

# Histoplasmosis in immunocompetent individuals living in an endemic area in the Brazilian Southeast

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## ABSTRACT

**Introduction:** The distribution of infection by *Histoplasma capsulatum* in Brazil is heterogeneous, and the number of cases affecting immunocompetent individuals is relatively small. This study reports the epidemiological and clinical data regarding histoplasmosis in non-immunosuppressed individuals. **Methods:** The study included only the immunocompetent patients with histoplasmosis who were diagnosed between 1970 and 2012 at a university hospital located in Ribeirão Preto, State of São Paulo, Brazil. Clinical and epidemiological data were collected retrospectively from the patient records. **Results:** Of the 123 patients analyzed, 95 had an active disease that manifested in the different clinical forms of histoplasmosis. Men were the predominant gender, and most patients resided in the Northeast of the State of São Paulo and in the nearby municipalities of the State of Minas Gerais. The risk factors for acquiring histoplasmosis and prolonged contact in a rural environment were recorded in 43.9% and 82.9% of cases, respectively. Smoking, alcoholism, and comorbidity rates were high among the patients with the chronic pulmonary and subacute/chronic disseminated forms of histoplasmosis. Many patients achieved clinical cure spontaneously, but 58.9% required antifungals; the disease lethality rate was 5.3%. **Conclusions:** Immunocompetent individuals manifested the diverse clinical forms of histoplasmosis over a period of 4 decades, revealing an additional endemic area of this fungal disease in the Brazilian Southeast.

**Keywords:** Histoplasmosis. Epidemiology of fungal diseases. Endemic mycoses. Interstitial pneumonia. Chronic meningitis.

## INTRODUCTION

Epidemiological surveys based on the histoplasmin intradermal test and case reports of disease caused by *Histoplasma capsulatum* suggest the existence of histoplasmosis endemic areas in the five major regions of Brazil<sup>1</sup>. Many cases of co-infection of *H. capsulatum* in Brazilian patients with acquired immunodeficiency syndrome (AIDS) have been reported in recent years, with some series including more than 100 patients<sup>2,3</sup>. In contrast, there have been relatively few reports of histoplasmosis affecting immunocompetent individuals. Until 1978, a short time before the human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS) epidemic, only 36 cases of this fungal disease had been reported in Brazilian patients<sup>4</sup>. A later series involving a larger number of immunocompetent patients included 54 cases in the State of Rio Grande do Sul<sup>5</sup>, 38 in Rio de Janeiro<sup>6</sup>, eight in the State of São Paulo<sup>7</sup>, eight in the State of Minas Gerais<sup>3</sup>, and five in the State of Mato Grosso do Sul<sup>8</sup>. Small outbreaks of

histoplasmosis have also occurred in different regions of Brazil, involving approximately 200 non-immunosuppressed persons<sup>9</sup>. The available data suggest a low prevalence in the population with intact immunological defenses and an irregular distribution of histoplasmosis in Brazil.

The risk of exposure to and acquisition of infection with *H. capsulatum* have been identified in patients with the acute pulmonary form of the disease. Often, exposure to caves and other locations with bats<sup>10</sup> or contact with and aspiration of guano from these animals and from birds<sup>11</sup> have been reported. Additionally, habitual smoking and non-immunosuppressive comorbidities may be associated with the chronification and dissemination of that fungal disease<sup>12,13</sup>.

This study presents epidemiological and clinical data regarding histoplasmosis in immunocompetent persons and reveals the characteristics of this fungal disease and the existence of an endemic area in the interior of Southeast Brazil.

## METHODS

A retrospective study was performed on immunocompetent patients with histoplasmosis who received medical care at the University Hospital of the Faculty of Medicine of Ribeirão Preto, University of São Paulo, between 1970 and 2012. The municipality of Ribeirão Preto is located in the northeastern region of the State of São Paulo, Brazil (21°12'42"S, 47°48'24"W).

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It is the regional seat and is surrounded by 26 other municipalities with economies based on agriculture and animal husbandry. The institution at which the study was conducted is a general university hospital that provides medical care to patients from the aforementioned region in addition to municipalities located at a distance up to approximately 150km.

All diagnosed histoplasmosis immunocompetent patients confirmed by mycologic, histopathological, and/or serologic tests were included in the study. A standardized chart was used to collect information from the medical records of these patients, including demographic, epidemiological, and clinical data as well as radiologic alterations and disease outcome. The patients were classified according to the following clinical forms of histoplasmosis: acute pulmonary, chronic pulmonary, subacute/chronic disseminated, and histoplasma<sup>14</sup>. Residual pulmonary histoplasmosis cases were also included. Patients with histoplasmosis and clear immunosuppression related to AIDS, with associated or previous neoplasias, organ transplants, and/or the use of immunosuppressive medications (e.g., corticosteroids and cytotoxic drugs) were excluded.

The identification of *H. capsulatum* isolated from a culture of secretions and lesion fragments was based on the macro- and microscopic characteristics of the filamentous form of the fungus. Hematoxylin-eosin (HE) and methenamine silver (GMS) staining was used for the histopathological examinations of the tissues and biopsied lesions. Anti-*H. capsulatum* antibodies were detected with counterimmunoelectrophoresis using histoplasmin as the antigen, and the patient serum samples were titrated with consecutive 2-fold serum dilutions with 0.9% saline<sup>15</sup>. The demographic data and other variables are presented by descriptive statistics.

## RESULTS

**Table 1** shows the demographic and epidemiological data of 123 immunocompetent patients according to the clinical form of histoplasmosis. Most patients were white males ranging in age from 3 to 79 years. More children and young subjects were

diagnosed with the acute forms of the disease, and more older persons had the chronic forms of histoplasmosis. More than 90% of the patients lived and worked in Ribeirão Preto and nearby towns in the northeast of the State of São Paulo and in part of the southwest of the State of Minas Gerais.

Patients with chronic disseminated or chronic pulmonary disease frequently reported smoking and alcoholism (**Table 2**). Prolonged permanence in the rural environment was observed in 82.9% of the patients. Of the 54 patients who were actively questioned about other risk factors for exposure to *H. capsulatum*, 10 patients recalled the presence of bats in their homes, eight reported visiting caves or being in sewers, 10 reported raising fowl (particularly chickens), six reported preparing organic fertilizer using mammalian or bird excrement, eight reported domestic or professional contact with tree limbs or wood, and 12 reported habitual exposure to forest or agricultural fields.

Three small outbreaks were identified among the patients with the acute pulmonary form, each outbreak involving two persons. Two patients were diagnosed after visiting caves in the southwest part of the State of Minas Gerais, and the other outbreak involved two firemen performing rescue work in the bottom of a septic tank in the municipality of Ribeirão Preto.

In the acute pulmonary form of histoplasmosis, the lungs had a diffuse reticulonodular infiltrate and/or scattered nodules. Some of these patients had cervical or generalized lymphadenomegaly and other manifestations of dissemination or of immunological hyperactivity (**Table 3**). Anti-*H. capsulatum* antibodies were detected in 30 (83.3%) of the 36 cases, and histopathological confirmation was obtained in 15 cases, with biopsies of a nodule or lung tissue. Antifungal agents were used by 57.9% of the patients because of the intensity or prolongation of the respiratory symptoms. The outcome was favorable in all cases, with the exception of one patient who also had cardiopathy caused by Chagas disease.

**Table 3** shows the characteristics of the acute disseminated form in 12 patients ranging in age from 3 to 22 years, with the exception of a 44-year-old man. This last patient had Noonan syndrome and died at the beginning of treatment. Typically, the patients

TABLE 1- Demographic data of patients according to the clinical form of histoplasmosis.

Clinical form	n	Age (mean ± SD)	Male		White <sup>a</sup>		Residence					
			n	%	n	%	Ribeirão Preto <sup>b</sup>		São Paulo <sup>c</sup>		Other <sup>d</sup>	
							n	%	n	%	n	%
Acute pulmonary	38	38.5 ± 20.5	27	71.1	30	78.9	32	84.2	0	0.0	6	15.8
Acute disseminated	12	13.0 ± 11.4	10	83.3	10	83.3	12	100.0	0	0.0	0	0.0
Subacute/chronic disseminated	32	50.0 ± 11.2	25	78.1	30	93.8	28	87.5	2	6.3	2	6.3
Chronic pulmonary	13	54.5 ± 15.8	11	84.6	10	76.9	11	84.6	1	7.7	1	7.7
Histoplasma	6	56.0 ± 12.4	3	50.0	5	83.3	5	83.3	0	0.0	1	16.7
Residual	22	48.7 ± 15.9	10	45.5	18	81.8	18	81.8	3	13.6	1	4.6
All patients	123	43.4 ± 19.5	86	69.9	103	83.7	106	86.2	6	4.9	11	8.9

<sup>a</sup>White skin color; <sup>b</sup>Ribeirão Preto and Northeastern region of the State of São Paulo; <sup>c</sup>Other municipalities of the State of São Paulo; <sup>d</sup>Other Brazilian states.

TABLE 2 - Epidemiologic data of the patients according to the clinical form of histoplasmosis.

Clinical form	Rural exposure*		Risk of infection**		Smoking habit		Alcoholism	
	n	%	n	%	n	%	n	%
Acute pulmonary (n=38)	15/22	68.2	16/38	42.1	11/33	33.3	6/32	18.8
Acute disseminated (n=12)	6/8	75.0	3/12	25.0	0/0	0.0	0/0	0.0
Subacute/chronic disseminated (n=32)	19/22	86.4	15/32	46.9	19/24	79.2	14/23	60.9
Chronic pulmonary (n=13)	9/10	90.0	9/13	69.2	11/13	84.6	10/12	83.3
Histoplasmosis (n=6)	1/1	100.0	4/6	66.7	4/6	66.7	1/6	16.7
Residual (n=22)	13/13	100.0	7/22	31.8	14/21	66.7	4/21	19.0
All patients (n=123)	63/76	82.9	54/123	43.9	59/97	60.8	35/94	37.2

\*Rural work or residence; \*\*Risk factors for exposure to *Histoplasma capsulatum*.

TABLE 3 - Clinical manifestations, diagnoses, and outcomes of the patients with acute pulmonary or acute disseminated histoplasmosis.

Organ involvement	AcP (n=38)		AcD (n=12)	
	n	%	n	%
Lungs	38	100.0	3	25.0
Cervical lymphadenopathy	8	21.1	2	16.7
Abdominal lymphadenopathy	0	0.0	1	6.3
Generalized lymphadenopathy	3	7.9	8	66.7
Hepatomegaly	5	13.2	8	66.7
Splenomegaly	1	2.6	8	66.7
Arthritis/arthritis	3	7.9	0	0.0
Pericarditis	1	2.6	0	0.0
Others*	1	2.6	1	8.3
Laboratory diagnosis				
<i>Histoplasma capsulatum</i> in histologic examination n (%)	15	39.5	7	58.3
<i>Histoplasma</i> antibodies				
reactive (%)	30/36	83.3	10/12	83.3
titer-median (range)**	32 (NR-256)		64 (NR-256)	
Treatment				
antifungal usage n (%)	22	57.9	6	50.0
outcome/cure n (%)	37	97.4	11	91.7
death n (%)	1	2.6	1	8.3

AcP: acute pulmonary form; AcD: acute disseminated form; NR: non-reactive; \*Erythema nodosum in 1 patient with AcP; oral mucosa (1), nasal mucosa and skin (1), meninges and adrenals (1), bone marrow (1) in different patients with the AcD form. \*\*titer: inverse of the serum dilution.

had generalized lymphadenopathy and hepatosplenomegaly. Additionally, 25% of patients had interstitial infiltrates in the lungs, and 5 of the 12 cases showed involvement of other tissues. Anti-*H. capsulatum* antibodies at generally high titers were detected in 10 (83.3%) of the 12 cases. Only 50% of these patients received antifungal agents, and 11 of the 12 patients were cured.

**Table 4** shows that many patients with the subacute/chronic disseminated form of histoplasmosis had ulcerations in the oral mucosa and/or injury to the upper and lower airways. Central nervous system involvement manifested as meningitis, myelitis, or brain granuloma, and 2 patients had Addison's disease caused by adrenal injuries. Associated diseases were present in approximately half of the cases: tuberculosis (n=3),

TABLE 4 - Organ and tissue involvement in patients with subacute and chronic disseminated histoplasmosis.

Involvement/lesion	Number	Percentage
Oropharyngeal/nasal mucosa	19	59.4
Interstitial pneumonitis	11	34.4
Larynx	8	25,0
Cervical lymphadenopathy	8	25,0
Hepatomegaly	10	31.3
Splenomegaly	4	12.5
Skin	2	6.3
Central nervous system	7	21.9
Adrenal	3	9.4
Esophagus	1	3.1
Total number of patients	32	100.0

leprosy (n=1), Chagas disease (n=3), leishmaniasis (n=1), cardiovascular disease (n=3), diabetes mellitus (n=2), liver disease (n=1), hypothyroidism (n=1), and chronic intestinal disease (n=1). *H. capsulatum* was isolated from 4 patients and specific antibodies (titers ranging from 1:2 to 1:512) were present in 27 of the 28 cases. Among the 27 patients who were followed up after the antifungal therapy, 25 were cured or showed clinical improvement, and 2 died during treatment.

Many patients with the chronic pulmonary form of the disease had associated diseases, including chronic obstructive pulmonary disorder (n=6), bullous emphysema (n=1), tuberculosis (n=2), paracoccidioidomycosis (n=1), diabetes (n=1), and chronic renal failure (n=1). A chest X-ray revealed an interstitial infiltrate of the lungs, usually bilateral, and micro- or macronodules. Six of the 13 patients had pulmonary cavitation. *H. capsulatum* was isolated from 4 patients. The histopathological exam was positive in 3 cases, and anti-*H. capsulatum* antibodies with titers ranging from 1:8 to 1:256 were present in 11 of the 12 cases. Among the 11 patients who were followed after the antifungal treatment, there was only 1 clinical cure, while the remaining patients continued to have chronic pulmonary disease (n=8) or died (n=2).

Histoplasmosis was detected in 6 patients who had no respiratory symptoms but did have chest X-rays taken because of trauma or other diseases. These patients had nodules measuring 1.0 to 1.5cm in diameter that were located most commonly in the lower lobe of the right lung. Three patients underwent surgery to remove the nodules. The nodule size remained stable over 1 to 6 years of follow-up in the remaining 3 patients.

The patients with the residual form of pulmonary histoplasmosis presented with lesions with variable degrees of calcification in the chest X-rays; the lesions were represented by a diffuse or localized reticulonodular infiltrate (n=7), single or multiple nodules measuring up to 1.0cm in diameter (n=12), and/or calcified perihilar or mediastinal lymph nodes (n=7). In 2 cases, the diagnosis was established by a histopathological

examination of the surgically removed nodules. The diagnosis of the remaining cases was determined by anti-*H. capsulatum* antibody titers ranging from 1:2 to 1:32. One of the patients whose pulmonary nodule contained granulomas with *H. capsulatum* reported professional exposure to mammals and birds. This patient had also experienced a fever of indeterminate origin that had spontaneously regressed a few years earlier.

Regarding the duration and the antifungal agent used, the treatments of 56 of the 95 (58.9%) patients with active disease varied widely. Sulfadiazine, sulfamethoxazole-trimethoprim, and amphotericin B were used during the first 2 decades of the treatment period, with the use of azole drugs prevailing thereafter. Five (5.3%) of the 95 patients with active histoplasmosis died: 2 did not receive antifungal agents, 2 had started treatment less than 3 weeks prior to their deaths, and 4 had comorbidities that contributed to the lethal outcomes.

## DISCUSSION

This study analyzed the largest Brazilian series of histoplasmosis cases affecting immunocompetent individuals. Compared to the 95 cases of active disease, 1,219 cases of paracoccidioidomycosis affecting immunocompetent individuals occurred in the same geographic area over an approximately equal period of time<sup>16</sup>. This result suggests that the incidence of histoplasmosis-disease is approximately 13 times lower than that of paracoccidioidomycosis, whose mean incidence in the Ribeirão Preto region has been estimated at 2.7 cases/100,000 inhabitants/year<sup>17</sup>. However, this ratio needs careful interpretation because the patients with chronic pulmonary and chronic disseminated histoplasmosis did not know the places or times of the fungal infections. Histoplasmosis occurred over a period of 4 decades in the study area (both endemically and as small outbreaks) and manifested in the clinical forms recognized in endemic areas in the United States and Brazil<sup>5,6,18</sup>. Outbreaks and the acute pulmonary form reveal recent exposure to *H. capsulatum* and, therefore, indicate that the region surrounding Ribeirão Preto is an endemic area of histoplasmosis.

Both the unequal distribution of the age ranges of the patients with acute or chronic histoplasmosis and the predominance of the disease among men have been observed in other case series<sup>13,19</sup>. The higher prevalence of women in the group with histoplasmosis or residual disease may be attributed to the habitual radiographic evaluation of the lungs in cases of mammary nodules and the better attention to personal health care among women. The predominance of white skin color among the patients is similar to that of the general population in the same area of residence.

In addition to the high rate of prolonged permanence in a rural environment, many patients remembered risk factors for acquiring *H. capsulatum*, such as exposure to bats in caves, houses, and holes dug in the ground. Contact with chicken farms and acute exposure to the excrements of these birds and of cattle were reported by several patients, revealing the occupational risk involved in agricultural and animal husbandry activities. Smoking and alcoholism were highly prevalent in the chronic forms of histoplasmosis, suggesting the relevance of both to the pathogeny

of the chronification and focal dissemination of this mycosis<sup>12,20</sup>. The analysis of the risk factors for histoplasmosis infection has limitations because of the lack of information in some medical records and the absence of a control group of histoplasmin-negative patients. The various comorbidities associated with the subacute/chronic disseminated form may be the consequence of the living conditions of the patients and may eventually have contributed to the onset of disease caused by *H. capsulatum*.

The present case series confirms the clinical polymorphism of histoplasmosis, the propensity to a spontaneous cure in the acute forms, and the lethality associated with the disease. The cases with residual histoplasmosis are examples of diagnoses that were not made during the active disease phase, reflecting the natural and common regression of the lung lesions. Considering the histoplasmin surveys<sup>21</sup> and autopsy studies<sup>22</sup> conducted in Brazil, the patients with the acute pulmonary form of the disease in this series most likely represent a small fraction of the real number of cases in the aforementioned region. Another possible cause of the diagnostic difficulty is the clinical similarity of the acute and chronic disseminated forms of the disease to paracoccidioidomycosis. This mycosis is more prevalent and also manifests as generalized lymphadenopathy in children and young people and as oropharyngeal ulcerations and visceral lesions in adults<sup>16</sup>. The serologic test to detect antibodies has provided great laboratory support to differentiate histoplasmosis from other fungal diseases and tuberculosis. Antibody titers may vary according to the clinical form, duration, and severity of histoplasmosis<sup>18,19</sup>.

Many patients received antifungal agents and were clinically cured, although a standardized treatment was not adopted. The clinical efficacy of currently recommended drugs, such as amphotericin B and itraconazole<sup>23</sup>, was observed, as was the efficacy of sulfamide drugs. Although these sulfamide drugs are not currently used for anti-*Histoplasma* therapy, 7 patients with subacute or chronic disseminated histoplasmosis obtained lesion regression after using sulfamethoxazole-trimethoprim or sulfadiazine.

This study revealed the presence of an endemic area for histoplasmosis in the Ribeirão Preto region, Southeast Brazil, and the occurrence of various clinical forms of the disease in immunocompetent persons over a 4-decade period.

## CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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