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TROPICAL MYCOSIS (D BOULWARE, SECTION EDITOR)

Histoplasmosis Infections Worldwide: Thinking Outside of the Ohio River Valley

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Abstract In the USA, histoplasmosis is generally thought to occur mainly in the Ohio and Mississippi river valleys, and the classic map of histoplasmosis distribution reflecting this is second nature to many US physicians. With the advent of the HIV pandemic, reports of patients with progressive disseminated histoplasmosis and AIDS came from regions of known endemicity, as well as from regions not thought to be endemic for histoplasmosis throughout the world. In addition, our expanding armamentarium of immunosuppressive medications and biologics has increased the diagnosis of histoplasmosis worldwide. While our knowledge of areas in which histoplasmosis is endemic has improved, it is still incomplete. Our contention is that physicians should consider *histoplasmosis* with the right constellations of symptoms in any febrile patient with immune suppression, regardless of geographic location or travel history.

Keywords Histoplasmosis · Progressive disseminated histoplasmosis · Pulmonary fungal infections · Human immunodeficiency virus · Acquired immunodeficiency syndrome · Immunosuppression · Infectious diseases, emerging, travelers · Biologic drugs · *Histoplasma capsulatum* var. *capsulatum* · *H. capsulatum* var. *duboisii*

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Introduction

Histoplasmosis, in the USA, is primarily seen in the Ohio and Mississippi river valleys [1]. The narrative regarding histoplasmosis is supported by solid epidemiologic evidence. By the midtwentieth century, a geographic clustering of patients with histoplasmosis was noted [2], and mapping of reactive histoplasmin skin tests was employed in patients with pulmonary calcifications on chest radiographs who did not react to tuberculin skin testing [3]. Edwards and colleagues constructed the now quite-familiar map of histoplasmin skin reactivity among naval recruits [4].

While the central USA seemed to have the greatest prevalence of *Histoplasma capsulatum* var. *capsulatum*, Brazil [5], Argentina [6], India [7], and South Africa [8] have all reported small case series, and *Histoplasma capsulatum* var. *duboisii* was thought to exist predominantly in West Africa. Additionally, sporadic cases have been reported from Central and South America, Oceania, northern sub-Saharan Africa, and Europe [6]. Histoplasmin skin-test sensitivity analyses showed fairly high levels throughout Central America and

parts of South America as well as Puerto Rico, Dominica, and Mexico in addition to the central USA with almost no skin-test sensitivity in Europe, and scant information available from the rest of the world [6]. These skin-test surveys appeared to support the idea that histoplasmosis exposure was infrequent in the rest of the world.

Over a number of years over which the authors have gained experience at multiple centers around the USA and Italy, it is extremely common for trainees at all stages to make assumptions about whether a diagnosis is even possible based on the geographical location alone. This review will focus on the truly global nature of histoplasmosis while acknowledging that the infection is certainly more common in certain areas and that our current knowledge of endemicity is incomplete.

Pathogenesis and Immunity

The portal of entry for *H. capsulatum* is the lung, and following inhalation, an area of pneumonitis develops. Neutrophils are unable to destroy the organism, although macrophages can ingest but cannot destroy the fungus [9]. Initially, during the pre-immune phase, the fungus disseminates widely throughout the body [9]. Once T cell-mediated immunity develops, the entire process is arrested and recovery occurs [9]—this allows for most infections to go unnoticed in persons without immune deficits. Primary infection by *H. capsulatum* is predominantly asymptomatic [9]; however, in patients exposed to a large infecting inoculum, symptomatic pulmonary infection is more common, and many patients require hospitalization [10].

The degree to which infection is often subclinical is illustrated well by a 1964 outbreak in Mason City, Iowa. Of the estimated 6000 predominantly asymptomatic infections, only 1 person developed progressive disseminated histoplasmosis and 87 persons developed acute pulmonary histoplasmosis [11]. This attack rate in the context of the estimated number of subclinical infections was possible because an outbreak 2 years prior allowed for serial skin testing.

In patients with faulty T cell-mediated immunity, this localized containment does not occur and progressive dissemination may take place, leading to clinical illness [9]. Faulty T cell-mediated immunity may be innate (e.g., Job syndrome, severe combined immunodeficiency syndrome, etc.), caused by immunosuppressive medications or may be caused by immunodeficiency states related to other diseases such as malignancy or HIV infection [9]. Inadequate T cell function allows progressive disseminated histoplasmosis due to reactivation of previous infection among patients with new immune compromise and has been particularly noted among immigrants from Latin America and sub-Saharan Africa in nonendemic geographic locales in Europe [12, 13]. Further evidence of the importance of T cell function in controlling *Histoplasma* infection was provided in a recent retrospective analysis of ~1400 HIV-infected persons in French Guiana in which the authors found a hazard ratio for the development of progressive disseminated histoplasmosis of 47.2 in patients with CD4 T lymphocyte counts of 0–50 cells/μL, as compared to >500 cells/μL, with an inverse relationship continuing between CD4 count and hazard ratio at higher CD4 counts [14•]. Table 1 reviews the more typical clinical manifestations of *H. capsulatum* infection as well as associated risk factors. Treatment varies by infection type [1–13, 14•, 15–18].

Global Histoplasmosis and the Advent of AIDS

In 1983, several patients who had been diagnosed with AIDS and progressive disseminated histoplasmosis were reported [19–23]. While one report came from a known hyperendemic area for histoplasmosis in Indiana [22], other reports came from areas in the USA (Texas, Michigan) where histoplasmosis was less common [19, 21] or had not been thought to be present (New York, Colorado) [20, 23]. These reports rapidly increased across the USA in endemic and non-endemic areas alike [24, 25]. In addition, patients from around the world were reported from areas where histoplasmosis had been rarely or never reported such as Trinidad [26], Thailand [27], and the Democratic Republic of Congo [28]. By 1990, Wheat and colleagues noted >100 cases of histoplasmosis in persons with AIDS [29], and although many came from Indiana, a sizeable minority were from areas outside of traditional endemic zones. Most of the reported symptomatic cases were patients with progressive disseminated histoplasmosis [29], as opposed to isolated pulmonary infections as had been the most common presentation in HIV-uninfected patients (when the infection did indeed lead to symptomatic clinical illness). In the decades since, numerous case series of progressive disseminated histoplasmosis associated with HIV infection have been reported around the globe in locations with few, if any, previously reported cases [30].

The widespread reporting of patients with progressive disseminated histoplasmosis since the advent of AIDS helped to identify previously unrecognized endemic areas where a great number of subclinical infections must have occurred but were not previously recognized. Similarly, for known outbreaks of histoplasmosis (including those reported in persons with AIDS), likely many more, subclinical, infections occur.

Ideally, antiretroviral therapy (ART) is started before immunocompromised occurs in HIV-infected persons and reverses the immune defect, reducing the likelihood of development of histoplasmosis. The idea of prevention is supported by a 2001 case-control study in which patients were matched for CD4 count among other factors—patients on ART had less risk all for developing disseminated histoplasmosis, even at low CD4 counts [31]. Interestingly, there have been reports of

Table 1 Major clinical manifestations of histoplasmosis and associated risk factors

Manifestation	Risk factors
Acute pulmonary histoplasmosis	Young age, exposure to a large inoculum of *Histoplasma*
Chronic pulmonary histoplasmosis	Older age, chronic obstructive lung disease related to tobacco use
Mediastinal lymphadenitis, granuloma, fibrosis	Young age undefined inflammatory or immunologic factors in mediastinal fibrosis
Pericarditis or rheumatologic syndrome	Young age, immunocompetence, male sex, and African American race in pericarditis and female sex in rheumatologic syndromes
Progressive disseminated histoplasmosis	An immunocompromising condition or medication, primary or acquired immunodeficiency, age <1 or >55 years

The table above notes major categories of histoplasmosis and risk factors associated with the development of this type of disease related to histoplasmosis

otherwise untreated histoplasmosis in persons with AIDS improving with ART alone [32]. In many high-income countries, guidelines recommend that all HIV-infected persons are started on ART regardless of CD4 count [33], and so, advanced immune suppression related to HIV infection and opportunistic infections such as histoplasmosis is less frequent in these countries. However, in many parts of the world, ART access is still not adequate and more cases of disseminated histoplasmosis are likely.

While AIDS illuminated many areas of hidden histoplasmosis endemicity, cases in areas not previously known to be endemic are still being reported and our knowledge regarding the distribution of histoplasmosis is expanding. With the incomplete nature of our understanding in mind, the reminder of the review will focus on the worldwide distribution of histoplasmosis and factors that might influence our understanding of histoplasmosis distribution in the future as HIV has done in the past and continues to do.

Global Distribution of Histoplasmosis

Our present knowledge of the worldwide distribution of *Histoplasma capsulatum* var. *capsulatum* relies most on the histoplasmin skin-test surveys with additional information coming from soil isolation of the fungus. Many of the pertinent studies were conducted in the 1950s–1970s [6, 34, 35]. Notably, a summary of skin-test studies by Mochi and Edwards in 1952 [6] highlighted that the "highest prevalence of histoplasmin sensitivity is found in east-central part of the USA, in southern Mexico, Central America and certain parts of South America. An isolated, low sensitivity area has been reported from South Africa [6], and almost no histoplasmin sensitivity has been found in Europe, with the possible exception of Italy" [6]. Much of Asia and nearby nations was excluded from their "preliminary attempt" to map the geographical distribution of histoplasmosis due to the lack of any data from these areas [6].

A review regarding soil isolation of *H. capsulatum* written in 1964 by Libero Ajello, added that in addition to well-known endemic areas such as North America (USA, Mexico), Central America (Panama), and South America (Brazil, French Guiana, Perù, and Venezuela), a few countries in Africa (Congo, Tanzania, and South Africa's Guateng and Limpopo provinces), Asia (Malaysia), and the Caribbean (Trinidad) [36] also housed *H. capsulatum* within their borders.

It is worth noting that, until now, the geopolitical isolation of several countries as well as the lack of microbiological facilities in many low-income areas of the world might have contributed to the difficulty in constructing an accurate map of worldwide histoplasmosis distribution. Table 2 shows studies from outside the USA [37–59], while Fig. 1 shows a world map constructed with estimated areas endemic to histoplasmosis based on case reports primarily among HIV-infected patients.

An important example of a country in which the increasing rate of infections has been recognized in recent years is China. A 2013 review found that from 1990 to 2011, 300 cases were reported in China of which 75 % occurred along the Yangtze river [60••]. Progressive disseminated histoplasmosis occurred in 257 of the 300 cases and immune suppression, HIV in most cases, was present in most patients [60••]. Studies from China report the prevalence of histoplasmin skin-test reactivity ranging from 6 to 50 % [37, 53, 54]. Interestingly, the distribution of *H. capsulatum* overlaps that of *Penicillium marneffei* [61] in several areas of China.

The occurrence of histoplasmosis in Asia has not been fully appreciated until recent years despite the fact that in 1970, Randhawa reviewed 30 autochthonous cases from India, Malaysia, Indonesia, Singapore, Thailand, Vietnam, and Japan [54]. *Histoplasma* has been isolated from the soil from these countries [62, 63]. Histoplasmin sensitivity was negligible in Japan, except in people working with soil and sand imported from overseas (including the USA) [54], and *H. capsulatum* has never been isolated from the environment nor detected by PCR in bat guano from Japan [64].

Table 2 Areas of endemicity for *Histoplasma capsulatum* outside United States of America (USA) according to histoplasmin skin reactivity

Country/year/reference	Number tested/population	Histoplasmin skin-test positivity (%)
Asia		
China	101	8.9
Hunan province 2001 [35]	292/healthy and pulmonary diseases	16.8
Nanjing district 2001	271 healthy students	6–35
Sichuan province 1996 [34]	28 TB patients	
India 1955 [33]	962/NR	1.9
India (Delhi) 1962	8062/NR	6.8
India (Delhi riverine) 1960	162/NR	12.3
India (Calcutta) 1954	64/NR	4.7
India (Calcutta) 1956	4855/NR	0.7
Malaysia (Kuala Lumpur) 1964 [33]	227/chest disease patients	10.5
Myanmar (Rangoon)1952 [33]	1089/NR	27.1
Myanmar (upper region) 1952	142/NR	8.4
Myanmar (Maguee) 1956	154/NR	86.4
Philippines (Manila) 1950–1964 [33]	3878/navy recruits, TB patients,	4.1–6.4
Philippines (Luzon island) 2000 [36]	Medical and nurse students 143/healthy electric company employees	26
Taiwan (Nantou) 1956 [33]	444	49.8
Thailand (Bangkok) 1967 [33]	497/medical and nurse students	5.6
Thailand 1961	329/student nurses	4.0
Thailand (northern region) 1987	NR/NR	7–14
Thailand (central region) 1987	NR/NR	3–9
Thailand (southern region) 1987 [37]	NR/NR	15–36
Vietnam (Saigon) 1960 [33]	303/NR	33.7
Central and South America		
Argentina (Chaco province) 1996	315/children	9.2
Brazil (Minas Gerais state) 1996 [38]	417/miners	17.5
Brazil (Rio Grande Do Sul) 1996 [39]	354/soldiers (17–19 years)	48–89
Brazil (Ceara State) 1992 [40]	138/residents	61.5
Brazil (Amazonas state) 1978 [41]	495/residents	37.8
Colombia (Department of Antioquia) 1971 [42]	NR/national survey	10
Mexico (Guerrero state) 1997 [43]	139/cave guides, peasants	36.4–88.6
Mexico (Guerrero, Queretaro, Tlaxcala state) 1994 [44]	253/NR	2 (Tlaxcala), 83 (Guerrero), 53 (Queretaro)
Venezuela (Bolivar state) 2005 [45]	182/residents	34
Venezuela (Bolivar state) 2004 [46]	157/farmers	42.7
Caribbean	392/poultry farmers	28.8
Cuba (Ciego de Avila)1992 [47]	NR	4
Barbados 1981 [48]	NR	42
Trinidad 1981	454/residents	7 Martinique, 4 Guadeloupe
Martinique and Guadeloupe 1972 [49]		
Africa		
Nigeria 1991 [50]	1087-226/healthy-hospital patients	3.5 (*Hcc*), 3.0 (*Hcd*) healthy
Nigeria (Anambra state) 1996 [51]	40/cave guides, traders, farmers 620/farmers, palm oil workers	8.85 (*Hcc*), 6.6 (*Hcd*) hospital patients 35 (*Hcd*), 8.8 (*Hcd*)
Somalia (Mogadishu and Jilib) 1979 [52]	1014/NR	0.3
Uganda (Gulu, Jinja, Amudat, Fort Portal and Kasese, Kampala, Pakwach) 1970 [53]	1144/residents	0.4–12 %

Hcc Histoplasma capsulatum var. *capsulatum*, *Hcd Histoplasma capsulatum* var. *duboisii*, *NR* not reported

In Thailand, the AIDS epidemic has been responsible of a dramatic upsurge of disseminated histoplasmosis with more than 1200 cases reported to the Ministry of Public Health from 1984 to 2010 [65]. A survey of histoplasmin sensitivity conducted in this country between 1966 and 1968 showed positivity rates of 7–14 % in the northern region and 15–36 % in

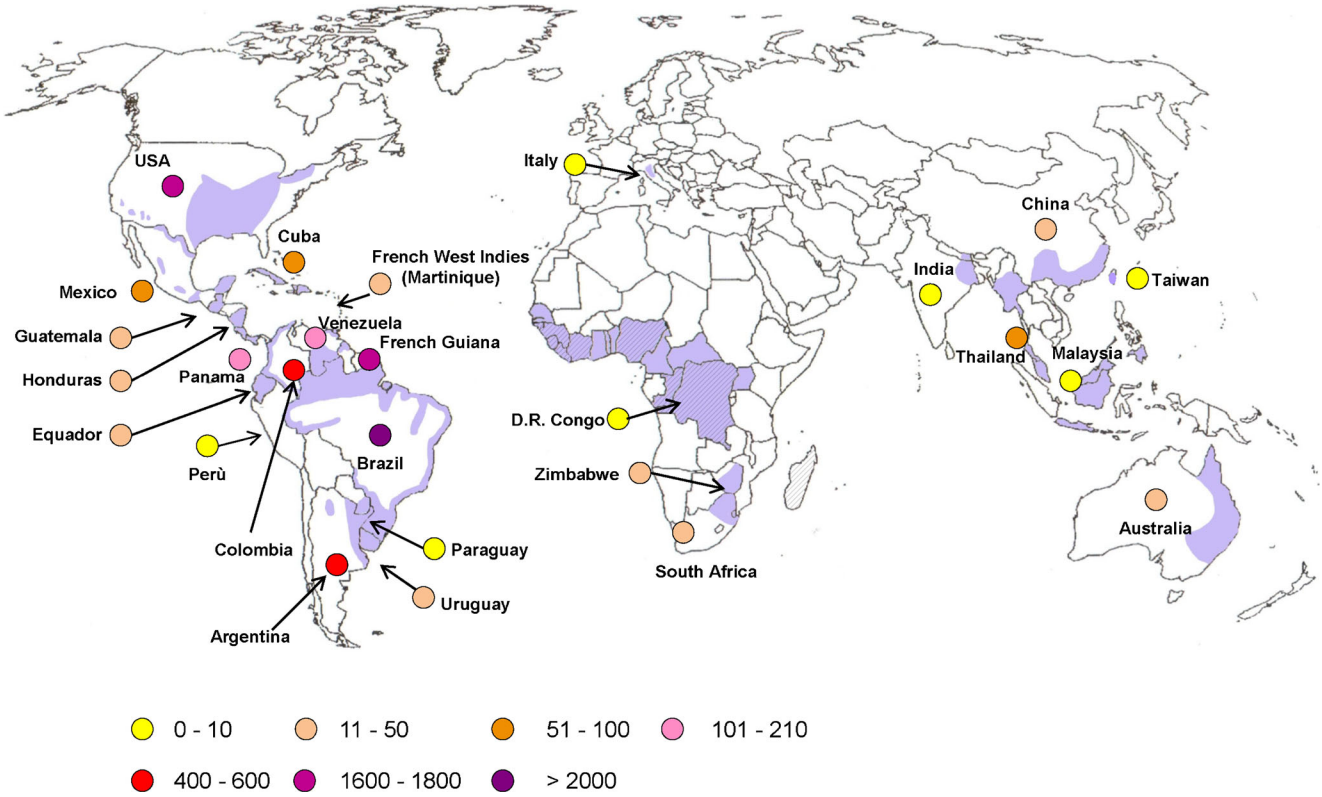

Fig. 1 Geographic distribution of *Histoplasma capsulatum* var. *capsulatum* (*purple*) and *H. capsulatum* var. *duboisii* (*shadow area*). The *circles* indicate the number of published cases of autochthonous AIDS-associated histoplasmosis (via Scopus query). The majority of African cases have been observed outside Africa

the southeast and southern regions [39], overlapping with areas containing *Penicillium marneffei* as determined by PCR [65].

Malaysia was the first country in Asia where *H. capsulatum* was successfully isolated from soil samples collected from bat-infested caves near Kuala Lumpur [66], and a survey of histoplasmin skin test sensitivity showed a prevalence of 10.5 % in that country [54]. Cases of histoplasmosis have been recognized both among HIV-positive and HIV-negative patients as well as among subjects traveling to Malaysia [67, 68].

In India, histoplasmin sensitivity has been reported to be relatively high in Calcutta and Delhi (4.7–12.3 %) [54] with most cases occurring in northeastern India in West Bengal and Assam states. Fungal isolation from soil has also occurred. An increasing number of cases of progressive disseminated histoplasmosis have been recognized in recent years in India among HIV-positive and/or diabetic patients, and some have suggested that histoplasmosis might be under-recognized due to being mistaken for tuberculosis [69]. In Australia, *H. capsulatum* has been cultured from different environmental sources (e.g., fowl yards and caves) in the states of Queensland and New South Wales. A recent review reported on 63 autochthonous cases from 1948 to 2009, including 11 with AIDS [70].

In South and Central America, large numbers of patients, many in persons infected with HIV, have been reported in Brazil, French Guiana, Argentina, Colombia, Venezuela, and Panama (Fig. 1) [14•, 71–74]. Importantly, a recently published map of histoplasmosis endemic areas in the region did not include French Guiana [75]. This would seem to have been an oversight as progressive disseminated histoplasmosis is the most common cause of AIDS-defining illness in that country with one retrospective study finding that ~41 % of HIV-positive hospitalized patients with fever and a CD4+ count <200 cells/μL had disseminated histoplasmosis [14•, 71, 72, 76••]. Similarly, more than 70 % of patients with histoplasmosis included in a survey conducted in Colombia from 1992 to 2008 had HIV/AIDS [77]. Argentina has an area of endemicity for histoplasmosis in the northeastern part of the country [78].

In Brazil, histoplasmosis is highly endemic especially in the northern (Amazona, Roraima, Parà, Amapà, Cearà, Rio Grande do Norte, Bahia) and midwestern (Minas Gerais, Sao Paulo) states as well as the southeastern portions of the country. Histoplasmin positivity may be up to ~90 % in some areas (although positivity varies widely by study, Table 2) [36, 42, 44–46]. Moreover, a recent study from 1996 to 2006 showed 4.73 per 1000 deaths associated with AIDS that were due to histoplasmosis [79].

A study conducted in metropolitan Caracas, Venezuela, from 2000 to 2005 reported that AIDS was the risk factor in

33.5 % of the 158 patients with histoplasmosis [73]. Histoplasmosis seems to be present in much of the region (Fig. 1) with HIV playing a crucial role in symptomatic infections.

The distribution of histoplasmosis in Africa is probably the most puzzling due to the lack of solid epidemiologic studies coupled with the limited laboratory capacity available in much of the continent [52, 58, 59, 80, 81]. Complicating matters, there is the coexistence of two varieties of the fungus: *H. capsulatum* var. *duboisii* ("African histoplasmosis") and *H. capsulatum* var. *capsulatum* on the continent. *H. capsulatum* var. *duboisii* has been primarily noted in Nigeria, Niger, Congo, Democratic Republic of Congo, and Uganda [80–82] although a few cases have also been observed in Madagascar, Chad, Ivory Coast, and Senegal [83–86]. Only 17 cases of *H. capsulatum* var. *duboisii* have been described among HIV-infected patients in Europe, with all being described as imported [12]. To the best of our knowledge, only two studies, from Zimbabwe and South Africa, respectively, described 12 and 14 persons coinfected with AIDS and *H. capsulatum* var. *capsulatum* [87, 88]. The majority of published cases of histoplasmosis caused by *H. capsulatum* var. *capsulatum* among HIV-infected Africans were observed in Europe as imported infections [12, 13, 89]. Although one study in Tanzania has identified patients with febrile illnesses that were likely due to histoplasmosis, the majority of patients tested were HIV-infected [90]. In this study, the testing was done retrospectively as *Histoplasma* antigen testing, the most sensitive method of diagnosis, is not available in the region [90]. Patients originated from Democratic Republic of Congo, Congo, Liberia, Ivory Coast, Gambia, Uganda, Central African Republic, Guinea Bissau, and Senegal. In actuality, the majority of histoplasmosis cases in Africa are likely due to *H. capsulatum* var. *capsulatum*.

Travel, Immigration, and Histoplasmosis

The increasing number of persons traveling to endemic areas for tourism or international cooperation programs, or migrating for work is responsible of the growing number of reports of single or, more frequently, clusters of acute histoplasmosis. Numerous histoplasmosis cases among immigrants from Latin America and sub-Saharan Africa have occurred. Of particular importance in these populations are the potential to reactivate a previous infection when starting on immune suppressive therapy [12, 13, 89, 91].

Table 3 shows cases related to international travel but not immigration [91–106]. Sleeping outdoors or spelunking (where bats are present) is associated with the development of acute pulmonary histoplasmosis among tourists. However, in an outbreak, involving more than 200 US students in Acapulco, Mexico, which is the largest reported outbreak among travelers, the infection source was soil from a hotel's ornamental potted plants that had been fertilized with compost [92, 107]. More recently, an outbreak with a high attack rate (61 %) was observed among three mission groups that had traveled to El Salvador to renovate a church. Participation in dust-generating activities, such as digging or sweeping outdoors, was associated with an increased risk of symptomatic illness [97]. Although the number of reports of travel-associated histoplasmosis increased steadily in recent years (Table 3), likely many cases go unnoticed, especially if not presenting as a cluster of patients.

Medical Immunosuppression and Histoplasmosis

The number of patients receiving immunosuppressive and cyto-reductive therapies is increasing, particularly among patients who receive biologic medications to treat rheumatologic, gastrointestinal, or dermatologic diseases [36, 108•, 109•, 110•]. The fact that an intact immune system is important to prevent progressive dissemination of *Histoplasma* infection has been recognized [9, 14•], and so, these patients are more susceptible to histoplasmosis. For example, since as early as the 1950s, immune suppression in the form of Hodgkin's lymphoma was recognized as a risk factor allowing for progressive disseminated histoplasmosis [111].

Assi and colleagues conducted a large retrospective multicenter study of solid-organ transplant patients with histoplasmosis in known endemic areas, reviewing 152 cases that occurred at 24 centers from 2003 to 2010 [110•]. Among 152 histoplasmosis infections, all patients were receiving immunosuppressive medications, most were receiving calcineurin inhibitors (138 of 152) and one or two other medications with mycophenolate preparations and corticosteroids being the most common [110•]. Seventy-eight patients had kidney transplantation, 24 had liver transplantation, 22 were pancreas/kidney transplant recipients, 14 received heart transplants, 8 lung transplants, and 3 received pancreas transplants while 2 other individual patients had kidney transplant combined with either heart or lung, and 1 had a small-bowel transplant [110•]. In this population, urine *Histoplasma* antigen was the most sensitive test detecting 132 of 142 cases and while the median time from transplant to diagnosis was 27 months, 34 % of cases occurred in the first years after transplant [110•]. Disseminated histoplasmosis occurred in 81 % (122/152), and 10 % (15/152) died [110•].

Patients with autoimmune conditions such as rheumatoid arthritis are also at risk for progressive disseminated histoplasmosis if immunosuppressive medications are used. In a single-center study in an endemic area, 26 cases of patients with rheumatoid arthritis who were infected with *Histoplasma* were summarized. Progressive disseminated histoplasmosis was present in 46 % (12/26) of patients with histoplasmosis [109•], 11 of the 12 patients were receiving multiple immune suppressive medications. Of the 26 total patients, 16 were

Table 3 Reports of cluster of acute imported histoplasmosis among travelers from 1988 to 2013

Author/year/reference	*N*	Syndrome	Country of observation	Country of acquisition	Risk activity/ies
CDC, 1988 [88]	15	Pulmonary	USA	Costa Rica	Visiting a bat cave
Nasta, 1997 [92]	4	Pulmonary	Italy	Peru	Visiting a bat cave
Valdez, 1999 [93]	11	Pulmonary	USA	Ecuador	Visiting a bat cave
Gascon,2000 [87]	7	Pulmonary	Spain	Santo Domingo (2), Perù, Guatemala (2), Nicaragua, Colombia	Visiting caves (Santo Domingo, Perù); sleeping in the forest (Nicaragua, Guatemala)
Buxton, 2002 [94]	14	Pulmonary	Canada	Belize	Visiting caves
Salomon, 2003 [95]	13	Pulmonary	France	Martinique (French West Indies)	Trekking (passage in a bat-infested tunnel)
Morgan, 2003 [90]	262	Pulmonary	USA	Mexico	Stay in a hotel with minor construction activities
Weinberg, 2003 [91]	5	Pulmonary	USA	Nicaragua	Visiting a bat cave
Lyon, 2004 [96]	14	Pulmonary	Usa	Costa Rica	Visiting a bat cave
Garcia-Vazquez, 2005 [97]	9	Pulmonary	Spain	Guatemala	Renovation of an old school
Alonso, 2007 [98]	4	Rheumatologic	Spain	Ecuador	Agricultural activity
CDC, 2008 [89]	20	Pulmonary	USA	El Salvador	Construction activities (church)
Norman, 2009 [99]	5	Pulmonary	Spain	Peru; El Salvador; Panama; Ecuador; multiple exposure (Costa Rica, French Guiana, Ecuador, Argentina)	Visiting a bat cave (3), entomologist (1), agricultural activity (1)
Buitrago, 2010 [100]	9	Rheumatologic (4), pulmonary (3)	Spain	Ecuador (5), Nicaragua (1), Venezuela (1), Africa (2)	Visiting rural areas (4), visiting a cave (1), traveling to rural areas
Kajfastz, 2012 [101]	4	Pulmonary	Poland	Ecuador	Visiting bat caves
Cottle, 2013 [102]	13	Pulmonary	UK	Uganda	Contact with a bat-infested tree trunk

receiving methotrexate, 15 were receiving tumor necrosis factor (TNF)-α inhibitors, 15 were receiving corticosteroids (mean dose 9.1 mg/day), 5 were receiving hydroxychloroquine, and 5 were receiving leflunomide [109•].

TNF-α inhibitors are particularly important as TNF-α is a key component of the granulomatous immune response to *Histoplasma capsulatum* [108•, 112]. As of 2010, 88 cases of histoplasmosis had been reported in patients using TNF-α inhibitors, a majority of cases were disseminated [108•]. While many cases come from endemic areas, cases outside of endemic areas have been reported as well [108•]. Cases continue to be reported, particularly in those patients using infliximab [108•]. As an example, in Indiana, of 19 reported cases related to TNF-α inhibitor use, 13 patients were using infliximab [108•]. A final note, paradoxical immune reconstitution inflammatory syndrome (IRIS) is a worsening of symptoms after successful microbiologic treatment upon improving a weakened immune system. Just as IRIS can occur in HIV-infected persons upon starting ART [113], IRIS can also occur when TNF-α inhibitors or other immunosuppressive medications are stopped [108•].

Conclusions

Histoplasmosis is much more widespread than was once thought, and current knowledge of its distribution is incomplete [30]. The AIDS pandemic has elucidated a worldwide risk for histoplasmosis, including areas previously unknown to be endemic. While ART access has improved to the point that histoplasmosis in the setting of HIV infection is rare in high-income countries, histoplasmosis remains a significant cause of AIDS-associated mortality in many parts of the world. Additionally, increased international travel and the use of immune suppressive medications are likely to lead to additional emergence of histoplasmosis infection from areas not previously known to be endemic, and the non-HIV-related incidence may continue to increase for progressive disseminated histoplasmosis. Thus, we believe histoplasmosis should be considered as a possible diagnosis in much of the world. Areas of higher density of exposure exist, and the consideration should be stronger if a patient has been to or lived in these locations. We advocate physicians considering disseminated histoplasmosis in patients with immune suppression, regardless of the location of the hospital to which the patient presents although the weight which one considers progressive disseminated histoplasmosis might vary widely depending on the patient's location. Currently, *Histoplasma* antigen testing is not available in many areas not previously thought to be endemic, and this may limit one's ability to diagnose the condition properly as it is currently the most sensitive method of diagnosis [32, 71, 110•]. We look forward to the day when we no longer hear a presentation that includes, "well, they haven't been to the Ohio River Valley so it can't be histoplasmosis" from trainees.

Compliance with Ethics Guidelines

Conflict of Interest Nathan C. Bahr, Spinello Antinori, L. Joseph Wheat, and George A. Sarosi declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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