Histoplamosis
en Centroamérica y el Caribe

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Historia

- Descrita en 1906 por Samuel Darling, patólogo norteamericano, investigador en Leishmaniasis, durante la construcción del Canal de Panamá.
- En la autopsia de un paciente fallecido en Martinica, llamó su atención la presencia de hepatomegalia, esplenomegalia y daño pulmonar, todos hallazgos observados en Leishmaniasis sistémica.
- En la histología encontró muchos cuerpos intracelulares semejantes a amastigotes, pero sin quinetonúcleos, y con células rodeadas por un halo transparente parecido a una cápsula. Darling lo consideró un protozoario, y lo denominó *Histoplasma capsulatum*.

Historia

- La confirmación de la causa de muerte se obtuvo en 1929, cuando Dood y De Mombreum de la Universidad de Vanderbilt, aislaron el microorganismo.
- En 1945, Christie y Peterson describieron con mayor precisión la Histoplasmosis, como una infección pulmonar primaria sintomática, que en ocasiones se disemina.
- El primer aislamiento del hongo en una muestra de suelo fue realizado por Emmons en 1949, y posteriormente se reportaron otros aislamientos en el suelo de las cavernas y minas.

Micosis Endémicas en Latinoamérica

- **Histoplasmosis:** causada por 2 de 8 grupos de especies de *Histoplasma capsulatum*
- **Paracoccidioidomicosis:** causada por *Paracoccidioides brasiliensis*
- **Coccidioidomicosis:** causada por *Coccidioides immitis* y *Coccidioides posadasii*

Datos Clínicos y Epidemiológicos en Latinoamérica

- Escasos y fragmentados
- Hacen referencia a situaciones clínicas excepcionales, mas que a las típicas o características de una entidad
- Brindan evidencia científica pobre (C-III)
- Escritos en español o portugués
- Con pocas excepciones, son usualmente publicados en revistas locales

Histoplasma capsulatum en Las Américas

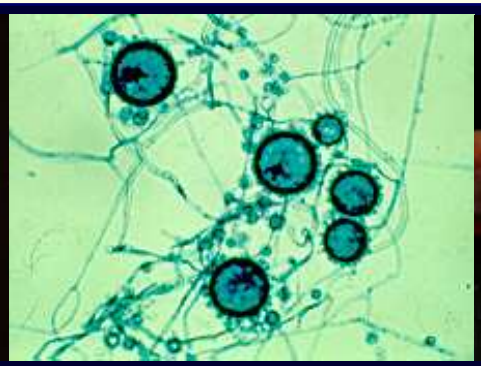
- De los 8 diferentes grupos de especies conocidos, 1 – 4 se encuentran en América, los restantes en Europa, Asia y Eurasia
- Se encuentra primariamente en microfocos, especialmente en el suelo que contiene grandes cantidades de excretas de aves domésticas (gallinas, pavos, gansos), palomas, aves migratorias o guano de murciélagos

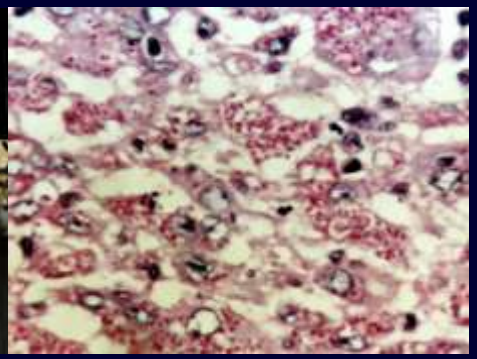
Histoplasma capsulatum en Las Américas

- El desarrollo del ***Histoplasma capsulatum*** está favorecido por condiciones climáticas
  - Suelo con pH entre 5 y 10
  - Temperatura < 40°C (media de 22 – 29 °C)
  - Precipitación anual aproximada de 1000 a 1200 mm.
  - Humedad relativa entre 67 – 87 %
- La época de mayor reproducción del hongo es en el verano, con temperatura y humedad altas
- Es la temporada seca cuando se adquiere la mayor parte de primoinfecciones, porque las esporas se transportan por el aire y polvo

Histoplasma capsulatum
Dimorfismo Térmico

Fase	Condiciones	Forma
Saprofítica	Suelo o cultivo a < 30 °C	Micelio con hifas y macroconidias tuberculadas y microconidias (elemento infectante)
Parasitaria	Tejidos vivos o cultivo a 37 °C	En forma de levadura, responsable de la patogénesis del hongo



Histoplasma capsulatum
Variedades Patógenas

- En humanos
  - Variedad *duboisii*
    - Existe en Africa
    - Casos reportados en Africa y Europa
  - Variedad *capsulatum*
    - Ocurre en América
    - Causa común de Histoplasmosis
- En animales (equinos)
  - Variedad *farciminosum*

Histoplasma capsulatum
Variedades Patógenas

- Las variedades *capsulatum* y *duboisii* son indistinguibles en su fase micelial.
- Sin embargo, en tejidos animales las levaduras de la variedad *duboisii* son ovoides, más grandes y de pared más gruesas que las de la variedad *capsulatum*.

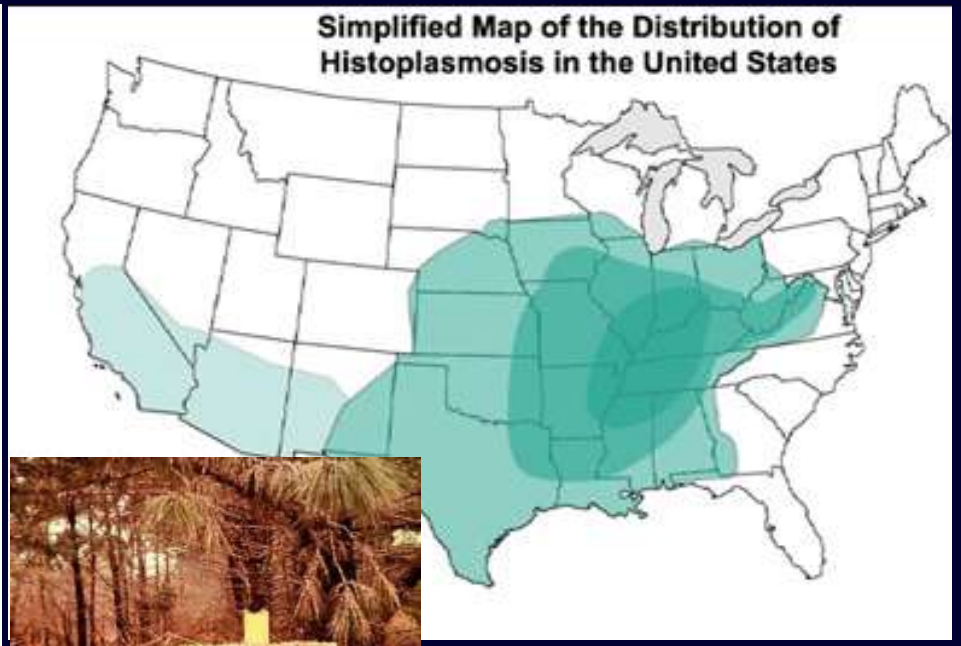
Histoplasmosis – Epidemiología 1

- Ocurre principalmente en Centroamérica, Sudamérica y Estados Unidos.
- En Estados Unidos, 80% de la población que reside en las riveras de los ríos Ohio y Mississippi ha estado en contacto con *H. capsulatum.*
- En estas zonas, hasta 25% de las personas infectadas por HIV, desarrollan enfermedad diseminada.
- En Estados Unidos la histoplasmosis se considera una infección emergente en personas inmunodeficientes, ya que en este grupo, las formas diseminadas y letales son comunes.

Distribución Geográfica

- Norteamérica: la enfermedad ha sido registrada en zonas endémicas de EUA (valles de los ríos Ohio y Mississippi) y México.
- Centroamérica: Guatemala, Honduras, Nicaragua, Costa Rica y Panamá
- Sudamérica: Uruguay, Colombia, Venezuela, Guyana Francesa, Ecuador, Perú, Chile, Brasil y Argentina.
- Se han descripto casos esporádicos autóctonos en África, Asia y Europa.

Histoplasmosis
Distribución Geográfica

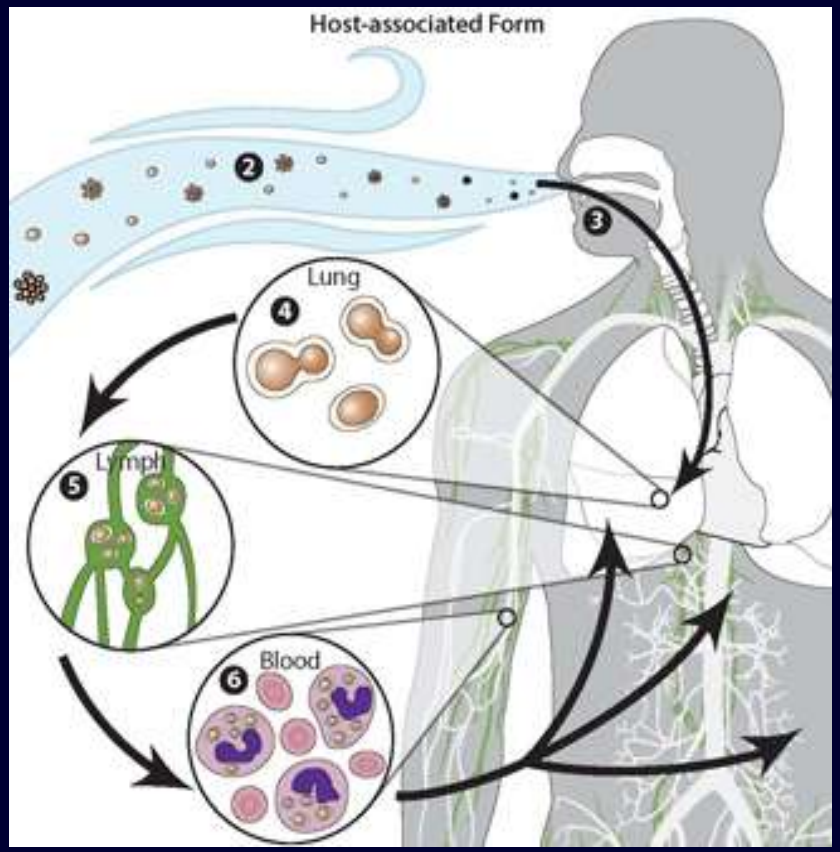


Histoplasmosis – Epidemiología 2

- Se le considera una enfermedad de tipo ocupacional, a la cual se encuentran expuestos mineros, espeleólogos, guaneros, agricultores y trabajadores rurales de bajo nivel socioeconómico.
- Ambientes muy cerrados como cuevas, grutas y construcciones abandonadas inducen morbilidad ocasional que puede generar casos severos, en cambio los espacios abiertos generan alta morbilidad con baja letalidad (huésped inmunocomprometido).
- La histoplasmosis es importante en los niños, debido a que en ellos es frecuente la forma diseminada,
- Es mas frecuente en hombres que en mujeres (4:1)

Histoplasmosis – Patogénesis

- La infección se adquiere mediante la inhalación de conidias o fragmentos de hifas transportadas por el aire a grandes distancias
- Tras la inhalación del inóculo infectante, este se instala en el alveolo y pasa a la forma de levadura
- Posteriormente se produce una intensa reacción granulomatosa seguida de caseificación o calcificación



Histoplasmosis – Mecanismos

- Infección primaria
- Reinfección
- Reactivación de foco latente

Factores que Influyen en la Presentación Clínica

- Duración de la exposición al *Histoplasma capsulatum*
- Edad
- Estado inmunológico del paciente
- Presencia de neumopatías crónicas

Histoplasmosis – Presentación

- Durmiente o latente
- Agudo
- Crónico
- Sistémico (Histoplasmosis diseminada)

Clasificación Clínica

- Histoplasmosis pulmonar aguda
- Histoplasmosis pulmonar cavitaria crónica
- Histoplasmosis diseminada progresiva
- Linfadenitis mediastinal

Knox KS & Hage CA. *Proc Am Thorac Soc 2010;* 7:169–172.

Histoplasmosis en el Viajero

- El sistema de vigilancia GeoSentinel, que comprende 25 clínicas para viajeros alrededor del mundo, detectó entre 04/1998 – 03/2002 que la histoplasmosis ocupa más de 70% de las micosis sistémicas adquiridas por viajeros en el mundo y junto a la coccidioidomicosis son las micosis más frecuentemente adquiridas por turistas.
- La mayor parte de los reportes proviene de viajeros de EUA que adquirieron la infección en América.
- Aunque la histoplasmosis ha sido considerada una infección de espeleólogos, 60 – 64 % con histoplasmina positiva, recientemente se han presentado brotes en viajeros (ecoturismo) que visitan América Latina.

Freedman DO et al. *J Travel Med* 1999;6:94-98

Histoplasmosis en el Viajero
Brotes en Viajeros a América Latina

Destino	Fuente	Origen	% Hist (n)*	Año
Martinica	Francia	Cueva	100 (13)	1995
Perú	Italia	Cueva	100 (4)	1995
Costa Rica	Costa Rica	Cueva	72 (75)	1998
Costa Rica	EUA, Canadá	Cueva	64(14)	1998
Ecuador	EUA	Cueva	23.5(17)**	1999
Dominicana	España	Cueva	100(6)	2000
Belice	Canadá	Cueva	87.5 (16)	2000
México	Japón	Cueva	2	2001
México	EUA	Hotel	54 (273)	2001
Nicaragua	EUA	Cueva	100 (14)	2001
Guatemala	España	Escuela	100(9)	2001
Salvador/Guatemala	Noruega	Cueva	57.1(14)	2004
México	Austria	Cueva	3	2007

* Proporción de individuos positivos a histoplasmina (total de individuos)

** Proporción de casos diagnosticados por clínica

Sánchez Alemán MA. *Enf In Microbiol* 2009;29:111-116.

Histoplasmosis en el Viajero
Brotes en Viajeros a Centro América

Severe Histoplasmosis in Travelers to Nicaragua

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Steven Wiersma,§ Quyen Phan,¶
David Dennison,# Pia MacDonald,* **
Mark Lindsley,* Jeannette Guarner,*
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and Rana Hajjeh*

We investigated an outbreak of unexpectedly severe histoplasmosis among 14 healthy adventure travelers from the United States who visited a bat-infested cave in Nicaragua. Although histoplasmosis has rarely been reported to cause serious illness among travelers, this outbreak demonstrates that cases may be severe among travelers, even young, healthy persons.

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- 15 turistas (8 mujeres), sanos, a Nicaragua entre 19-30/05/2001
- El 21/05 14/15 ingresaron por 10' a una cueva (mina de plata)
- Tasa de infección fue 100 %, con 86 % (12) cursando sintomáticos
- Incubación: 11 días

Table: Summary of laboratory testing results and clinical outcomes among persons with histoplasmosis

Characteristic	N (%)
Diagnostic test result[a]	
CF[b] and ID[c] positive	5 (36)
CF positive, ID negative	8 (57)
ID positive, CF negative	1 (7)
Urine antigen positive[d]	7 (58), range 1.2–4.6, median 2.8
Clinical outcomes[e]	
Missed work, school, or both[f]	10 (83)
Treated with itraconazole	9 (75)
Treated with steroids	7 (58)
Hospitalized	6 (50)
Duration of hospitalization	Median 6 d (range 2–11 d)
Duration of fever	Median 12 d (range 4–26 d)
Duration of symptoms	Median 42 d (range 16–210 d)

[a]Among 14 persons with histoplasmosis.
[b]CF: complement fixation.
[c]ID: immunodiffusion.
[d]Urine antigen tests were performed for 12 persons.
[e]Among the 12 symptomatic persons.
[f]Five persons missed 2 weeks–3 months of work, and five persons missed one semester of school.

Histoplasmosis en el Viajero
Brotes en Viajeros a Centro América

HISTOPLASMOSIS ASSOCIATED WITH EXPLORING A BAT-INHABITED CAVE IN COSTA RICA, 1998–1999

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Abstract. Between October 1998 and April 1999, 51 persons belonging to two separate groups developed acute pulmonary histoplasmosis after visiting a cave in Costa Rica. The first group consisted of 61 children and 14 adults from San Jose, Costa Rica; 44 (72%) were diagnosed with acute histoplasmosis. The second group comprised 14 tourists from the United States and Canada; 9 (64%) were diagnosed with histoplasmosis. After a median incubation time of 14 days, the most common symptoms were headache, fever, cough, and myalgias. Risk factors for developing histoplasmosis included crawling (odds ratio [OR] = 17.5, 95% confidence interval [CI] = 2.3–802) and visiting one specific room (OR = 3.4, 95% CI = 1.0–12.3) in the cave. Washing hands (OR = 0.1, 95% CI = 0.01–0.6) after exiting the cave was associated with a decreased risk of developing histoplasmosis. *Histoplasma capsulatum* was isolated from bat guano collected from inside the cave. Persons who explore caves, whether for recreation or science, should be aware of the risk bat-inhabited caves pose for developing histoplasmosis, especially if they are immunocompromised in any way.

Am. J. Trop. Med. Hyg., 70(4), 2004, pp. 438–442

TABLE 1

Demographic, serologic, and clinical data from both the Costa Rican and United States/Canada cohorts*

	Costa Rica cohort No. (%)	United States/Canada cohort No. (%)
Total members	76	14
Questionnaires completed	62	14
One or more serum samples	69 (91)	14 (100)
Acute sera	54 (71)	0
Convalescent sera	55 (72)	14 (100)
Met case definition	44 (79)	9 (64)
Four-fold increase in titer	15	NA
Single CF titer ≥ 1:32	38	3
M band on immunodiffusion	35	8
Urine EIA ≥ 1.0 unit	2	NA
Questionnaire + ≥1 serum sample	56 (75)	14 (100)
Median age, years (range)	14 (9–48)	56 (36–69)
Female	15 (34)	8 (57)
Prior knowledge of histoplasmosis	14 (23)	4 (29)
Symptomatic	36 (82% of cases)	7 (78% of cases)
Symptoms		
Headache	35 (97)	2 (29)
Fever	29 (83)	4 (57)
Cough	23 (64)	5 (71)
Myalgias	20 (56)	4 (57)
Chest pain	20 (56)	3 (43)
Nausea	18 (50)	1 (11)
Dyspnea	17 (47)	4 (57)

* NA = not applicable; CF = complement fixation; EIA = enzyme immunoassay.

Histoplasmosis en el Viajero
Brotes en Viajeros a Centro América

Outbreak of Histoplasmosis in a School Party That Visited a Cave in Belize: Role of Antigen Testing in Diagnosis

Jane A. Buxton, Meenakshi Dawar, L. Joseph Wheat, William A. Black, Nelson G. Ames, Marcella Mugford, and David M. Patrick

Histoplasmosis is endemic in parts of South and Central America and the role of bat guano is widely recognized in promoting the growth of the organism.[1,2] Previous outbreaks have been reported among cavers in the United States[3,4] and South America,[5] often in travelers upon return to their home country. The illness may be quite severe, as the exposure is often extensive, emphasizing the importance of recognition of the risk for histoplasmosis in cavers and understanding the approach to diagnosis.

Thirteen students (aged 16 to18 years) and 2 teachers from a school in Trail, British Columbia, Canada, traveled in Belize with 2 guides (1 Canadian, 1 from Belize) from March 16 to 26, 2000. Local BC physicians reported complaints of fever and chills in returning travelers to the BC Centre for Disease Control (BCCDC).

Histoplasmosis y SIDA

- Desde 1987, mas del 90 % de las personas infectadas con HIV con histoplasmosis, tienen enfermedad diseminada con SIDA, por lo que se le considera una enfermedad determinante de SIDA
- Esta micosis es la primera manifestación de SIDA en 50 – 75 % de los pacientes HIV positivo
- Los pacientes con recuentos de CD4 < 150 cel/µl estan en el mayor riesgo de adquirirla

Histoplasmosis y SIDA

- Desde 1990's, la prevalencia de histoplasmosis diseminada ha disminuido en poblaciones HIV positivas que tienen acceso a HAART, pero permanece alta en poblaciones sin acceso o no adherentes a HAART
- Las tasas de mortalidad por enfermedad diseminada son elevadas

Histoplasmosis y SIDA

- En pacientes con SIDA la enfermedad puede producirse por:
  - Reactivación de una infección latente
  - Tras la inhalación de conidios
- En ambos casos se produce enfermedad diseminada.
- Estudios de seroprevalencia en residentes de áreas endémicas en EUA indicaron que la incidencia en pacientes con SIDA osciló entre 2 – 26.7 %, mientras que en Argentina se reporta entre 6 – 7 %.

Histoplasmosis y SIDA

Disseminated Histoplasmosis and Human Immunodeficiency Virus Type 1 Infection: Risk Factors in Guatemala

Clinical Infectious Diseases 1997;25:343–4

L. Segura, M. Rojas, N. Pelaez, G. Shor-Posner, D. RosaRe, J. Moreno, W. Klaskala, and M. K. Baum

CORRESPONDENCE

Table 1. Characteristics of HIV-1–infected patients with progressive disseminated histoplasmosis.

Patient no.	Age (y)	Clinical findings	Diagnosis at admission	Possible risk factors for PDH	Diagnostic test for PDH
1	18	Hypotension, weight loss, splenomegaly, sensory alteration	Disseminated TB	HIV+, perihilar adenopathy, farm area resident	Blood and bone marrow smear
2	26	Fatigue, fever, weight loss, adenopathy, diarrhea	TB	HIV+, perihilar adenopathy	Blood and bone marrow smear
3	35	Cough, fever, fatigue, splenomegaly, hypotension	TB	HIV+, cave area resident, calcifications	Hepatic biopsy (postmortem)
4	32	Pallor, hepatomegaly, diarrhea, hypotension	Disseminated TB	HIV+ farm area resident calcifications	Blood and bone marrow smear
5	17	Cough, hypotension, weight loss, splenomegaly, pallor, fever, sensory alteration	Disseminated TB, PCP	HIV+, farm area resident, perihilar adenopathy	Hepatic biopsy (postmortem)
6	29	Fatigue, cough, diarrhea, pallor	TB	HIV+, cave area resident, perihilar adenopathy, calcifications	Blood and bone marrow smear
7	21	Fever, cough, pallor, hepatomegaly	TB	HIV+, calcifications	Bone marrow smear
8	19	Hypotension, fatigue, cough, fever, splenomegaly, adenopathy	Disseminated TB	HIV+, perihilar adenopathy, calcifications	Blood and bone marrow smear

Note. PCP = *Pneumocystis carinii* pneumonia; PDH = progressive pulmonary histoplasmosis; TB = tuberculosis; + = positive.

Histoplasmosis y SIDA

Am. J. Trop. Med. Hyg., 73(3), 2005, pp. 576–582

DISSEMINATED HISTOPLASMOSIS: A COMPARATIVE STUDY BETWEEN PATIENTS WITH ACQUIRED IMMUNODEFICIENCY SYNDROME AND NON-HUMAN IMMUNODEFICIENCY VIRUS–INFECTED INDIVIDUALS

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Abstract. We studied 52 patients with disseminated histoplasmosis, 30 with the acquired immunodeficiency syndrome (AIDS) (cohort 1) and 22 not co-infected with the human immunodeficiency virus (cohort 2). Demographic, clinical, laboratory, mycologic findings, as well as antifungal therapy and highly active antiretroviral (HAART), were analyzed. Skin lesions were significantly higher in cohort 1 than in cohort 2 ($P = 0.001$). Anemia, leukopenia, and an elevated erythrocyte sedimentation rate were also more pronounced in cohort 1 than in cohort 2 ($P < 0.001$). *Histoplasma capsulatum* was isolated more often in cohort 1 than in cohort 2 ($P < 0.05$) patients, but antibodies to *H. capsulatum* were detected more frequently in cohort 2 than in cohort 1 ($P < 0.05$). Itraconazole treatment was less effective in cohort 1 than in cohort 2 ($P = 0.012$). In cohort 1 patients, HAART improved response to antifungals when compared with individuals not given HAART ($P = 0.003$), who exhibited higher mortality rates ($P = 0.025$). Cohort 1 patients who were given dual antifungal and anti-retroviral therapies responded as well as the non-HIV patients in cohort 2, who were treated only with itraconazole. These results indicate the need to promote restoration of the immune system in patients with AIDS and histoplasmosis.

Histoplasmosis y SIDA

Differences in Histoplasmosis in Patients with Acquired Immunodeficiency Syndrome in the United States and Brazil

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Demographic and clinical parameters among patients with acquired immunodeficiency syndrome and histoplasmosis in Brazil and United States were compared. The Brazilian isolates were typed by restriction-fragment length polymorphism analysis and were DNA fingerprinted by random amplification of polymorphic DNA (RAPD)–polymerase chain reaction (PCR). Skin lesions occurred in 66% of Brazilian case patients, compared with 1%–7% of US case patients. Of 21 treated case patients, 4 (19%) died, a rate similar to that of the US case patients (5%–13%). By nuclear gene typing, the Brazilian isolates were equally divided between South American classes 5 and 6, and RAPD-PCR showed 18 distinct genetic fingerprints in 20 isolates. Skin lesions are more common in infection with class 2 *Histoplasma capsulatum*. The role of genetic differences in the organism as a cause for the clinical differences requires investigation.

The Journal of Infectious Diseases 2002;186:1655–60

Histoplasmosis y SIDA

Disseminated Histoplasmosis in Patients with AIDS in Panama: A Review of 104 Cases

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We identified the incidence and primary clinical characteristics of histoplasmosis in patients with acquired immunodeficiency syndrome (AIDS) in our hospital. Disseminated histoplasmosis is a common and severe disease among patients with AIDS in Panama and should be suspected for patients with a CD4 cell count of <100 cells/μL, fever, respiratory symptoms, weight loss, and diarrhea.

Clinical Infectious Diseases 2005; 40:1199–202

Table 1. Cases of histoplasmosis in patients with AIDS who were hospitalized from 1997 to 2003 in the AIDS ward of Arnulfo Arias Madrid Hospital, Panama City.

Year	No. of patients hospitalized[a]	No. (%) of patients with histoplasmosis[b]
1997	337	13 (3.86)
1998	326	29 (8.89)
1999	366	31 (8.47)
2000	372	47 (12.63)
2001	371	26 (7.0)
2002	310	18 (5.8)
2003	297	18 (6.0)
Total	2379	182 (7.65)

[a] Includes all patients admitted to the AIDS ward for any reason.

[b] Includes all patients with a culture-proven diagnosis of histoplasmosis, whether or not the patients' medical records were reviewed for the present study.

Histoplasmosis en la Infancia

Disseminated histoplasmosis in infants

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Background. Disseminated histoplasmosis usually occurs in immunocompromised patients who reside in Histoplasma capsulatum-endemic regions. It has also been described in immunocompetent infants after exposure to a large inoculum of the pathogen resulting in case fatality rates of 40 to 50%.
Methods. From 1983 through 1996 all infants with documented disseminated histoplasmosis were treated with amphotericin B followed by daily ketoconazole for 3 months. Immunologic workups were performed at the time of diagnosis and at 4 to 6 weeks of therapy. Surviving patients were followed for at least 1 year. Time to resolution of signs and symptoms was recorded, as were complications.
Results. We managed 40 patients with disseminated histoplasmosis. The age in months at diagnosis was 15.3 ± 10.2 (mean ± SD), and 24 were male. All patients were from endemic regions and they presented with fever, spleen and/or liver enlargement and hematologic abnormalities. Diagnosis was made by histology and culture of bone marrow, spleen, lymph node, bronchoalveolar or liver samples. Twenty patients presented with T cell deficiency that resolved at 4 to 6 weeks of therapy in all of the retested patients, and 10 of 12 tested patients had hyperglobulinemia that resolved. Thirty-five (88%) patients were cured by treatment; 4 died and 1 relapsed.
Conclusions. Disseminated histoplasmosis should be considered in infants from endemic areas who present with fever, hepatosplenomegaly and hematologic abnormalities. These patients develop transient hyperglobulinemia and T cell deficiency that resolve with treatment. Treatment with amphotericin B followed by an oral azole for 3 months is effective in most patients.