demonstrates the presence of caseating and non-caseating granulomas. Then the yeast is confirmed by special fungal stains, commonly, Gomori-methenamine silver, Giemsa or periodic acid-Schiff stains. *H. capsulatum* yeasts are about 1–4 μm in diameter, ovoid shape, predominantly intracellular (within macrophage) and giant cells with characteristic, single-celled narrow-based budding [7]. As a limitation, histopathology requires highly skilled personnel who may not be accessible across all levels of health care. Histopathology has a sensitivity of 70–80%, depending on the quality of the sample and the experience of the pathologist [10]. Because of the above limitations, we have advocated for universal access to rapid testing for histoplasmosis (antigen or PCR/molecular) [30, 47].

Histoplasma antigen detection is the most sensitive method for diagnosis. The sensitivity of the MVista® Quantitative *Histoplasma* antigen enzyme immunoassay is 95–100% in urine, over 90% in serum and bronchoalveolar lavage (BAL) antigen and 78% in cerebral spinal fluid (CSF) [10]. Sensitivity of antigen testing differs

with respect to the clinical picture. A sensitivity of 91.8% in disseminated histoplasmosis, 87.5% in chronic pulmonary histoplasmosis, and 83% in acute pulmonary histoplasmosis has been reported [45, 46, 48]. Antigen testing can be used to monitor improvement on therapy, determine prognosis of patients, and ascertain possibility of relapse especially for patients with co-infections like tuberculosis [45, 46, 48]. The limitation of antigen testing is in its cross reactivity with organisms that have the same class of cell wall galactomannan such as, *Blastomyces*, *Aspergillus*, *Talaromyces*, *Coccidioides*, and *Paracoccidioides* spp. [45, 46, 48].

Antibody detection is done by different methods. The two standard assays are complement fixation and immunodiffusion [14]. Immunodiffusion detects the presence of antigens C, H and M precipitin bands. The C antigen suggests cross reactivity between fungal species; H antigen indicates active infection; and M antigen shows acute, subacute or chronic infection. Complement fixation assay generates antibody titres. The sensitivity of antibody detection by immunodiffusion or complement fixation was between 60 and 70% [10]. Immunodiffusion assay is more specific than complement fixation assay.

Polymerase Chain Reaction (PCR) assay has been widely accepted for detection of reservoirs for *H. capsulatum* in the environment [43, 49]. Bone marrow and blood specimen have high sensitivity especially in patients with disseminated disease but less in immunocompetent [50, 51]. Respiratory biopsies and samples have shown good sensitivity [14].

5. Treatment

Acute and subcute pulmonary histoplasmosis are usually self-limiting hence do not require therapy [43]. But if symptoms persist for more than a month, then oral itraconazole is given for a period of 6–12 weeks [43]. Cases of histoplasmosis-related acute respiratory distress syndrome may benefit from adjunctive corticosteroid steroid therapy.

In chronic pulmonary histoplasmosis, patients require long-term oral treatment with itraconazole for about 12–24 months or until radiological improvement on follow-up chest imaging [43]. Relapse is common following discontinuation of antifungal treatment [43].

In acute progressive disseminated histoplasmosis, induction therapy with liposomal amphotericin B for 1–2 weeks (or 2–6 weeks for central nervous system histoplasmosis) followed by a step-down therapy with oral itraconazole for 12 months [43]. Life-long oral itraconazole therapy is advised for patients with on-going immunosuppression. Liposomal amphotericin B is associated with better outcome than any other preparations of amphotericin B [52].

6. Conclusions

Human histoplasmosis is of global distribution, with patchy areas of high endemicity. The protean manifestations of histoplasmosis require a heightened index of clinical suspicion for early diagnosis and institution of appropriate treatment. Antigen-based diagnostics are the cornerstone for microbiological confirmation of histoplasmosis, given their high sensitivity and specificity, short-turn around time and non-invasiveness. Treatment is reserved for those with moderate to severe forms of pulmonary diseases, the immunocompromised, and those with disseminated diseases. Itraconazole singly or as a follow through treatment following amphotericin B are the basis of antifungal treatment.

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References

[1] Darling ST. Histoplasmosis: A fatal infectious disease resembling kala-azar found among natives of tropical America. Archives of Internal Medicine. 1908;**II**(2):107

[2] Darling ST. The morphology of the parasite (*Histoplasma capsulatum*) and the lesions of histoplasmosis, a fatal disease of tropical America. The Journal of Experimental Medicine. 1909;**11**(4):515-531

[3] Uloko A, Maiyaki M, Nagoda M, Babashani M. Histoplasmosis: An elusive re-emerging chest infection. Nigerian Journal of Clinical Practice. 2012;**15**(2):235

[4] Godwin, RA Des Prez R. Histoplasmosis. The American Review of Respiratory Disease. 1978;**117**:929-956

[5] Wheat LJ, Azar MM, Bahr NC, Spec A, Relich RF, Hage C. Histoplasmosis. Infectious Disease Clinics of North America. 2016;**30**:207-227

[6] Bahr NC, Antinori S, Wheat LJ, Sarosi GA. Histoplasmosis infections worldwide: Thinking outside of the Ohio River valley. Current Tropical Medicine Reports. 2015;**2**(2):70-80. Available from: http://link.springer.com/10.1007/s40475-015-0044-0

[7] Guarner J, Brandt ME. Histopathologic diagnosis of fungal infections in the 21st century. Clinical Microbiology Reviews. 2011;**24**:247-280

[8] Anonymous. Protean clinical manifestations of histoplasmosis. The New England Journal of Medicine. 1966;**275**(2):110. DOI: 10.1056/NEJM196607142750214

[9] Oladele RO, Ayanlowo OO, Richardson MD, Denning DW. Histoplasmosis in Africa: An emerging or a neglected disease? PLoS Neglected Tropical Diseases. 2018;**12**(1):e0006046

[10] Myint T, Leedy N, Villacorta Cari E, Wheat LJ. HIV-associated histoplasmosis: Current perspectives. HIV/AIDS - Research and Palliative Care. 2020;**12**:113-125. Available from: https://www.dovepress.com/hiv-associated-histoplasmosis-current-perspectives-peer-reviewed-article-HIV

[11] Vergidis P, Avery RK, Wheat LJ, Dotson JL, Assi MA, Antoun SA, et al. Histoplasmosis complicating tumor necrosis factor–α blocker therapy: A retrospective analysis of 98 cases. Clinical Infectious Diseases. 2015;**61**(3):409-417. Available from: https://academic.oup.com/cid/article-lookup/doi/10.1093/cid/civ299

[12] Bezjak V. Histoplasmin tests in Ugandan sawmill workers. Tropical and Geographical Medicine. 1971;**23**(1):71-78

[13] Oladele RO, Toriello C, Ogunsola FT, Ayanlowo OO, Foden P, Fayemiwo AS, et al. Prior subclinical histoplasmosis revealed in Nigeria using histoplasmin skin testing. PLoS One. 2018;**13**(5):e0196224

[14] Buitrago MJ, Martín-Gómez MT. Timely diagnosis of histoplasmosis in non-endemic countries: A laboratory challenge. Frontiers in Microbiology. 2020;**11**(March):1-8

[15] Ashraf N, Kubat RC, Poplin V, Adenis AA, Denning DW, Wright L, et al. Re-drawing the maps for endemic mycoses. Mycopathologia. 2020:2. DOI: 10.1007/s11046-020-00431-2

[16] Richardson MD, Warnock DW. Fungal Infection: Diagnosis and Mangement. 4th ed. Oxford, UK: Blackwell Publ Ltd; 2012. p. 28

[17] Linder KA, Kauffman CA. Histoplasmosis: Epidemiology, diagnosis, and clinical manifestations. Current Fungal Infection Reports. 2019;**13**(3):120-128

[18] Edwards PQ, Palmer CE. Nationwide histoplasmin sensitivity and histoplasmal infection. Public Health Reports. 1963;**78**(3):241-260

[19] Johnson PC, Sarosi GA, Septimus EJ, Satterwhite TK. Progressive disseminated histoplasmosis in patients with the acquired immune deficiency syndrome: A report of 12 cases and a literature review. Seminars in Respiratory Infections. 1986;**1**:1-8

[20] Adenis A, Nacher M, Hanf M, Basurko C, Dufour J, Huber F, et al. Tuberculosis and histoplasmosis among human immunodeficiency virus-infected patients: A comparative study. The American Journal of Tropical Medicine and Hygiene. 2014;**90**(2):216-223

[21] Adenis A, Nacher M, Hanf M, Vantilcke V, Boukhari R, Blachet D, et al. HIV-associated histoplasmosis early mortality and incidence trends: From neglect to priority. PLoS Neglected Tropical Diseases. 2014;**8**(8):6-10

[22] Kauffman CA. Histoplasmosis. Clinics in Chest Medicine. 2009;**30**(2):217

[23] Baker J, Kosmidis C, Rozaliyani A, Wahyuningsih R, Denning DW. Chronic pulmonary Histoplasmosis—A scoping literature review. Open Forum Infectious Diseases. 2020;**7**(5). Available from: https://academic.oup.com/ofid/article/doi/10.1093/ofid/ofaa119/5816327

[24] Bongomin F, Gago S, Oladele R, Denning D. Global and multi-national prevalence of fungal diseases—Estimate precision. Journal of Fungi. 2017;**3**(4):57. Available from: http://www.mdpi.com/2309-608X/3/4/57

[25] Denning DW. Minimizing fungal disease deaths will allow the UNAIDS target of reducing annual AIDS deaths below 500 000 by 2020 to be realized. Philosophical Transactions of the Royal Society B. 2016;**371**:20150468. DOI: 10.1098/rstb.2015.0468

[26] Brown GD. Hidden killers: Human fungal infections. Science Translational Medicine. 2012;**4**:165rv13

[27] Almeida MA, Almeida-Silva F, Guimarães AJ, Almeida-Paes R, Zancopé-Oliveira RM. The occurrence of histoplasmosis in Brazil: A systematic review. International Journal of Infectious Diseases. 2019;**62**(3):261-267. Available from: http://www.ncbi.nlm.nih.gov/pubmed/31330326

[28] Nacher M, Adenis A, Adriouch L, Dufour J, Papot E, Hanf M, et al. Short report: What is AIDS in the Amazon and the Guianas? Establishing the burden of disseminated histoplasmosis. The American Journal of Tropical Medicine and Hygiene. 2011;**84**(2):239-240

[29] Nacher M, Leitao TS, Gómez BL, Couppié P, Adenis A, Damasceno L, et al. The fight against HIV-associated disseminated histoplasmosis in the Americas: Unfolding the different stories of four centers. Journal of Fungi. 2019;**5**(2). Available from: http://www.ncbi.nlm.nih.gov/pubmed/31212897

[30] Bongomin F, Kwizera R, Denning DW. Getting histoplasmosis on the map of international recommendations for patients with advanced HIV disease. Journal of Fungi. 2019;**5**(3):80. Available from: http://www.ncbi.nlm.nih.gov/pubmed/31480775

[31] Disseminated histoplasmosis in Central and South America. The invisible elephant: The lethal blind spot

of international health organizations. AIDS (London, England). 2016;**30**: 167-170

[32] Adenis AA, Valdes A, Cropet C, McCotter OZ, Derado G, Couppie P, et al. Burden of HIV-associated histoplasmosis compared with tuberculosis in Latin America: A modelling study. The Lancet Infectious Diseases. 2018;**18**(10):1150-1159. Available from: http://www.ncbi.nlm.nih.gov/pubmed/30146320

[33] Samayoa B, Aguirre L, Bonilla O, Medina N, Lau-Bonilla D, Mercado D, et al. The diagnostic laboratory hub: A new health care system reveals the incidence and mortality of tuberculosis, histoplasmosis, and cryptococcosis of PWH in Guatemala. Open Forum Infectious Diseases. 2020;7(1). Available from: https://academic.oup.com/ofid/article/doi/10.1093/ofid/ofz534/5678075

[34] Baker J, Setianingrum F, Wahyuningsih R, Denning DW. Mapping histoplasmosis in South East Asia – Implications for diagnosis in AIDS. Emerging Microbes & Infections. 2019;**8**(1):1139-1145. Available from: https://www.tandfonline.com/doi/full/10.1080/22221751.2019.1644539

[35] Rahim MA, Zaman S, Amin MR, Uddin KN, Chowdhury MAJ. Histoplasmosis: An emerging or neglected disease in Bangladesh? A systematic review. Oman Medical Journal. 2020;**35**(1):4-11

[36] Rozaliyani A, Setianingrum F. The Review of Histoplasmosis Endemicity and Current Status in Asia [Online First]. London, UK: IntechOpen; 2020. DOI: 10.5772/intechopen.92448. Available from: https://www.intechopen.com/online-first/the-review-of-hi

[37] Lofgren SM, Kirsch EJ, Maro VP, Morrissey AB, Msuya LJ, Kinabo GD, et al. Histoplasmosis among hospitalized febrile patients in northern Tanzania. Transactions of the Royal Society of Tropical Medicine and Hygiene. 2012;**106**(8):504-507

[38] Bahr NC, Sarosi GA, Meya DB, Bohjanen PR, Richer SM, Swartzentruber S, et al. Seroprevalence of histoplasmosis in Kampala, Uganda. Medical Mycology. 2016;**54**(3):295-300

[39] Peabody JW. Histoplasmosis. The New England Journal of Medicine. 1956;**255**(9):408-413. DOI: 10.1056/NEJM195608302550902

[40] Kauffman CA. Histoplasmosis: A clinical and laboratory update. Clinical Microbiology Reviews. 2007;**20**(1):115

[41] Azar MM, Hage CA. Clinical perspectives in the diagnosis and management of histoplasmosis. Clinics in Chest Medicine. 2017;**38**(3):403-415. DOI: 10.1016/j.ccm.2017.04.004

[42] Staffolani S, Buonfrate D, Angheben A, Gobbi F, Giorli G, Guerriero M, et al. Acute histoplasmosis in immunocompetent travelers: A systematic review of literature. BMC Infectious Diseases. 2018;**18**(1):673. Available from: https://bmcinfectdis.biomedcentral.com/articles/10.1186/s12879-018-3476-z

[43] 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. Clinical Infectious Diseases. 2007;**45**(7):807-825

[44] Wheat J, Myint T, Guo Y, Kemmer P, Hage C, Terry C, et al. Central nervous system histoplasmosis. Medicine. 2018;**97**(13):1-8

[45] Hage CA, Ribes JA, Wengenack NL, Baddour LM, Assi M, McKinsey DS, et al. A multicenter evaluation of tests

for diagnosis of histoplasmosis. Clinical Infectious Diseases. 2011;**53**(5):448-454

[46] Hage CA, Knox KS, Davis TE, Wheat LJ. Antigen detection in bronchoalveolar lavage fluid for diagnosis of fungal pneumonia. Current Opinion in Pulmonary Medicine. 2011;**17**(3):167-171

[47] 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 Neglected Tropical Diseases. 2018;**12**:e0006802

[48] Cáceres DH, Samayoa BE, Medina NG, Tobón AM, Guzmán BJ, Mercado D, et al. Multicenter validation of commercial antigenuria reagents to diagnose progressive disseminated histoplasmosis in people living with HIV/AIDS in two Latin American countries. The Journal of Clinical Microbiology. 2018;**56**(6):JCM.01959-17. Available from: http://jcm.asm.org/lookup/doi/10.1128/JCM.01959-17

[49] Bracca A, Tosello ME, Girardini JE, Amigot SL, Gomez C, Serra E. Molecular detection of *Histoplasma capsulatum* var. capsulatum in human clinical samples. Journal of Clinical Microbiology. 2003;**41**(4):1753-1755

[50] Dieng T, Massaly A, Sow D, Vellaissamy S, Sylla K, Tine RC, et al. Amplification of blood smear DNA to confirm disseminated histoplasmosis. Infection. 2017

[51] Gago S, Esteban C, Valero C, Zaragoza Ó, De La Bellacasa JP, Buitrago MJ. A multiplex real-time PCR assay for identification of pneumocystis jirovecii, histoplasma capsulatum,and cryptococcus neoformans/cryptococcus gattii in samples from AIDS patients with opportunistic pneumonia. The Journal of Clinical Microbiology. 2014;**52**(4):1168-1176. Available from: http://jcm.asm.org/content/52/4/1168.full.pdf+html http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed16&NEWS=N&AN=372725898

[52] Botero Aguirre JP, Restrepo Hamid AM. Amphotericin B deoxycholate versus liposomal amphotericin B: Effects on kidney function. Cochrane Database of Systematic Reviews. 2015. Available from: http://doi.wiley.com/10.1002/14651858.CD010481.pub2