Supplementary Material for 2025 Clinical Practice Guideline Update by the Infectious Diseases Society of America on Histoplasmosis: Treatment of Asymptomatic *Histoplasma* Pulmonary Nodules (Histoplasmomas) in Adults, Children, and Pregnant People

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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. Additional literature searches specific to latent reactivation of infection and coccidioidomycoses (as potential indirect evidence) were also conducted. 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
- *Intervention*- Antifungal treatment
- *Outcomes*- Possible late reactivation
- *Study design***-** Case reports and case series, English language

Exclusion criteria:

- *Patient population*- Animals, newborns, patients with African histoplasmosis or possible ocular histoplasmosis syndrome (POHS)
- *Outcomes*- Unlikely late reactivation
- *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

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

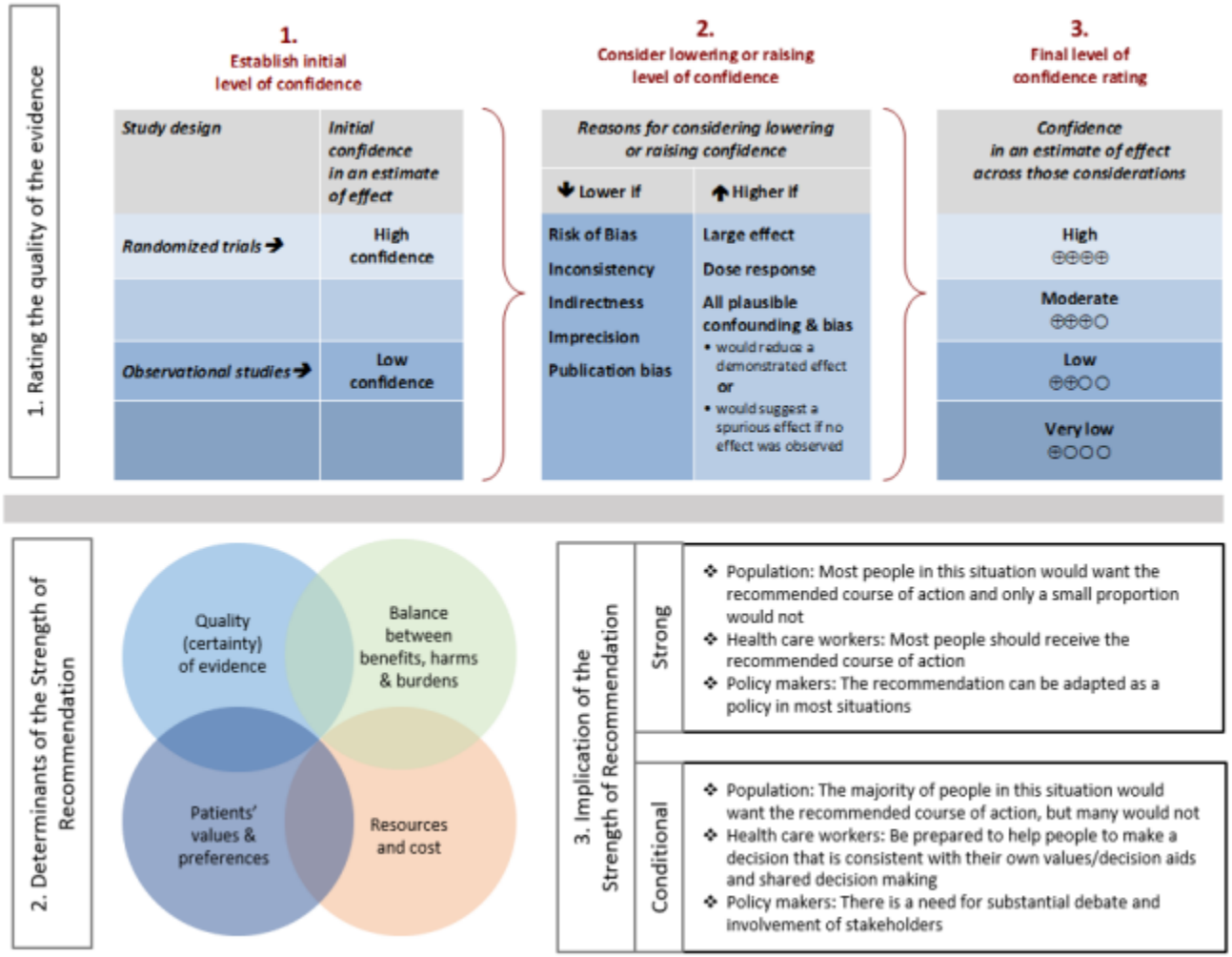
Guideline methodologists prepared the evidence summaries for each question and assessed the risk of bias and the certainty of evidence. The certainty of evidence was determined first for each critical and important outcome and then for each recommendation using the GRADE approach for rating the confidence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

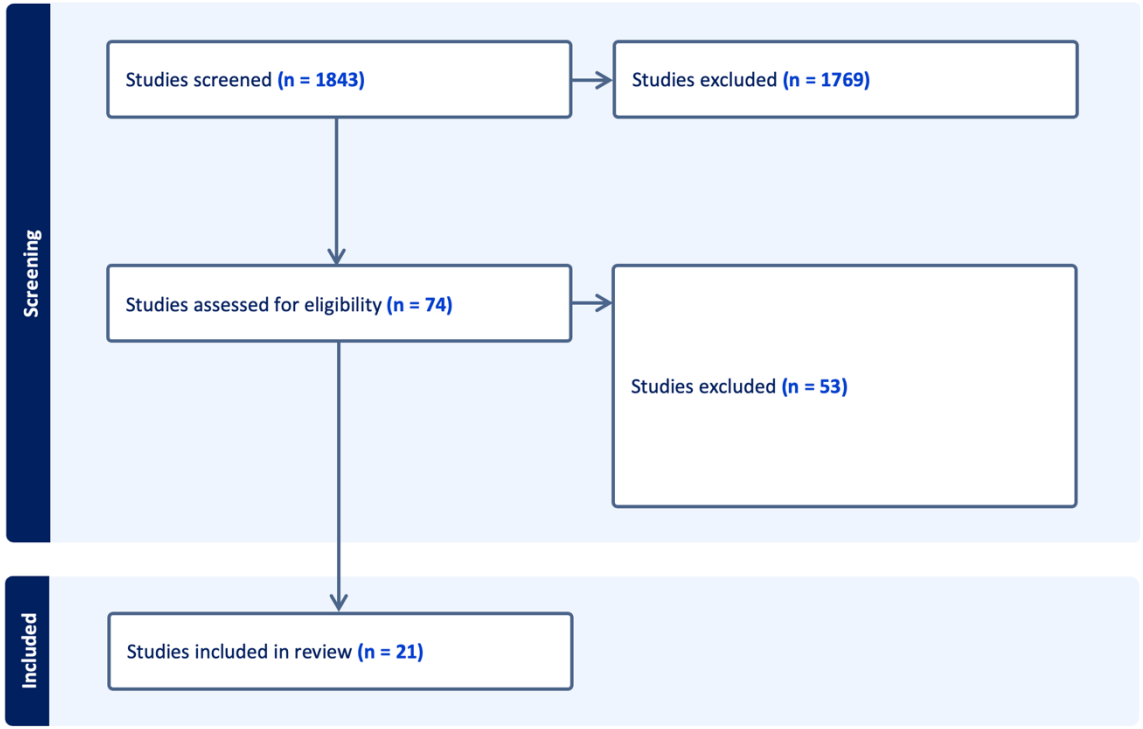
All members of the panel participated in the preparation of the draft guideline and approved the recommendations.

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: Progression to disseminated disease/significant pulmonary disease

Author, year of publication	Location, years of data collection	Study design	Population, diagnosis, and age	Follow-up	Reference standard	Results/Notes
Demkowicz 2021	USA 2006-2016	Retrospective review	62 Patients with a diagnosis of histoplasmoma, Histoplasma granuloma, or hyalinized granuloma with Histoplasma; 42 specimens with available slides from lymph node, lung,	1 year following surgery	Surgical pathology reports used to determine the type and anatomic location of the granuloma; if the slides were available for review (42/62), the tissue type containing the granuloma was confirmed and the degree of resolution (the grade).	23/62 received antifungals (11 of whom were transplant recipients). All patients with a positive clinical lab were treated. None developed progressive or disseminated histoplasmosis. 39/62 patients did not receive antifungals and none developed progressive or disseminated histoplasmosis.

			lung and associated lymph node, fibrous nodule, soft tissue, spleen, or spleen and associated lymph node Unclear		Medical records for the year following surgery were reviewed. **Grade 1** (n = 3): **Active** granulomas ± necrosis with minimal-to-no fibrous rim formation **Grade 2** (n = 19; **resolving**): Minimal to moderate granulomatous inflammation remaining associated with a well-developed fibrous rim **Grade 3** (n = 20; **resolved**): No granulomatous inflammation remained and a well-developed fibrous rim present, usually with associated clusters or lymphocytes	
Hess 2017	USA (Iowa)	Case series	2 pediatric oncology patients who developed pulmonary nodules (suspected reactivation of latent infection); neither presented with pulmonary symptoms 14 and 16 years	Unclear	Positive serum antibodies and CT imaging	Both patients received itraconazole and showed improvement on follow-up testing (chest CT showed decreased nodule size and serum antibodies decreasing titers).

Outcome: Reactivation of latent disease

Author, year of publication	Location, years of data collection	Study design	Population, diagnosis, and age	Time delay between exposure and reactivation	Location of (presumed) initial exposure	Results/Notes
Alamri 2021	Saudi Arabia	Case report	1 heart transplant recipient outside known endemic areas 68 years	2 years	India (LVAD insertion); ruled out donor-derived infection	1 presumed reactivation in post-cardiac surgery patient
Anderson 2010	USA (Atlanta, GA) 2004-2007	Retrospective review/Case series	27 patients with histoplasmosis (19 proven, 8 probable histoplasmosis) in a nonendemic area; all HIV positive Median 41.6 years (range 27-55)	Unclear	8 were from Latin America (5 from Mexico, 2 Guatemala, 1 Honduras), 5 were known to be from or to have lived 1+ year in endemic areas in the US (1 AL, 1 KY, 1 IN, 1 Michigan, 1 Mississippi), 6 Atlanta natives or other nonendemic area, 8 US natives but birthplace and other geographical history unknown	27 HIV positive patients with histoplasmosis in nonendemic area; "…it is probable that these patients in our study such as those from Latin America had imported histoplasmosis."
Antinori 2006	Europe 1984-2004	Review of published cases and case reports, including 4 new cases	72 patients with HIV-associated histoplasmosis reported in Europe, 65 travel- or immigration-related Median age 35 years (range 24-65)	Median interval of 24 months (range 1-24 months)	South America, Africa, USA, Southeast Asia	65 patients with likely reactivation of latent infection
Ashbee 2008	Germany, Italy, UK, France, Belgium, Sweden, Switzerland,	Survey (some retrospective data and some prospective data)	118 patients with proven or probable histoplasmosis (62 with disseminated disease, 31 acute pulmonary infection, 6 chronic pulmonary infection, 2 localized disease, and 17 incidental);	2 months to 5+ years, even exceeding 50 years	Africa, North America, Central America, South America, India, Pakistan and Myanmar, China, Southeast Asia	29 patients with very likely reactivation of latent histoplasmosis with possibly an additional 36. Underlying diseases or predisposing factors in disseminated disease

	Austria, Bulgaria, Turkey 1995-1999		26 primary infections/within 2 months of travel to endemic area, 36 within 2 months to 5 years of travel, 29 5+ years after travel, 27 unknown; 43 patients HIV positive Almost half of individuals were in the age range 21-40 years; some children included.			included: HIV infection (n = 42), COPD (n = 2), leukemia (n = 1), liver transplantation (n = 1), and SLE (n = 1).
Bourgeois 2011	France 1995-2006	Retrospective case series	7 patients with histoplasmosis diagnosed in a non-endemic area (2 born in endemic areas but living in France for 7 and >25 years, respectively, and no return to endemic area; 3 living in endemic areas at the time of diagnosis but monitored in France for HIV infection; 2 previously lived in endemic areas (4-7 years prior); 6/7 HIV positive Median 44 years	A few months to >25 years (4 years, 7 years, 7 years, >25 years, a few months, a few months, a few months)	Cameroon, Cambodia, other endemic areas	Presumably 4 cases of latent reactivation
Buitrago 2010	Spain 2006-(approx.) 2010	Retrospective case series	30 patients with imported histoplasmosis 29/30 proven, 29/30 with AIDS) Median 34 years (range 22-54)	Unclear	South America (mostly Ecuador), Africa	30 cases of latent reactivation of histoplasmosis
Carmans 2020	Belgium	Case report	1 kidney liver transplant patient with disseminated histoplasmosis in a nonendemic area 63 years	3 years (probably)	Probably acquired in Northern America, Suriname or Indonesia many years prior to transplantation with reactivation 3 years after transplantation	Probable reactivation in a nonendemic area (though donor-derived nor autochthonous infection could not be definitely excluded)
Choi 2019	USA (Southern CA)	Case report	1 patient with HIV in a non-endemic area who developed disseminated histoplasmosis and coinfection with disseminated nontuberculous mycobacteria 50 years	>20 years	OH or GA	Patient with AIDS in a non-endemic area who developed disseminated histoplasmosis/Histoplasma capsulatum and coinfection with disseminated nontuberculous mycobacteria; patient presented with generalized weakness and productive cough with clear-yellow sputum without hemoptysis for 1 month; fevers, chills, rigors for 1 week; and 15-pound unintentional weight loss (i.e., not asymptomatic). Patient was born in OH but moved to CA at 2yo, had remote military service in GA in his 20s but otherwise never left CA.
Gandhi 2015	USA (NYC)	Case series	2 cases of reactivated histoplasmosis (immigrant from Peru 20 years prior; immigrant from Ecuador 4 years prior) with risk factors of HIV and immune-suppressive agents 77 years and 27 years	20 years and 4 years	Peru and Ecuador	2 cases of reactivation (immigrant from Peru 20 years prior; immigrant from Ecuador 4 years prior) with risk factors of HIV and immune-suppressive agents
Garcia-Marron 2008	Spain	Case report	1 non-immunosuppressed patient who was a chronic alcoholic and smoker and developed chronic cavitary pulmonary histoplasmosis 46 years	10+ years	Venezuela	Latent reactivation of histoplasmosis

Hess 2017	USA (Iowa)	Case series	3 pediatric oncology patients with suspected latent reactivation of pulmonary histoplasmosis (2 with pulmonary nodules) 8, 14, and 16 years	Unknown	Unknown	Latent reactivation of histoplasmosis
Jain 2006	USA (CA)	Case report	1 patient with reactivation of latent histoplasmosis after anti-TNF-alpha therapy 40 years	5 years	"An area endemic for Histoplasma capsulatum," specific area not stated	Reactivation of latent histoplasmosis after anti-TNF-alpha therapy
Lucey 2018	UK	Case report	1 non-HIV patient with latent reactivation of histoplasmosis/progressive disseminated histoplasmosis 62 years	Either 6 months or 48 years	Bangladesh	Reactivation of latent histoplasmosis in a non-HIV patient in a nonendemic area
Martin-Iguacel 2014	Denmark 2011	Case report	1 patient with HIV and progressive disseminated histoplasmosis in a non-endemic area 30 years	2+ years	Trinidad and Tobago	Case in a nonendemic area
Norman 2009	Spain (Madrid) 1996-2006	Case series	10 patients with histoplasmosis (5 HIV-positive all with progressive disseminated disease and 5 HIV-negative all with pulmonary disease; 4 immigrants, 1 expatriate, 5 travelers) Age range: 26-59 years	>5 years for 3 migrant patients	Spain (n = 4), Mexico and south USA, Peru, Costa Rica/French Guyana/Ecuador/Argentina, El Salvador, Panama, Ecuador	Imported histoplasmosis, presumably latent reactivation in all migrants (though acute infection could not be ruled out in 1)
Peigne 2011	Metropolitan France 2 time periods: 1985-1994 and 1997-2006	Retrospective analysis/Case series	104 patients with AIDS-related histoplasmosis in a non-endemic area; 93 with available travel history, 55 of whom with apparent latent reactivation	1-10 years for 42 patients, >10 years for 13 patients (longest time interval recorded was 15 years)	Mostly Africa and French Guiana	Cases in nonendemic areas, ~50% of cases due to latent reactivation
Prakash 2019	USA (CA)	Case report	1 patient with disseminated histoplasmosis and cryptococcal meningitis 51 years	Unclear	Born in Guam, stationed in TX, AZ, and KS	Case in a non-endemic area/likely reactivation of latent histoplasmosis
Sani 2018	USA (AZ)	Case report	1 patient with Behcet's disease receiving TNFi therapy who developed disseminated histoplasmosis 44 years	1 year	TX	Possible reactivation of histoplasmosis
Wallis 2004	USA (unclear where within USA) 1998-2002	Case series	42 patients treated with TNF antagonists (etanercept and infliximab) plus other immunomodulatory agents (data from FDA Adverse Event Reporting System)	Unclear	Unclear	Possible reactivation of histoplasmosis (insufficient data to determine)

Outcome: Possible predisposing factors

Consider the table above along with the study below.

Author, year of publication	Location, years of data collection	Study design	Population, diagnosis, and age	Results/Notes
Hage 2010	USA (IN)	Case series	19 patients with histoplasmosis, all diagnosed while receiving TNF blockers (9 of whom had history of or probable exposure to Histoplasma); most were receiving add'l immunosuppressive agents Age range 8-66 years (5 children <18 years)	TNF blockers and other immunosuppressive agents as risk factors

Supplementary Table 2. GRADE Evidence Profile: In patients with asymptomatic, previously untreated *Histoplasma* pulmonary nodules (histoplasmomas), for which patients should antifungal treatment be initiated?

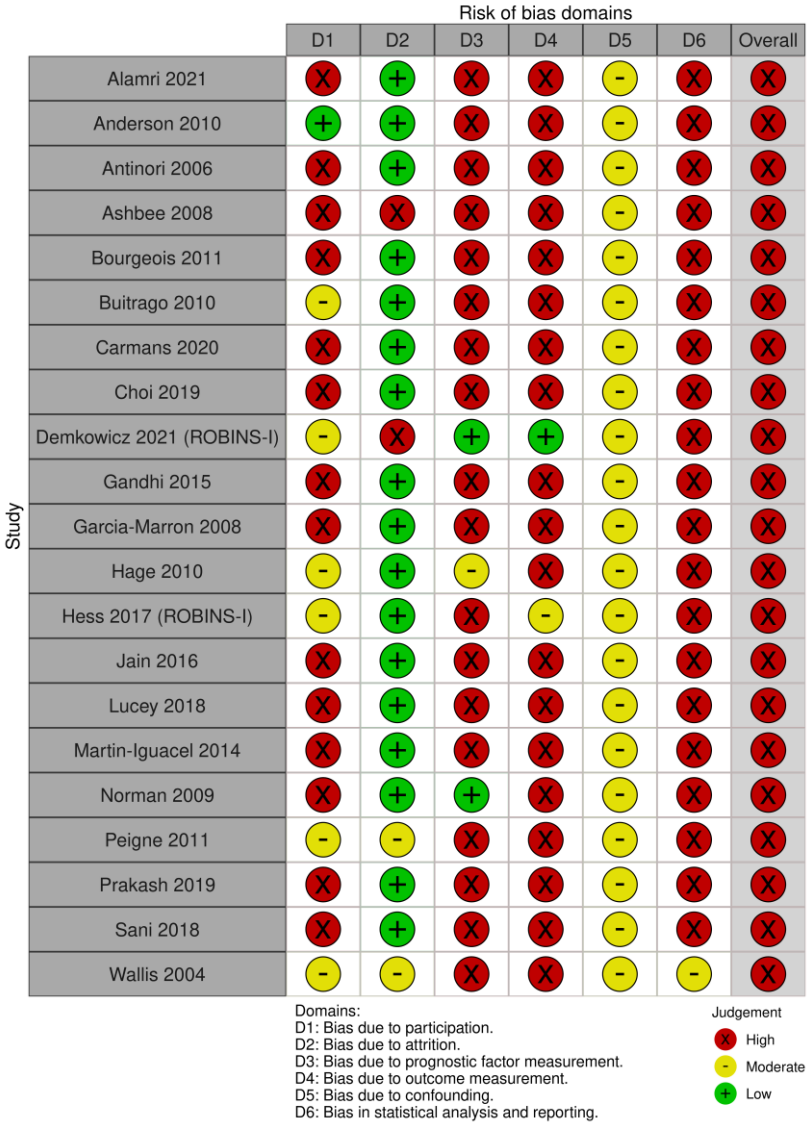
Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Progression to disseminated disease/significant pulmonary disease									
2 [Demkowicz 2021, Hess 2017]	non-randomized studies	very serious[a]	not serious	not serious	very serious[b]	none	In Demkowicz 2021, 39 of 62 patients with pulmonary granulomas did not receive antifungal treatment and did not have reactivation within 12 months after diagnosis. Hess 2017 presented 2 patients with pulmonary nodules who were treated with itraconazole and showed improvement on follow-up testing.	⊕◯◯◯ Very low	CRITICAL
Reactivation of latent disease									
19 [Alamri 2021, Anderson 2010, Antinori 2006, Ashbee 2008, Bourgeois 2011, Buitrago 2010, Carmans 2020, Choi 2019, Gandhi 2015, Garcia-Marron 2008, Hess 2017, Jain 2006, Lucey 2018, Martin-Iguacel 2014, Norman 2009, Peigne 2011, Prakash 2019, Sani 2018, Wallis 2004]	non-randomized studies	very serious[a]	not serious	not serious	very serious[b]	none	19 studies provided evidence of possible or probable latent reactivation of infection in at least 276 patients.	⊕◯◯◯ Very low	CRITICAL
Possible predisposing factors									
19 [Alamri 2021, Anderson 2010, Antinori 2006, Ashbee 2008, Bourgeois 2011, Buitrago 2010, Carmans 2020, Choi 2019, Gandhi 2015, Garcia-Marron 2008, Hage 2010, Hess 2017, Jain 2006, Lucey 2018, Martin-Iguacel 2014, Norman 2009, Peigne 2011, Prakash 2019, Sani 2018, Wallis 2004]	non-randomized studies	very serious[a]	not serious	not serious	very serious[b]	none	19 studies noted various immunocompromising conditions as possible predisposing factors for reactivation. Immunocompromising conditions most often cited included HIV infection and immunomodulatory agents. Some case reports also named malignancy, heart transplant, renal transplant, and excessive alcohol use as possible predisposing factors.	⊕◯◯◯ Very low	IMPORTANT

CI: confidence interval

Explanations

a. According to QUIPS and ROBINS-I assessments
b. Small sample size/number of events

Supplementary Table 3: Risk of bias for included studies



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