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*Full Length Research Paper*

# A review of literature on unusual clinical presentations and potential challenges in diagnosis of histoplasmosis

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**Histoplasmosis is not a rare disease though its clinical diagnosis sometimes may prove a daunting task among clinicians. This study was therefore set up to review the various clinical presentations of the disease. The study was based on literature review on clinical features of histoplasmosis from original research articles, review articles, short communications, letters to editor and case reports on the disease for the past 10 years (April 2000 to April 2010). The results were analysed using simple descriptive methods and Epi Info 6 version. From 881 literature views on 7,791 patients with histoplasmosis, 75.0% (5,843) presented with pulmonary features while 25.0% (1,948) presented as disseminated histoplasmosis (DH). Some of the rare and unusual presentations of DH encountered were: mimicking of teratomas, urinary bladder ulcerations, prostatic abscess,, Addison's disease, macular degeneration and choroidal neovascularization, mimicking celiac and Crohn's diseases, gall bladder tumours, psoas abscess, carpal tunnel syndrome and advanced breast cancer as well as Hodgkin's and Non-Hodgkin's lymphomas (0.1 - 2.2%). Pyrexia of unknown origin (PUO) was significantly common among DH patients with HIV AIDS (P = 0.05). More possibilities should be accommodated and facilities deployed as much as possible while investigating patients with these features and many more by clinicians so as to skip probable diagnostic and therapeutic dilemmas occasioned by histoplasmosis. Also, HIV AIDS patients presenting with persistent fever or PUO unresponsive to available medications could be given a therapeutic trial for disseminated histoplasmosis with amphotericin B.**

**Key words:** Clinical features, histoplasmosis, unusual.

## INTRODUCTION

Histoplasmosis also called Cave disease, Darling's disease, Ohio valley disease or Reticuloendotheliosis was first described by Samuel Darling in 1906 when he isolated *Histoplasma capsulatum* from autopsy specimens of a patient who died of an 'unknown' wasting disease (Salhab et al., 2006). The actual global burden of the disease is not exactly known due to the morbid and pre-morbid factors associated with its epidemiology (Ohji et al., 2010; Gisela et al., 2004). The disease is however endemic in central and eastern USA, and parts of central, east and southern Africa, Mexico, central and south America, the far east and Australia, parts of France and Italy (Gisela et al., 2004). At least 80% of population living in areas with endemic disease are skin test positive while 10 - 25% of HIV-infected persons in these areas develop disseminated histoplasmosis (Gisela et al., 2004; Sethi, 2005; Daher et al., 2007). The disease can be diagnosed by detecting organism from sputum, blood or infected organs, detection of antigens in blood or urine by

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ELISA or PCR, or by detection of antibodies against Histoplasma in blood. Histoplasma skin test is non-definitive while culture and isolation is the gold standard for diagnosis (Lo et al., 2010; Santos et al., 2009; Knox and Hage, 2010). Treatment is usually effective with amphotericin B if diagnosis is established early and correctly.

Histoplasmosis usually presents in two main forms- pulmonary and extra-pulmonary also called disseminated histoplasmosis (DH). The common pulmonary presentations include- acute pneumonia with lung consolidation, chronic cavitatory pulmonary histoplasmosis, and with pleural effusion (Knox and Hage, 2010; Aide, 2009; Adams and Cook, 2008). Presently, clinical and laboratory diagnosis of histoplasmosis is often ridden with unusual and complex *scenarios* due to amorphous features of the disease (Salhab et al., 2006; Heninger et al., 2006). This creates avenues for probable wrong diagnosis with attendant wrong treatments and subsequent losses in man hours, human and material resources (Lai et al., 2007; Wheat et al., 2000). In South Korea for example, histoplasmosis presented with a form of lobular mastitis with features indistinguishable from that of an advanced breast cancer (Lee et al., 2006) and in Agrentia, a 13 year old immunocompetent male presented with headache, vomiting, low visual acuity and auditive deficit on the left and paresis on the right which was at long last traced to solitary cerebral histoplasmoma (Gasparello et al., 2005).

In Nigeria as in many other parts of Sub-saharan Africa and other parts of developing world, clinical laboratories are, for various factors often ill equipped (Adelusola et al., 2008; Bassey et al., 2009; Ramsey, 2004). This makes precise diagnosis of diseases with complex clinical features usually challenging (Huhn et al., 2005; Park et al., 2004; Gandi et al., 2004). This leaves clinicians with limited viable options for efficient management of these patients with probable uncertain treatment outcomes (Valle et al., 2006; Salhab et al., 2006; Croft et al., 2002). In the midst of these daunting challenges, clinical judgements still have to be made with limited facilities as much as possible and appropriate treatments given. It is in the light of these observed daunting challenges in diagnosis of histoplasmosis that a study was carried out on various clinical presentations of the disease from available literature. The findings would serve as a guide to clinicians practicing in climes where adequate skilled and experienced personnel, and laboratory facilities are lacking to establish valid clinical and laboratory diagnosis, but are however not immune against incessant encounters with 'wild' presentations of histoplasmosis in the course of their practice (Gandi et al., 2004; Rachid et al., 2003; Yang et al., 2003; Oliveira et al., 2007).

## MATERIALS AND METHODS

The study was based on systematic literature review on histoplasmosis for the past 10 years April 2000 - April 2010. Available literature on symptoms and signs associated with histoplasmosis, and clinical and laboratory diagnosis of histoplasmosis from scientific journals. Medical subjects used to perform the literature search include a search in: NCBI, EBSCO, MD Consult, Ohio Link Electronic Journal centre, Ovid Technologies Inc, Swets Information Services, COS Scholer Universe, Genetic Alliance, ISPUB, AJOL, MESH, PubMed, ELSEVIER, www.scielo.org, MMWR-CDC, MLM Catalog, and Enterez cross as well as other international scientific websites and local journals. This consists of original research articles, letters to editors, case reports and short communications. Review articles which reported only previously published works were not considered. Information obtained was on various forms of clinical presentations of histoplasmosis through clinical and laboratory diagnosis with the use of facilities such as, but not restricted to: Roentgenography, Computer Assissted Tomography, Positron Emission Tomography, Ultrasound scan, Magnetic resonance imaging, Tissue and Fine Needle aspiration biopsy, histology and cytology, Fibreoptic bronchoscopy, Specific staining procedures, Serological and Chromatographic procedures, Utilization of stoichiometric parameters, Microscopy and Culture, and Post mortem examinations. The scopes of investigations from the literatures were dependent on the available facilities at respective centres, the purpose for diagnosis and clinical picture of the patient. The total presentations of each individual clinical picture were added up into the total presentations of all the cases of histoplasmosis encountered and the respective percentages determined. Data obtained was analysed using simple descriptive methods of sum, mean and frequency, and Epi Info 6 statistical software where applicable, p values $\leq 0.05$ were considered significant.

## RESULTS

From the available literatures on histoplasmosis within the study period 7,791 patients from 881 literature reviews were encountered of which 75.0% (5,843) presented with pulmonary features while 25.0% (1,948) presented as disseminated histoplasmosis (DH). The most common pulmonary presentations of histoplasmosis encountered were pneumonia with lung consolidation 39.6% (2,311), chronic cavitatory histoplasmosis 29.6% (1,732), pleural effusion 8.2% (477), and lung mass 6.1% (354). The rarest presentations of pulmonary histoplasmosis encountered were emphysematous histoplasmosis 1.4% (81) and sarcoid granulomas in the lungs 1.1% (67) (Table 1).

Rare presentations of extrapulmonary or disseminated histoplasmosis encountered were mimicking of teratomas 0.2% (5); bladder ulcerations and tumours 0.2% (3); prostatic abscess 2.1% (41); ataxia 1.6%% (54); Addison's disease 0.3% (5); macular degeneration and choroidal neovascularization 0.9% (17); mimicking of celiac disease 0.3% (5); gall bladder tumours 0.2% (3); atrial myxomas 0.5% (9); psoas abscess 0.2 (3); carpal tunnel syndrome 0.1% (2); mediastinal fibrosis 4.2% (82); Bilateral adrenal nodules 1.4% (27), Cutaneous plaques 0.9% (17); lithoptysis 0.1% (3); and laryngeal mass 0.1% (3) (Table 1).

Other less frequent features of disseminated

**Table 1.** Clinical features (Symptoms, Signs and Laboratory Findings) associated with histoplasmosis from 7,791 patients in 881 literature reviews.

| Clinical features | Frequency | Percent (%) |
|---|---|---|
| Pulmonary histoplasmosis | 5.843 | 75.0 |
| Pulmonary nodules with lung dissemination | 189 | 3.2 |
| Sarcoid granulomas in the lung | 67 | 1.1 |
| Emphysematous histoplasmosis | 81 | 1.4 |
| Pleural effusion | 752 | 12.9 (1.2 - 22) |
| Pneumonia with lung consolidation | 2.311 | 39.6 (13-57) |
| Hilar and Mediastinal lymphadenopathy | 477 | 8.2 |
| Chronic cavitatory histoplasmosis | 1.732 | 29.6 |
| Lung mass | 354 | 6.1 |
| Disseminated histoplasmosis | 1.948 | 25.0 |
| | | |
| Thorax (n = 212) | | |
| Mediastinal fibrosis | 82 | 4.2 |
| Granulomatous mediastinitis | 72 | 3.4 |
| Breast lump | 12 | 0.6 |
| Idiopathic granulomatous mastitis with skin changes | 3 | 0.2 |
| Infectious mastitis | 2 | 0.1 |
| Anterior mediastinal masses (thyroid and thymus; parathyroid and thymic cysts mimicking neurogenic germ cell tumours) | 41 | 2.1 |
| Musculoskeletal System (n=128) | | |
| Tendonitis (Presenting as Carpal tunnel syndrome) | 2 | 0.1 |
| Septic arthritis of native and prosthetic joints | 21 | 1.1 |
| Psoas abscess | 3 | 0.2 |
| Infectious myositis | 2 | 0.1 |
| Chronic Osteomyelitis | 19 | 1.0 |
| | | |
| Cardiovascular System (62) | | |
| Myocarditis | 21 | 1.1 |
| Pericarditis | 17 | 0.9 |
| Endocarditis (native and prosthetic valves) | 33 | 1.7 |
| Atrial myxomas | 9 | 0.5 |
| Skin and Connective Tissue (n= 156) | | |
| Mucous membrane ulcerations | 26 | 1.3 |
| Cutaneous plaques | 17 | 0.9 |
| Skin ulcerations | 31 | 1.6 |
| Subareolar infiltration | 5 | 0.3 |
| Diffuse macrophage | 3 | 0.2 |
| Granulomatous Inflammation | 47 | 2.4 |
| Vasculitic with Leucocytoclastic histoplasmosis | 23 | 1.2 |
| Scarce inflammatory reaction | 7 | 0.4 |
| | | |
| Gastrointestinal system and abdomen (578) | | |
| Gall bladder tumours | 3 | 0.2 |
| Duodenitis | 21 | 1.1 |
| Bilateral adrenal nodules | 27 | 1.4 |
| Splenomegaly | 288 | 14.8 (2 - 36) |
| Hepatomegaly | 89 | 4.6 (1 - 17) |
| Hepatosplenomegaly | 173 | 8.9 (4 - 15) |
| Ileocaecal ulcers mimicking Crohn's disease | 9 | 0.5 |
| Coeliac disease | 5 | 0.3 |

**Table 1.** Contd.

| | | |
|---|---|---|
| Ophthalmic features (128) | | |
| Scleritis | 63 | 3.2 (0.3 - 6) |
| Keratitis | 41 | 2.1 |
| Macular degeneration and choroidal neovascularization | 17 | 0.9 |
| Ocular histoplasmosis syndrome | 5 | 0.3 |
| Metabolic Changes (49) | | |
| Hypercalcaemia | 44 | 2.3 |
| Addison's disease | 5 | 0.3 |
| Central Nervous System (n=418) | | |
| Chronic Meningitis | 53 | 2.7 |
| Acute Meningitis | 35 | 1.8 (0.2 - 7) |
| Focal brain abscess | 41 | 2.1 (0.08 - 6) |
| Cranial nerve palsies | 7 | 0.4 |
| Pyrexia of Unknown Origin | 282 | 14.5 (1 - 27) |
| Genitourinary features (n = 217) | | |
| Pelvic Inflammatory disease | 33 | 1.7 |
| Testicular abscess | 3 | 0.2 |
| Prostatic abscess | 41 | 2.1 |
| Epididymitis | 32 | 1.6 |
| Acute renal failure | 54 | 2.8 |
| Penile lesions | 11 | 0.6 |
| Bladder ulcerations and tumours | 43 | 2.2 |
| Signs and symptoms (n = 3. 455) | | |
| Haemoptysis | 312 | 9.0 |
| Cough | 877 | 25.4 |
| Shortness of breath | 441 | 11.9 |
| Lithoptysis | 3 | 0.1 |
| Diarrhoea | 66 | 1.9 |
| Ataxia | 54 | 1.6 |
| Weight loss | 1.221 | 35.4 |
| Changes in mental status | 178 | 5.2 |
| Night sweats | 218 | 6.3 |
| Fever | 667 | 19.3 |
| Sore throat | 3 | 0.1 |
| Laryngeal mass | 3 | 0.1 |
| Headache | 577 | 16.7 |
| Generalised peripheral lymphadenopathy | 61 | 1.8 |
| Anorexia | 57 | 1.6 |
| Weakness | 382 | 11.1 |
| Mimicking Teratomas | 5 | 0.2 |
| Laboratory features (n = 2.449) | | |
| Thrombocytopaenia | 662 | 27.0 |
| Elevated Lactate Dehydrogenase (LDH)** | 457 | 18.7 (97 - 100) |
| Pancytopaenia | 507 | 20.7 |
| Leucopenia | 579 | 23.6 |
| Anaemia | 1.229 | 50.2 |

Different features or parameters occurring in same person or groups of individuals were considered separately. Ranges were quoted only where were properly reported and were usually findings from immunosuppressed individuals. **98% of those with PUO, HIV AIDS had elevated LDH.

histoplasmosis encountered were: Pyrexia of unknown origin (PUO), 14.5% (282), idiopathic granulomatous mastitis with skin changes 0.2% (3); breast lump 0.6% (12); acute renal failure 2.8% (54); granulomatous mediastinitis 3.4% (72); anterior mediastinal masses 2.1% (41); and endocarditis 1.7% (33) (Table 1).

The common clinical symptoms among the patients with both pulmonary and extrapulmonary histoplasmosis were fever 19.3% (667), cough 25.4% (877), shortness of breath 11.9% (441), headache 16.7% (577); haemoptysis 9.0% (312); and night sweats 6.3% (218). The common Laboratory findings encountered were thrombocytopaenia 27.0% (662), pancytopaenia 20.7% (507), leucopaenia 23.6% (579), and anaemia 50.2% (1,229) (Table 1).

A review of immune status of patients presenting with histoplasmosis showed that there was significant association of both pulmonary and extrapulmonary histoplasmosis with immunosupression; 83.1 and 91.6% of the 4,377 and 1,948, respectively, with pulmonary and disseminated histoplasmosis were immunosuppressed ($p < 0.0001$); there was however no significant difference in the degree of association between the two ($p > 0.05$) (Figure 1).

Analysis of patients with pyrexia of unknown origin (PUO) with disseminated histoplasmosis showed that 89.1% (251) were immunosuppressed while 10.4% (31) were immunocompetent ($p < 0.0001$); 98% (246) of the immunosuppressed individuals were HIV positive while 98% (241/246) of these had elevated serum Lactate dehydrogenase (LDH) levels (Figure 2).

## DISCUSSION

The most common pulmonary presentations of histoplasmosis encountered were pneumonia with lung consolidation 39.6%, chronic cavitatory histoplasmosis 29.6%, pleural effusion 8.2%, and lung mass 6.1%. The rarest presentations of pulmonary histoplasmosis encountered were emphysematous histoplasmosis 1.4% and sarcoid granulomas in the lungs 1.1%. On the other hand, the rare presentations of extrapulmonary or disseminated histoplasmosis encountered were mimicking of teratomas 0.2%; bladder ulcerations and tumours 0.2%; prostatic abscess 2.1%; ataxia 1.6%%; Addison's disease 0.3%; macular degeneration and choroidal neovascularization 0.9%; mimicking of celiac disease 0.3%; gall bladder tumours 0.2%; atrial myxomas 0.5%; psoas abscess 0.2; carpal tunnel syndrome 0.1%; mediastinal fibrosis 4.2%; Bilateral adrenal nodules 1.4%, Cutaneous plaques 0.9%; lithoptysis 0.1%; and laryngeal mass 0.1%. Immmunosupression was a common underlining factor for both forms of the disease ($p < 0.05$), while pyrexia of unknown origin (PUO) was significantly most common among those with underlining HIV AIDS disease compared to the immunocompetent hosts ($p < 0.05$).

The association of fever, headache, loss of appetite and weakness with histoplasmosis makes it clinical diagnosis difficult especially in sub-saharan Africa where malaria, typhoid and paratyphoid fevers, and tuberculosis are still at the epidemic levels and often present with similar but varying clinical pictures (Jombo et al., 2007; Jombo et al., 2008; Jombo et al., 2010). Furthermore, with the pre-sently high prevalence of HIV AIDS and the associated increase in infectious diseases burden including that of histoplasmosis, the disease is still often regarded as a remote possibility among clinicians when confronted with cases of high possibility index (Heninger et al., 2006; Goel et al., 2007; Gutierrez et al., 2008). Lack of adequate facilities as well as experienced personnel may delay or make accurate diagnosis of the disease impossi-ble obviously with dire consequences (Salhab et al., 2006; Lai et al., 2007). Prompt and accurate diagnosis of histoplasmosis from the available literatures still appears to be a global medical challenge. In South Korea, a form of idiopathic granulomatous lobular mastitis with skin changes and subareolar infiltration was found to have several features indistinguishable from that of advanced breast cancer on computed tomography (CT), magnetic resonance imaging (MRI) mamographies and ultra-sonography (US) which was only confirmed by culture, histology and cytology (Salhab et al., 2006). In Taiwan, the disease was found to present as Addison's disease (Tseng et al., 2005); in USA histoplasmosis presented with anterior mediastinal masses indistinguishable from Hodgkins and Non-Hodgkins lymphomas and other secondary metastasis (Quint, 2007), and in Panama, progressive disseminated histoplasmosis was found to be a common occurrence among AIDS patients (Gutierrez et al., 2008).

In another study in Seoul, South Korea, ileocecal ulcers similar to those of tuberculosis were encountered with no significant improvement after commencement of anti-tuberculosis treatment (Park et al., 2008), and in British Colombia, Crohn's and sprue-like intestinal diseases were encountered with difficulties in associating histoplasmosis with (Freeman, 2008). The ocular manifestations observed in England (SSTRG, 2004), the atrial masses in Virginia (Schietinger et al., 2008), duodenitis in Toronto, Canada (Serra and Jani, 2006) and its mimicry of cholangiocarcinoma in Turkey (Ustundag and Bayraktar, 2008) all tasked the diagnostic efficiency and professional competence exhibited at the respective centres.

Wrong diagnosis would have led to avoidable and unnecessary amputations or radical surgeries with the attendant sequelae instead of a simple administration of amphotericin B with usually quick clinical response. Some of the difficulties associated with prompt diagnosis of disseminated histoplasmosis from patients in several parts of Latin America were due to the presentations of the disease in form of pyrexia of unknown origin (PUO) with no obvious pulmonary features and was very rampant in patients with HIV AIDS (De Francesco et al., 2006; Ribeiro et al., 2009; Wheat et al., 2000). In the state of

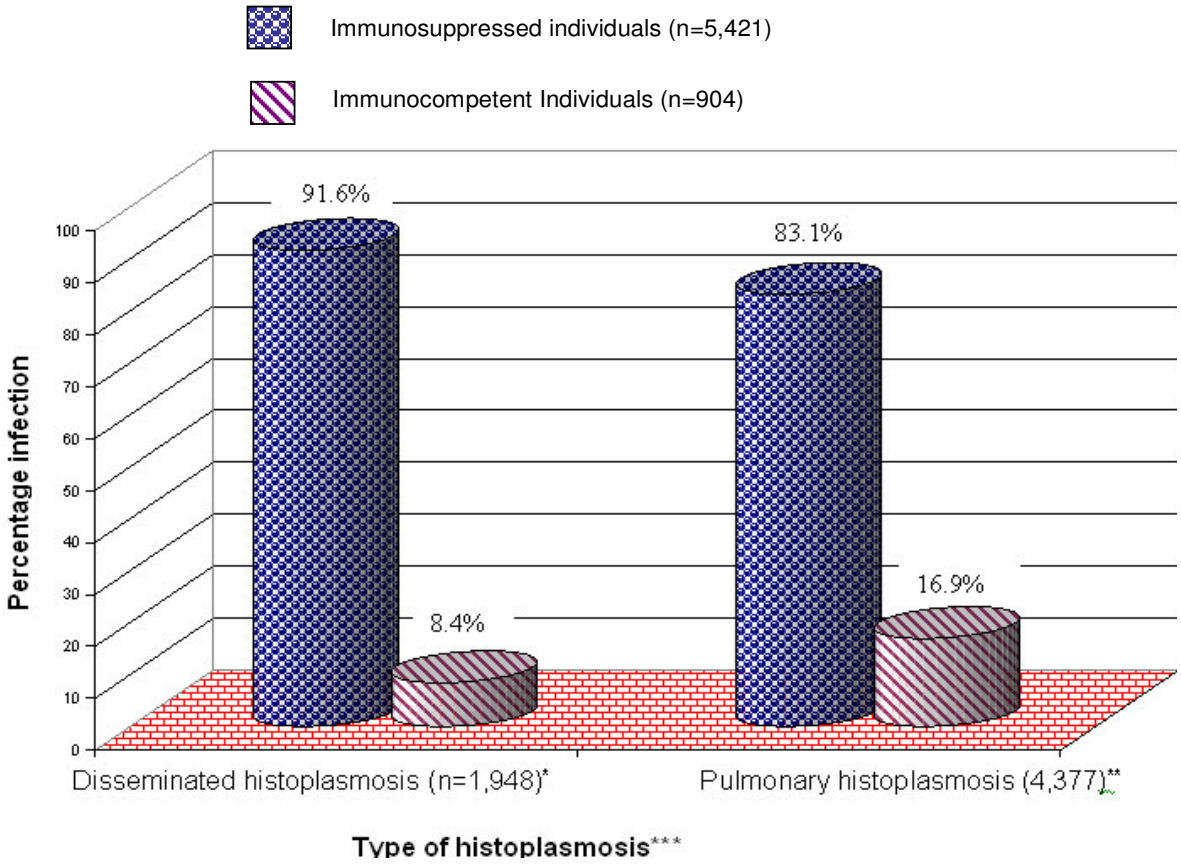


**Figure 1.** Association of pulmonary and extra-pulmonary or disseminated histoplasmosis with immunosupression. *$X^2$ (Mantel-Haenszel) = 48.28, OR = 10.11, RR=5.77, $p < 0.0001$. **$X^2$ (Mantel-Haenszel) = 30.42, OR = 4.88, RR=3.12, $p < 0.0001$. ***$X^2$ (Mantel-Haenszel) = 0.2, OR = 1.10, RR=1.05, $p = 0.66$

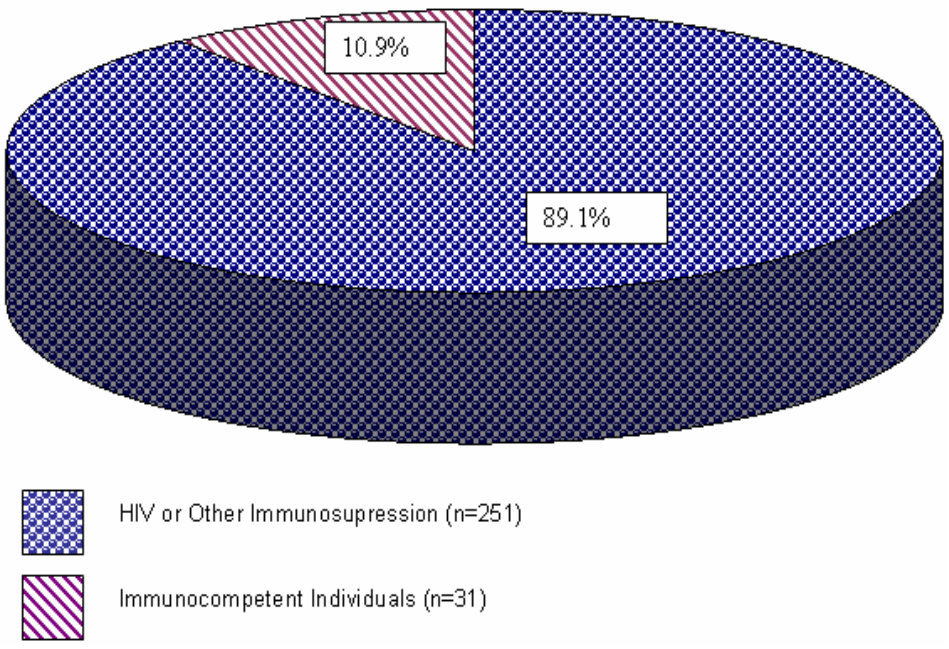


**Figure 2.** Association of pyrexia of unknown origin (PUO) in immunocompromised hosts with histoplasmosis (n = 282). $X^2$ (Mantel-Haenszel) = 43.36, OR = 8.09, RR = 4.75, $p < 0.0001$.

Ceara, over 97% of patients presenting with PUO and HIV AIDS had DH (Pontes et al., 2010), also among the 12 cases of HIV AIDS with PUO in Espirito Santo state, over 89% had DH while all of them (100%) had ele-vated levels of lactate dehydrogenase (LDH) (Schineider et al., 2006), and also in Sao Paulo, over 92% of the HIV AIDS patients with PUO had DH (Borges et al., 2010).

Similar findings on HIV AIDS patients presenting with PUO were documented in Argentina (Carbo et al., 2008). This was compounded in instances where immune-competent hosts with disseminated histoplasmosis also occasionally presented with PUO with no other significant clinical features (Rokatoarivelo et al., 2010; Ohno et al., 2010; Cairoli et al., 2010). While investigating HIV AIDS patients with PUO with minimal success at arriving the cause of the persistent fever, extending the horizon of investigations to cover histoplasmosis could just be what may be needed to salvage the life of a patient (Hanf et al., 2010; Parikh et al., 2009; Fischer et al., 2009).

## Recommendations

In view of the diverse challenges thrown up by histo-plasmosis as well as may by other emerging infections, hospitals and clinics in Sub-saharan Africa and other parts of the developing world should be equipped with adequate diagnostic facilities to enable them carry out adequate, elaborate and exhaustive clinical diagnosis. Facilities such as CT scan, MRI, US, Enzyme Immuno-assey (EIA), PCR, RFLP, Specific and general stains for Microbiology and histology, 18-Fluoro-Deoxyglucose uptake and Positron emission Tomography should be provided to rule out malignancies with precision and ease the diagnostic dilemma of histoplasmosis. A percentage of the multi-billion- dollar 'global fund' earmarked to fight malaria, tuberculosis and HIV AIDS in Africa could be devoted to remedy this challenge while soliciting the co-operation of member nations to design health policies towards attaining same goal as a long time measure. Clinicians practicing in sub-saharan Africa and other parts of the world where hospitals and clinics may be ill equipped, histoplasmosis should not be considered a distant possibility when making preferential diagnosis on patients with these unique features.

In HIV AIDS patients presenting with PUO and with ele-vated serum levels of LDH, where there are challenges arriving at the cause of the persistent fever, disseminated histoplasmosis should be seriously given a thought. Therapeutic trial with amphotericin B should therefore be initiated especially where appropriate facilities for laboratory diagnosis may be lacking or in short supply. And finally, in the present era of information technology, both expertise and diagnostic knowledge should be shared among centres across the globe on per second basis through appropriate collaboration with the less equipped centres so as to aid quick and prompt diagnosis of diseases with complex clinical presentations.

## Conclusion

In the 21st century, histoplasmosis, due to its unique and often complex clinical presentations is still a disease that clinicians should familiarize themselves with. In climes where facilities may be lacking to establish a definitive diagnosis, a thought of it may just be what is needed to avoid a diagnostic and hence therapeutic logjam.

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