Supplementary Material for 2025 Clinical Practice Guideline Update by the Infectious Diseases Society of America on Histoplasmosis: Treatment of Mild or Moderate Acute Pulmonary Histoplasmosis in Adults, Children, and Pregnant People

Table of Contents

METHODS

Panel formation and conflicts of interest

The chair of the guideline panel was selected by the leadership of IDSA. Fifteen additional panelists comprised the full panel. The panel included clinicians with expertise in infectious diseases, pediatric infectious diseases, surgery, emergency medicine, microbiology, and pharmacology. Panelists were diverse in gender, geographic distribution, and years of clinical experience. Guideline methodologists oversaw all methodological aspects of the guideline development and identified and summarized the scientific evidence for each clinical question. IDSA staff oversaw all administrative and logistic issues related to the guideline panel.

All members of the expert panel complied with the IDSA policy on conflict of interest (COI), which requires disclosure of any financial, intellectual, or other interest that might be construed as constituting an actual, potential, or apparent conflict. Evaluation of such relationships as potential conflicts of interest was determined by a review process which included assessment by the Standards and Practice

Guideline Committee (SPGC) Chair, the SPGC liaison to the Guideline panel and the Board of Directors liaison to the SPGC, and if necessary, the Conflicts of Interests Task Force of the Board. This assessment of disclosed relationships for possible COI was based on the relative weight of the financial relationship (i.e., monetary amount) and the relevance of the relationship (i.e., the degree to which an independent observer might reasonably interpret an association as related to the topic or recommendation of consideration). The reader of these guidelines should be mindful of this when the list of disclosures is reviewed. See the Notes section at the end of this guideline for the disclosures reported to IDSA.

Practice recommendations

Clinical Practice Guidelines are statements that include recommendations intended to optimize patient care by assisting practitioners and patients in making shared decisions about appropriate health care for specific clinical circumstances. These are informed by a systematic review of evidence and an assessment of the benefits and harms of alternative care options [IOM 2011]. The "IDSA Handbook on Clinical Practice Guideline Development" provides more detailed information on the processes followed throughout the development of this guideline [IDSA CPG Handbook].

Approval process

Feedback was obtained from five external individual peer expert reviewers. The IDSA Standards and Practice Guidelines Committee (SPGC) and Board of Directors reviewed and approved the guideline prior to publication.

Process for updating

IDSA guidelines are regularly reviewed for currency. The need for updates to the guideline is determined by a scan of current literature and the likelihood that any new data would impact the recommendations. Any changes to the guideline will be submitted for review and approval to the appropriate Committees and Board of IDSA.

Clinical questions

Each clinical question was formatted according to the PICO style: Patient/Population (P), Intervention/Indicator (I), Comparator/Control (C), Outcome (O). For each PICO question, outcomes of interest were identified a priori and rated for their relative importance for decision-making.

Literature search

A medical librarian designed the literature searches and MeSH terms for Ovid Medline, Scopus, and Cochrane Library. The initial literature search was performed in January 2023 and then updated in January 2024. To supplement the electronic searches, reference lists of related articles and guidelines were reviewed for relevance.

(histoplasm* OR histoplasmosis OR histoplasmosis[Mesh] OR Histoplasma OR Histoplasma[Mesh])
AND
(antifungal OR antifungal agents[pharmacological action] OR azole OR azoles[Mesh] OR itraconazole OR voriconazole OR fluconazole OR posaconazole OR ketoconazole OR isavuconazole OR SUBA-itraconazole

OR amphotericin OR amphotericin B[Mesh] OR liposomal amphotericin b [supplementary concept] OR sporonox OR diflucan OR nizoral OR vfend or cresemba or isavuconazonium sulfate OR noxafil or fungizone OR ambisome OR amphocil or amphotec or abelcet)

Limits: 2006-now, humans

Study selection

Titles and abstracts were screened in duplicate for all identified citations using Rayyan [Ouzzani 2016]. All potentially relevant citations were subjected to a full-text review, using predefined inclusion and exclusion criteria tailored to meet the specific population, intervention, and comparator of each clinical question. The steps of the literature selection process were supervised and reviewed by a guideline methodologist for the final selection of the relevant articles.

The eligibility criteria below were used.

Inclusion criteria:

- *Patient population*- Humans, patients with mild or moderate histoplasmosis
- *Intervention*- Antifungal treatment
- *Outcomes*- Resolution of symptoms, mortality
- *Study design***-** Case reports and case series, English language

Exclusion criteria:

- *Patient population*- Animals, newborns, patients with severe or disseminated histoplasmosis, patients with African histoplasmosis or possible ocular histoplasmosis syndrome (POHS)
- *Study design***-** Systematic reviews (only primary studies are included), abstracts and conference proceedings, letters to the editor, editorials, and review articles; studies in languages other than English

In May 2024, another literature search was performed in Ovid Medline specific to itraconazole therapeutic drug monitoring:

("Itraconazole"[Mesh] OR itraconazole) AND ("Drug Monitoring"[Mesh] OR "drug monitoring" OR "therapeutic drug monitoring" OR TDM)

Limits: None

Data extraction and analysis

A guideline methodologist in conjunction with panelists extracted the data for each pre-determined patient-important outcome. If a relevant publication was missing raw data for an outcome prioritized by the panel, an attempt was made to contact the author(s) for the missing data.

Evidence to decision

Guideline methodologists prepared the evidence summaries for each question and assessed the risk of bias and the certainty of evidence. The certainty of evidence was determined first for each critical and important outcome and then for each recommendation using the GRADE approach for rating the

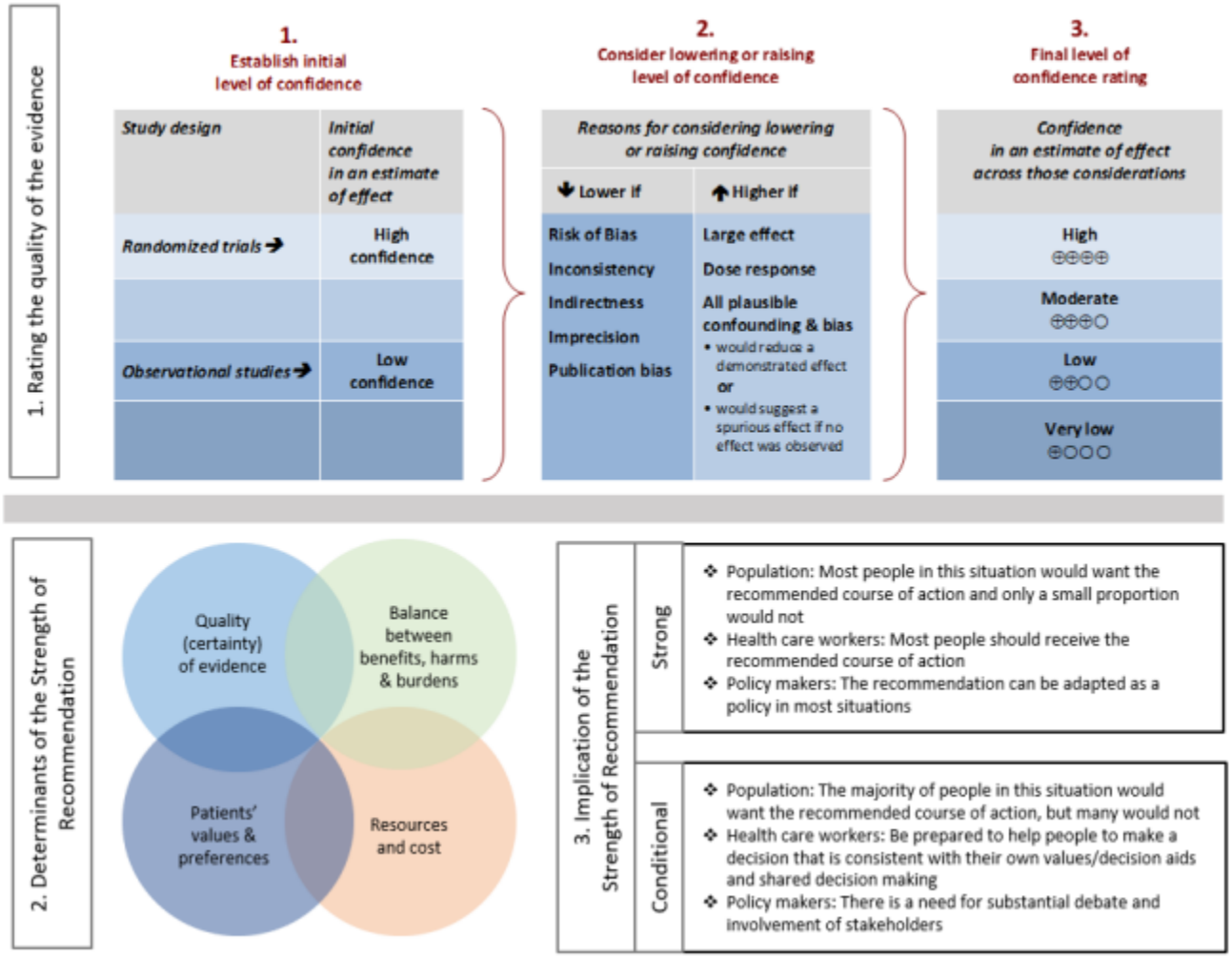
confidence in the evidence [Guyatt 2008, Schunemann 2020]. Evidence profiles were developed using the GRADEpro Guideline Development Tool [Guyatt 2008] and reviewed by panel members responsible for each PICO.

The Evidence to Decision framework [GRADEpro] was used to translate the evidence summaries into practice recommendations. All recommendations were labeled as either “strong” or “conditional” according to the GRADE approach [IDSA CPG Handbook]. The words “we recommend” indicate strong recommendations and “we suggest” indicate conditional recommendations. Supplementary Figure 1 provides the suggested interpretation of strong and conditional recommendations for patients, clinicians, and healthcare policymakers. For recommendations where the comparator treatment or tests are not formally stated, the comparison of interest is implicitly referred to as “not using the intervention” (either not using a specific treatment or a diagnostic test).

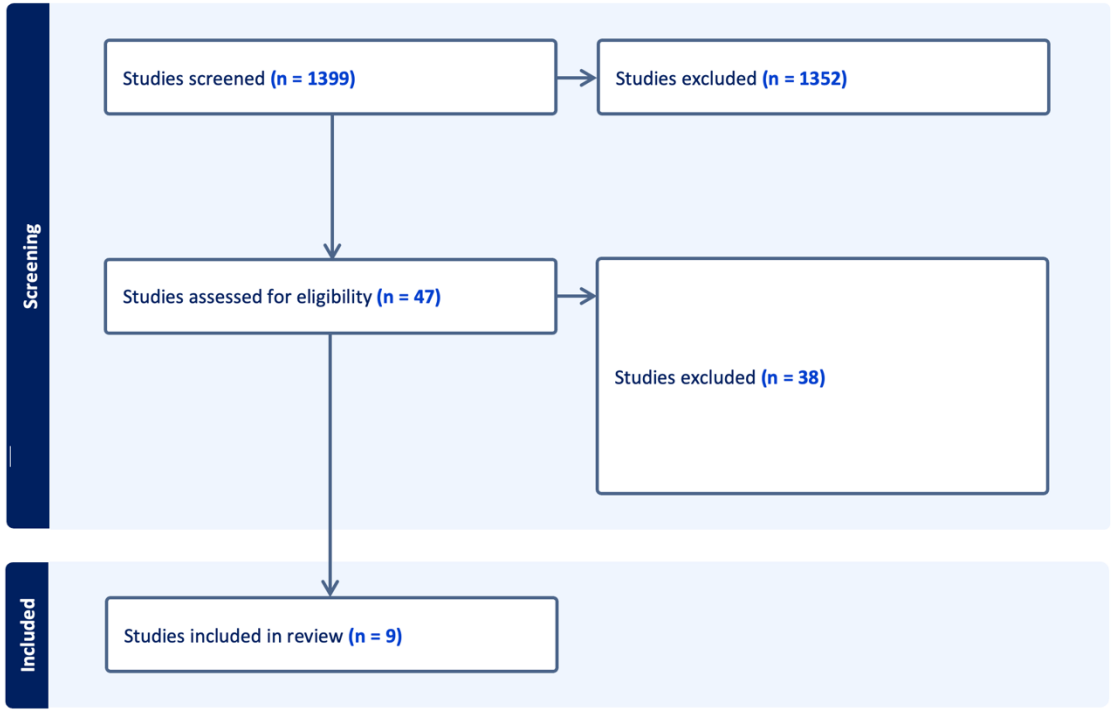
All members of the panel participated in the preparation of the draft guideline and approved the recommendations.

TABLES AND FIGURES

Supplementary Figure 1. Approach and implications to rating the quality of evidence and strength of recommendations using GRADE methodology (unrestricted use of figure granted by the U.S. GRADE Network)



Supplementary Figure 2. PRISMA flow diagram



Supplementary Table 1. Characteristics and results of included studies

Outcome: Symptom resolution/Radiographic regression

Author, year of publication	Location, years of data collection	Study design	Population, diagnosis, and age	Intervention	Follow-up	Results/Notes
Brodsky 1973	USA (OH); outbreak at a junior high 1970	Retrospective cohort	**353** symptomatic patients (5 people hospitalized but only 1 for >1 week) 6th-8th graders, faculty and staff (exacts unclear)	No treatment No patients required treatment with amphotericin B.	Questionnaire was filled out 3 weeks after the peak of the epidemic.	>75% of persons affected were ill for 1 week or less. All affected recovered completely within 2 months.

Chamany 2004	USA (IN); outbreak at a high school November to December 2001	Retrospective cohort	682 study participants, 523 with serologic evidence of infection, **355** of whom developed symptoms; 98 had an underlying illness (4 receiving immunocompromising medications) Median age 16 years (range 8-80)	Most not treated Clinical care was sought by 170 patients; 13 received an antifungal-fluconazole, itraconazole, ketoconazole, and/or amphotericin B	Questionnaire asking about illness in the previous month	170/355 sought clinical care; 75 received a chest radiograph and 85 were given an antibiotic (78 received an antibacterial agent, 13 received an antifungal agent). 9 patients were hospitalized (3/9 immunocompromised).
Dismukes 1992	USA (14 centers) Unclear	Prospective, nonrandomized, open-label trial	37 non-pregnant adults with confirmed histoplasmosis (chronic cavitary in 20, **mediastinal or nodular parenchymal disease in 7** [unable to determine severity], extrapulmonary localized or disseminated disease in 10)	All treated All treated with itraconazole 200-400 mg/d for a median of 9 months	Median duration of post-treatment evaluation for successfully treated patients was 12.1 months.	Treatment was successful (cured) in all 7 patients with mediastinal or nodular parenchymal disease. All patients who failed treatment had chronic cavitary disease.
Hess 2017	USA (IA) 2010-2015	Case report (part of a case series)	**1** pediatric oncology patient with acute pulmonary histoplasmosis 8 years	All treated Itraconazole	Follow-up testing	Improvement
Muhi 2019	Guatemala (treated in Australia) 2018	Case report	**2** cases of mild acute histoplasmosis (part of an outbreak in a documentary film crew) in patients with no significant past medical history 33 and 54 years	No treatment Supportive care, no antifungal treatment	Monitoring in hospital for 72 hours, then follow-up "correspondence" at 4 weeks	Significant improvement during monitoring and confirmed recovery at follow-up.
Oulette 2019	USA (OH) 2008-2014	Retrospective review	73 children with proven/probable histoplasmosis (all symptomatic), **52** of which manifested as pulmonary (7/52 immunocompromised); 58/73 had mild or moderate disease, though unable to determine severity of pulmonary patients and unable to stratify outcomes by severity Median age 13 years (range 3-18)	Some treated, some not Of those with acute pulmonary histoplasmosis, 6 received L-AmB, 24 itraconazole, 1 voriconazole. 21 did not receive antifungals (including 9 patients with mild-to-moderate disease).	Medical record review for outpatient follow-up (if present) for up to 2 years after diagnosis or completion of therapy, whichever was longer. For *all* patients who did not receive treatment (n=24), 17 had follow-up info available, which occurred at a median of 54 days (IQR 18-77) after diagnosis.	7/9 patients with mild-to-moderate acute pulmonary histoplasmosis who did not receive antifungals had follow-up information available, and all of them experienced clinical improvement. All patients with evaluable acute pulmonary histoplasmosis showed improvement at follow-up. Over the entire cohort, immunocompromised children received a longer duration of antifungal therapy than non-immunocompromised children (323 vs. 91 days, p = 0.002) and were more likely to have disseminated histoplasmosis. The median duration of antigenuria (403 vs. 120 days) and antigenemia (451 vs. 149 days) were longer in immunocompromised children compared to non-immunocompromised. No immunocompromised child who received antifungal therapy experienced recurrence up to 2 years after their initial diagnosis. Itraconazole TDM was performed for 30 patients after a median of 20 days of therapy. Initial serum itraconazole concentrations were therapeutic for 26 (87%) patients, 19 of whom achieved a therapeutic level while receiving the capsule formulation.

Staffolani 2020	Cluster tied to Ecuador, others Panama, Bolivia, Mexico, Cuba, South America (treated in Italy) 2005-2015	Retrospective case series	23 cases of acute histoplasmosis (2 immunocompromised) presenting to hospital or outpatient clinic; 7 admitted (severity undetermined), **16** treated as outpatients (presumably mild/moderate) Mean age of Ecuador cluster 38.5 years (range 23-57); mean age of others 46.7 years (30-71)	Some treated, some not 13/23 treated with itraconazole. At least 1 of 2 immunocompromised received treatment.	Serology performed at 12-month follow-up	All patients recovered, though 9 had persistence of radiological findings. Serology at follow-up was negative for all.
Wheat 1981	USA (IN); outbreak in Indianapolis, with 100,000 presumed infected 1978-1979 (nearly 1 year)	Retrospective and prospective outbreak study	435 cases presenting to a hospital, 46 with progressive disseminated infection, 31 of whom were immunocompromised (hematologic malignancy or significant steroid/cytotoxic meds); 285 with proven, highly suggestive, or presumptive acute respiratory histoplasmosis; 54 with asymptomatic infection	Some treated, some not 43/435 treated	Some had follow-up during the subsequent year	>300 hospitalized, 15 patients died due to histoplasmosis; 7 immunocompromised disseminated cases recovered without amphotericin B treatment. In all comers, symptom duration was >1 month in 35%.

Outcome: Mortality

Author, year of publication	Location, years of data collection	Study design	Population, diagnosis, and age	Intervention	Follow-up	Results/Notes
Brodsky 1973	USA (OH); outbreak at a junior high 1970	Retrospective cohort	**353** symptomatic patients (5 people hospitalized but only 1 for >1 week) 6th-8th graders, faculty and staff (exacts unclear)	No treatment No patients required treatment with amphotericin B.	Questionnaire was filled out 3 weeks after the peak of the epidemic.	No deaths
Chamany 2004	USA (IN); outbreak at a high school November to December 2001	Retrospective cohort	682 study participants, 523 with serologic evidence of infection, **355** of whom developed symptoms; 98 had an underlying illness (4 receiving immunocompromising medications) Median age 16 years (range 8-80)	Some treated, some not Clinical care was sought by 170 patients; 85 of those received an antibiotic (13/85 received an antifungal-fluconazole, itraconazole, ketoconazole, and/or amphotericin B); 9	Questionnaire asking about illness in the previous month	No deaths

				patients were hospitalized (3/9 immunocompromised)		
Dismukes 1992	USA (14 centers) Unclear	Prospective, nonrandomized, open-label trial	37 non-pregnant adults with confirmed histoplasmosis (chronic cavitary in 20, **mediastinal or nodular parenchymal disease in 7** (unable to determine severity), extrapulmonary localized or disseminated disease in 10)	All treated All treated with itraconazole 200-400 mg/d for a median of 9 months	Median duration of post-treatment evaluation for successfully treated patients was 12.1 months.	No deaths in patients with acute pulmonary histoplasmosis.
Hess 2017	USA (IA) 2010-2015	Case report (part of a case series)	1 pediatric oncology patient with acute pulmonary histoplasmosis 8 years	All treated Itraconazole	Follow-up testing	No deaths
Muhi 2019	Guatemala (treated in Australia) 2018	Case report	2 cases of mild acute histoplasmosis (part of an outbreak in a documentary film crew) in patients with no significant past medical history 33 and 54 years	No treatment Supportive care, no antifungal treatment	Monitoring in hospital for 72 hours, then follow-up "correspondence" at 4 weeks	No deaths
Olson 2011	USA (MN) 1998-2009	Retrospective review	26 immunocompromised (rheumatoid arthritis) adults with new histoplasmosis (*approximately* 14 non-severe pulmonary histoplasmosis) Mean age 59.6 years	Most treated 24/26 received antifungal therapy (diagnosis in question for 1 of 2 untreated)	Mean follow-up of 2.1 years	No deaths attributable to histoplasmosis
Oulette 2019	USA (OH) 2008-2014	Retrospective review	73 children with proven/probable histoplasmosis (all symptomatic, 58 mild/moderate), 52 of which manifested as pulmonary (7/52 immunocompromised); 58/73 had mild or moderate disease, though unable to determine severity of pulmonary patients and unable to stratify outcomes by severity Median age 13 years (range 3-18)	Some treated, some not Of those with acute pulmonary histoplasmosis, 6 received L-AmB, for a median duration of 6 days, 24 itraconazole for ~90 days, 1 voriconazole. 21 did not receive antifungals (including 9 patients with mild-to-moderate disease).	Medical record review for outpatient follow-up (if present) for up to 2 years after diagnosis or completion of therapy, whichever was longer For *all* patients who did not receive treatment (n=24), 17 had follow-up info available, which occurred at a median of 54 days (IQR 18-77) after diagnosis.	No deaths attributable to histoplasmosis.
Staffolani 2020	Cluster tied to Ecuador, others	Retrospective case series	23 cases of acute histoplasmosis (2	Some treated, some not	Serology performed at 12-month follow-up	No deaths

	Panama, Bolivia, Mexico, Cuba, South America (treated in Italy) 2005-2015		immunocompromised) presenting to hospital or outpatient clinic; 7 admitted (severity undetermined), 16 treated as outpatients (presumably mild/moderate) Mean age of Ecuador cluster 38.5 years (range 23-57); mean age of others 46.7 years (30-71)	13/23 treated with itraconazole. At least 1 of 2 immunocompromised received treatment.		

Outcome: Toxicity

Author, year of publication	Location, years of data collection	Study design	Population, diagnosis, and age	Intervention	Follow-up	Results/Notes
Dismukes 1992	USA (14 centers) Unclear	Prospective, nonrandomized, open-label trial	37 non-pregnant adults with confirmed histoplasmosis (chronic cavitary in 20, mediastinal or nodular parenchymal disease in 7, localized or disseminated disease in 10)	All treated All treated with itraconazole 200-400 mg/d for a median of 9 months	Median duration of post-treatment evaluation for successfully treated patients was 12.1 months.	25/85 exhibited an adverse effect. Itraconazole was stopped in 1 patient with chronic cavitary disease due to toxicity.

Supplementary Table 2. GRADE Evidence Profile: In patients presenting with mild or moderate acute pulmonary histoplasmosis, should antifungal treatment be given for resolution of symptoms?

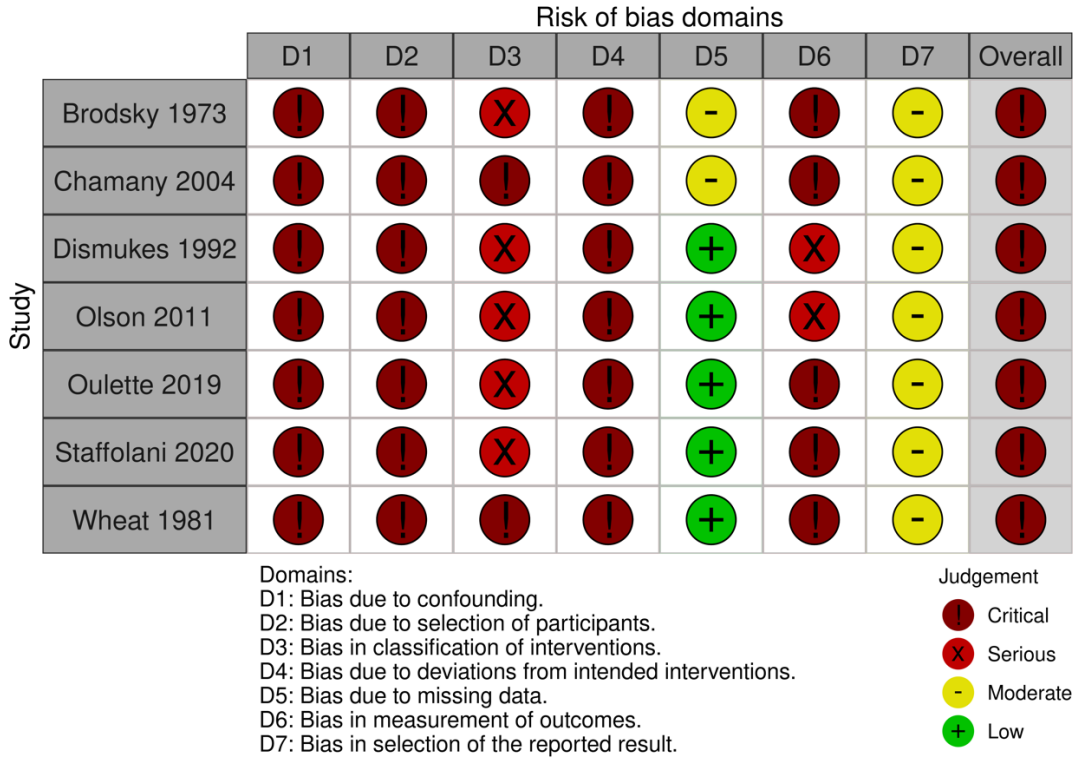
Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Resolution of symptoms									
8 [Brodsky 1973, Chamany 2004, Dismukes 1992, Hess 2017, Muhi 2019, Oulette 2019, Staffolani 2020, Wheat 1981]	non-randomized studies	very serious[a]	serious[b]	not serious	serious[c]	none	In one of the outbreak studies, 353 people were symptomatic but received no treatment, and >75% were ill for 1 week or less, all recovering within 2 months. In another outbreak, only 13/682 participants with serologic evidence of infection received an antifungal. In the largest outbreak, of over 100,000 presumed infected, only 43 received treatment. Several studies reported treatment of individuals with immunocompromising conditions.	⨁◯◯◯ Very low	IMPORTANT
Toxicity									
1 [Dismukes 1992]	non-randomized studies	very serious[a]	not serious	serious[d]	extremely serious[c]	none	37 patients were treated with itraconazole 200-400 mg/day for a median 9 months, and itraconazole was stopped in 1/37 patients due to toxicity.	⨁◯◯◯ Very low	IMPORTANT
Mortality									
8 [Brodsky 1973, Chamany 2004, Dismukes 1992, Hess 2017, Muhi 2019, Olson 2011, Oulette 2019, Staffolani 2020]	non-randomized studies	very serious[a]	serious[b]	not serious	extremely serious[c]	none	No deaths attributable to histoplasmosis in any study regardless of whether patients were treated.	⨁◯◯◯ Very low	CRITICAL

CI: confidence interval

Explanations

a. According to ROBINS-I and JBI Checklist for Case Reports assessments
Patients in an outbreak study have a higher inoculum than those in case series.
b. Small number of events
c. Indirect population

Supplementary Table 3. Risk of bias for included studies*



*In addition to the studies in Supplementary Table 3, risk of bias was assessed as high for 2 case reports (Hess 2017, Muhi 2019) according to the JBI Checklist.

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