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MAJOR ARTICLE

Management of Histoplasmosis by Infectious Disease Physicians

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Background. The Infectious Diseases Society of America (IDSA) guidelines for the management of histoplasmosis were last revised 15 years ago. Since those guidelines were compiled, new antifungal treatment options have been developed. Furthermore, the ongoing development of immunomodulatory therapies has increased the population at increased risk to develop histoplasmosis.

Methods. An electronic survey about the management practices of histoplasmosis was distributed to the adult infectious disease (ID) physician members of the IDSA's Emerging Infections Network.

Results. The survey response rate was 37% (551/1477). Only 46% (253/551) of respondents reported seeing patients with histoplasmosis. Regions considered endemic had 82% (158/193) of physicians report seeing patients with histoplasmosis compared to 27% (95/358) of physicians in regions not classically considered endemic ($P < 0.001$). Most ID physicians follow IDSA treatment guidelines recommending itraconazole for acute pulmonary (189/253 [75%]), mild-moderate disseminated (189/253 [75%]), and as step-down therapy for severe disseminated histoplasmosis with (232/253 [92%]) and without (145/253 [57%]) central nervous system involvement. There were no consensus recommendations observed for survey questions regarding immunocompromised patients.

Conclusions. Though there are increased reports of histoplasmosis diagnoses outside regions classically considered endemic, a majority of ID physicians reported not seeing patients with histoplasmosis. Most respondents reported adherence to IDSA guidelines recommending itraconazole in each clinical situation. New histoplasmosis guidelines need to reflect the growing need for updated general guidance, particularly for immunocompromised populations.

Keywords. amphotericin; clinical practice; *Histoplasma capsulatum*; histoplasmosis; itraconazole.

Histoplasmosis is caused by the dimorphic fungal pathogen *Histoplasma capsulatum*. It exists as a mold in the environment, converting to the yeast form upon infection of a human host. Infection usually occurs by inhalation of environmental spores and can occur in both immunocompetent and immunocompromised hosts [1]. Given this mode of transmission, respiratory infection is the most common manifestation. The spectrum of disease ranges from asymptomatic to severe, life-threatening disseminated infection. The most severe manifestations occur in immunocompromised individuals, with mortality ranging from 7% to 44% [2–5].

A timely diagnosis requires high clinical suspicion by clinicians. This suspicion is frequently reliant on a patient exposure to an area considered to be endemic for *Histoplasma*—the Ohio and Mississippi river valleys. Despite ample evidence of its presence globally, *Histoplasma* is still considered by many to be predominately endemic to specific regions of North America [6, 7]. This perception can result in clinicians failing to consider histoplasmosis on a differential diagnosis, contributing to delayed diagnosis and poor outcomes.

The Infectious Diseases Society of America (IDSA) last updated clinical guidelines for the management of histoplasmosis in 2007, using literature from 1 January 1999 through 31 June 2006 [8]. Since the release of the guidelines, new treatment options have been developed. Posaconazole was approved by the United States (US) Food and Drug Administration shortly before the release of the 2007 guidelines and isavuconazole was approved in 2015. Both maintain in vitro activity against *Histoplasma* even in the setting of fluconazole resistance [9, 10], though there are limited clinical data to support their

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use in treating histoplasmosis [11–13]. Since the arrival of these new medications, there have been no changes to clinical practice recommendations [14], and very little new data have been published to guide therapy [15, 16]. Additionally, the population at risk to develop clinically significant histoplasmosis has increased substantially with millions of patients on an ever-expanding variety of immunosuppressive medications and/or with immunosuppressive medical conditions [17–19].

Limited data have been added to the histoplasmosis literature since the last IDSA guidelines were published, though physicians have gained an additional 15 years of experience managing histoplasmosis. The aim of this study was to characterize the current histoplasmosis management patterns of infectious disease (ID) physicians, identify areas of disagreement, and extract clinical insights gained from our collective experience.

METHODS

An electronic survey was distributed among the physician members of the IDSA Emerging Infections Network (EIN) who practice adult ID. EIN is an IDSA and Centers for Disease Control and Prevention (CDC)–supported provider-based surveillance network [20]. EIN has a well-established history of leveraging surveys of its membership to provide key insights into the practice of ID. Its membership represents approximately 20% of ID physicians in the US. The survey consisted of 11 questions and 1 additional space to provide free-text commentary. Five questions were case-based scenarios and the remainder referred to specific aspects of histoplasmosis management. An opt-out response was provided for physicians who do not see patients with histoplasmosis. The US Census Bureau geographic region/division [21], years of experience, and clinical practice characteristics for each EIN member were available from an existing EIN member database. The survey was distributed on 16 November 2021. Two reminder invitations were sent out for nonresponders prior to closure of the survey on 1 January 2022.

Each of the clinical scenarios was designed to suggest a specific manifestation of histoplasmosis using definitions from the current guidelines [8]. Each case also sought to reflect the often-ambiguous presentation of histoplasmosis. During development of the survey, the diagnosis in each case was agreed upon by the authors, who are ID physicians practicing in *Histoplasma*-endemic regions, regularly see patients with histoplasmosis, and have a history of histoplasmosis clinical research. The remainder of the questions were generated to inquire about real-world practice patterns regarding specific aspects of histoplasmosis management where there are few data to guide clinical decisions. The full survey is available in the Supplementary Materials.

The following US Census Bureau divisions are defined as endemic: East North Central, West North Central, East South Central, and West South Central.

RESULTS

The survey was distributed to 1477 EIN physician members with an adult ID practice who have previously responded to an EIN survey of whom 37% (551/1477) responded; 46% (253/551) of the respondents reported seeing patients diagnosed with histoplasmosis. Years of ID experience was significantly different between respondents and nonrespondents ($P < 0.001$). The only experience group with more respondents than nonrespondents was physicians with 25 years or more of ID experience (52% response rate [167/324]). No other group had a response rate higher than 37%. Baseline characteristics of survey respondents are provided in Supplementary Table 1. There was no difference in survey response between physicians practicing in endemic regions vs physicians in other areas—193/519 (37%) vs 358/948 (38%) ($P = 0.83$).

Endemicity

Survey respondents who reported seeing patients with histoplasmosis were significantly different from those who did not based on years of experience and region of practice (Table 1). In *Histoplasma*-endemic areas, 82% (158/193) of physicians reported seeing patients with histoplasmosis compared to 27% (95/358) of physicians in areas not considered endemic ($P < 0.001$). The percentages of physicians who reported seeing histoplasmosis are presented by geographic region in Figure 1 and by US state and Canadian province in Supplementary Table 2.

Management of Acute Pulmonary and Progressive Disseminated Histoplasmosis

For a patient with mild-to-moderate acute pulmonary histoplasmosis, 75% (189/253) of respondents treat with itraconazole as is recommended in both the IDSA and the European Confederation of Medical Mycology guidelines [8, 14]. Six percent (16/253) chose treatment with another azole and 4% (9/253) chose amphotericin B. Forty-seven (19%) respondents recommended no treatment for the patient in this case.

For a patient presenting with mild-to-moderate disseminated histoplasmosis in the outpatient setting, 75% (189/253) of respondents chose to treat with itraconazole in concordance with the guidelines. Fewer respondents recommended no treatment in this situation (14% [35/253]) and more recommended amphotericin B induction therapy (9% [22/253]). The remainder of respondents chose another azole.

Preferences in Azole Therapy

Most respondents chose itraconazole as their azole of choice in each clinical scenario. Preferred formulations of itraconazole were evenly split between oral solution (46% [117/253]) and capsules (43% [110/253]). A minority of physicians (7% [18/253]) preferred the newest formulation, SUBA-itraconazole. There were 6 physicians (2%) who did not treat histoplasmosis with itraconazole.

Table 1. Baseline Characteristics of Survey Respondents Who Do and Do Not See Patients With Histoplasmosis

Characteristic	Do Not See Histoplasmosis (n = 298)	See Histoplasmosis (n = 253)	*P* Value
Years of experience			
<5	43 (40)	65 (60)	**<.001**
5–14	90 (50)	92 (50)	
15–24	53 (56)	41 (44)	
≥25	112 (67)	55 (33)	
Primary employment			
Hospital/clinic	123 (57)	94 (43)	.64
University/medical school	86 (50)	87 (50)	
Private practice group	69 (54)	59 (46)	
Federal government	18 (60)	12 (40)	
Military	2 (67)	1 (33)	
Primary hospital setting			
University hospital	111 (54)	94 (46)	.51
Community hospital	84 (58)	60 (42)	
Non-university teaching hospital	69 (51)	66 (49)	
City/county hospital	12 (44)	15 (56)	
VA hospital or DOD	20 (53)	18 (47)	
Outpatient only	2 (100)	0 (0)	
Census division of practice[a]			
New England	37 (84)	7 (16)	**<.001**
Mid-Atlantic	66 (79)	18 (21)	
East North Central[b]	17 (24)	54 (76)	
West North Central[b]	8 (13)	55 (87)	
South Atlantic	55 (56)	44 (44)	
East South Central[b]	2 (10)	17 (90)	
West South Central[b]	8 (20)	32 (80)	
Mountain	19 (83)	3 (17)	
Pacific	81 (79)	21 (21)	
Canada	5 (83)	1 (17)	

Data are presented as No. (%). Values in bold are statistically significant.

Abbreviations: DOD, US Department of Defense; VA, Veterans Affairs.

[a]States in the US Census Bureau divisions are as follows: New England (Maine, New Hampshire, Vermont, Massachusetts, Rhode Island, Connecticut); Mid-Atlantic (New York, New Jersey, Pennsylvania); East North Central (Ohio, Indiana, Illinois, Michigan, Wisconsin); West North Central (Minnesota, Iowa, Missouri, North Dakota, South Dakota, Nebraska, Kansas); South Atlantic (Delaware, Maryland, District of Columbia, Virginia, West Virginia, North Carolina, South Carolina, Georgia, Florida); East South Central (Kentucky, Tennessee, Alabama, Mississippi); West South Central (Arkansas, Louisiana, Oklahoma, Texas); Mountain (Montana, Idaho, Wyoming, Colorado, New Mexico, Arizona, Utah, Nevada); Pacific (Washington, Oregon, California, Alaska, Hawaii).

[b]US Census Bureau divisions considered to be traditionally endemic for *Histoplasma*.

Itraconazole was recommended for step-down therapy for severe disseminated histoplasmosis without central nervous system (CNS) involvement by 92% (232/253) of respondents. Where severe disseminated histoplasmosis was complicated by CNS involvement, a smaller majority (145/253 [57%]) recommended itraconazole. For CNS involvement, 19% (48/253) recommended voriconazole, 5% (12/253) posaconazole, 4% (9/253) isavuconazole, and 8% (20/253) fluconazole. Continued therapy with amphotericin B was recommended by 7% (17/253) of respondents.

Antifungal preferences for these specific clinical scenarios are presented in Table 2.

Discontinuation of Antifungal Therapy in the Setting of Persistent Antigenuria

Forty-one percent (105/253) of respondents recommended to discontinue antifungal treatment after 12 months of therapy for an immunocompetent patient with disseminated histoplasmosis and resolution of symptoms but with persistent *Histoplasma* antigenuria (>19 ng/mL to 1.1 ng/mL). Twenty percent (51/253) of respondents chose to extend therapy for 1–12 months and 37% (93/253) recommended continuing treatment until antigenuria had resolved.

Management of Fibrosing Mediastinitis

Consistent with the 2007 guidelines, most respondents (170/253 [67%]) chose to recommend a stenting procedure for a patient with fibrosing mediastinitis complicated by several episodes of postobstructive pneumonia and new constriction of a main pulmonary bronchus and superior vena cava. Other options recommended were surgery (111/253 [44%]), steroids (81/253 [32%]), an azole (37/253 [15%]), amphotericin B (32/253 [13%]), rituximab (12/253 [5%]), and nonsteroidal anti-inflammatory medications (8/253 [3%]). This question allowed for multiple treatment modalities to be recommended and the totals add up to >100%.

Management of Histoplasmosis in Immunocompromised Patients

The majority of physicians that reported seeing patients with histoplasmosis (165/253 [65%]) did not recommend screening for histoplasmosis prior to patients starting immunosuppression (eg, during pretransplant evaluation, prior to starting biologics). This response did not vary by the endemicity of practice location ($P = 0.10$).

Survey respondents did not reach a majority consensus for 3 scenarios: restarting immunosuppression after a diagnosis of disseminated histoplasmosis in a patient with Crohn disease on adalimumab; recommending lifelong *Histoplasma* suppression after histoplasmosis treatment in various immunocompromising conditions; and deciding when to recommend treatment of an isolated, asymptomatic pulmonary nodule (histoplasmoma). Responses for these questions are available in Supplementary Table 3.

The question about lifelong antifungal suppression prompted 30 free-text responses. Nearly all of the responses (29/30 [97%]) commented that a more nuanced approach to recommendations was required. Examples include "decision based on level of ongoing immunosuppression," "case-by-case risks vs benefits discussion," and "highly depends on depth and duration of immunosuppression." Comments about basing recommendations on specific aspects of clinical situations continued in the last free-text box asking for general comments

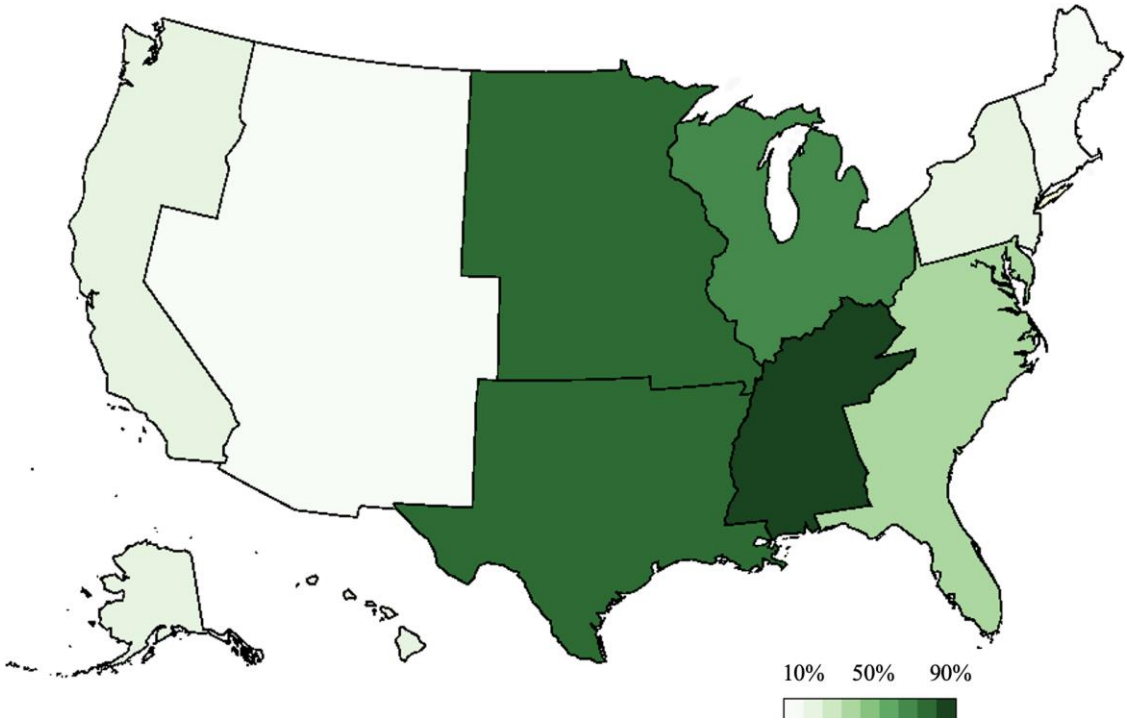

Figure 1. Percentage breakdown of survey respondents reporting seeing patients with histoplasmosis, by United States Census Bureau division.

about the survey. An additional 22 comments mentioned needing additional information in the survey clinical scenarios. Examples of these responses include: "Some of my answers would be more nuanced," "Great questions but some lack sufficient data to make a single firm conclusion," and "Several scenarios are hard to answer with absolute confidence. There are perhaps various potential peculiarities to each patient scenario that might cause me to act differently."

DISCUSSION

We report survey results for 551 physicians describing management of histoplasmosis by ID specialists. Less than half of respondents indicated that they see patients diagnosed with histoplasmosis, which limits the strength of conclusions that may be made from these data. There is a growing number of reports of locally acquired *Histoplasm*a (ie, without documented travel to an endemic region) in areas not known to be endemic, with documented cases crossing North America from Alaska to Florida [22–26]. These cases suggest an evolving geographic distribution of *Histoplasma*.

The geographic distribution of *Histoplasma* was defined in the 1950s with no systematic update since 1969 [27, 28]. These studies were based on histoplasmin skin testing rather than histoplasmosis diagnoses (incidence) or isolation of *Histoplasma* from environmental reservoirs. Despite using an indirect measure to determine geographic distribution, these historical maps have been the foundation for *Histoplasma*'s endemic mycosis

Table 2. Infectious Disease Physician Preferences in Antifungal Therapy Based on Clinical Scenario

Clinical Situation	Itraconazole	Voriconazole	Posaconazole	Isavuconazole	Fluconazole	AmB	No Treatment	Not Answered
Mild-moderate acute pulmonary histoplasmosis with symptoms lasting >1 mo	189 (75)	3 (1)	2 (<1)	0 (0)	2 (<1)	9 (4)	47 (19)	1 (<1)
Mild-moderate progressive disseminated histoplasmosis (outpatient presentation)	189 (75)	3 (1)	2 (<1)	0 (0)	1 (<1)	22 (9)	35 (14)	1 (<1)
Step-down therapy for disseminated histoplasmosis *without* CNS involvement after AmB induction	232 (92)	8 (3)	9 (4)	0 (0)	3 (1)	NA	NA	1 (<1)
Step-down therapy for disseminated histoplasmosis *with* CNS involvement after AmB induction	145 (57)	48 (19)	12 (5)	9 (4)	20 (8)	17 (7)	NA	2 (<1)

Data are presented as No. (%) of respondents (n = 253).

Abbreviations: AmB, amphotericin B; CNS central nervous system; NA, not applicable.

classification, persisting with few changes for >50 years. The maps delineated from these classical studies have been used to train generations of physicians. Efforts to better characterize endemic areas are limited by the financial impracticality of repeating the historical studies, the lack of histoplasmin availability, and, in the US, by histoplasmosis only being reportable in 13 states [29, 30]. Several research groups and the CDC have produced maps with expanded areas of likely *Histoplasma* endemicity [6, 24, 26, 31]. The data in our survey are comprised of ID physicians practicing in North America, though histoplasmosis has been reported on every continent except Antarctica [6]. Practice patterns in North America may not be applicable worldwide, though the need for better histoplasmosis data applies broadly.

Given the data suggesting an expanded geographic distribution of *Histoplasma*, it is the recommendation of the authors that histoplasmosis be broadly considered as a potential diagnosis for a patient with a compatible clinical syndrome. The amount of subsequent consideration given to a histoplasmosis diagnosis can later be adjusted after accounting for geographic, environmental (eg, employment as an excavator, spelunking enthusiast), and host risk factors (eg, immunocompromise). This recommendation is intended to mitigate diagnostic delay. Another recent EIN survey found that only 23% of ID physicians "never" or "rarely" observed a diagnostic delay when treating endemic fungal infections, including histoplasmosis [32]. The most common reason given for the diagnostic delay was failure to consider the diagnosis initially and was found to have a moderate to major impact in 66% of cases [32]. The majority of survey respondents did not recommend screening for histoplasmosis prior to the initiation of immunocompromising medications. The clinical impact of diagnostic delays combined with the low cost and minimally invasive nature of histoplasmosis screening may support consideration of more common screening in high-risk patients. It is easy to envision more widespread histoplasmosis screening in appropriate clinical scenarios, such as cryptococcus and tuberculosis, especially with additional data to support this practice and the development of improved diagnostics.

Many clinical conundrums in the management of histoplasmosis occur in the growing number of immunocompromised hosts [17]. Management decisions in this population must balance the severity of the histoplasmosis, type and degree of immunosuppression, necessity for ongoing immunosuppression (eg, transplants or rheumatologic conditions), potential for immune recovery (eg, following myeloablative chemotherapy), and potential interactions of antifungal medications (eg, triazoles with tacrolimus or antineoplastic agents [33]). There are limited data addressing these situations. Clinical trial data are often limited to immunocompromise secondary to human immunodeficiency virus [34, 35], and guideline recommendations are available specifically for this patient population [36]. The literature addressing histoplasmosis with other forms of immunocompromise is composed of retrospective, observational studies [37, 38]. The lack of majority consensus to our survey questions about immunocompromised patients is a manifestation of the lack of data available to guide complex management decisions. The free-text commentaries from our survey expressed a similar sentiment; there is limited literature to guide the management of immunocompromised patients with histoplasmosis, and updated guideline recommendation are needed to address the management of immunocompromised patients with histoplasmosis.

The 2007 IDSA guideline recommendations were followed by the majority of respondents in most of the clinical scenarios in our survey [8]. The importance of the IDSA guidelines was demonstrated explicitly by survey comments such as "I would generally refer to published guidelines for every scenario which the guidelines address" and "I follow the IDSA guidelines always." A less explicit example of guideline importance is the majority recommendation for itraconazole as step-down therapy for histoplasmosis of the CNS. Though there have been no head-to-head trials comparing itraconazole to newer azoles, voriconazole and isavuconazole are known to achieve higher concentrations in the CNS [39–41]. Better CNS penetration with antifungal medications with activity against *Histoplasma* is an attractive treatment option, though an option recommended by a minority of respondents in our survey.

CONCLUSIONS

Histoplasmosis is a challenging infection to manage and there is a paucity of research to guide management decisions. This reality reiterates the need for more investment and research into fungal pathogens, including *Histoplasma*. Medical providers need to adapt to the expanded geographical distribution of *Histoplasma* when considering fungal diagnoses. The new IDSA guidelines must reflect the growing need for general guidance for histoplasmosis management, particularly in immunocompromised populations.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Disclaimer. The findings and conclusions presented in this manuscript are those of the authors and do not necessarily represent the views of the US Centers for Disease Control and Prevention (CDC) or the US Department of Health and Human Services.

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