# Histoplasmosis: Pulmonary Nodules & Mild/Moderate Disease

Severity definitions, treatment of asymptomatic pulmonary nodules and mild/moderate acute pulmonary histoplasmosis, immunocompromise risk stratification, and itraconazole dosing/monitoring.

**2025 IDSA Guideline Update**
Histoplasmosis — Part 1 (Nodules & Mild/Moderate Pulmonary Disease)
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FORMAT *4 GRADE recommendations — all conditional strength, very low certainty of evidence; shared decision-making emphasized throughout.*

## 1 Severity Definitions

| CATEGORY | DEFINITION |
|---|---|
| Asymptomatic | No symptoms but evidence of recent/active infection — new or progressive imaging abnormality, urine/serum antigen, high-titer (≥1:32) or rising CF antibody, or H-band by immunodiffusion |
| Mild | Cough, fever, dyspnea, or chest discomfort that does **not** interfere with normal activities |
| Moderate | Symptoms significant enough to interfere with normal activities; may need low-flow $O_2$ or hospitalization |
| Severe | Respiratory failure requiring substantial supplemental $O_2$; significant weight loss/malaise; hospitalization ± ICU (outside scope of this update) |

## 2 Asymptomatic Pulmonary Nodules (Histoplasmomas)

| STATEMENT | STRENGTH |
|---|---|
| **R1** — Noncalcified nodule(s), no other active sites, or known untreated prior infection: **suggest against** routine treatment to prevent reactivation<br>Calcified-only nodules → no treatment. High/moderate immunocompromise risk (Table below) → closely monitor or consider treatment. Pregnancy: weigh benefit/harm with MFM + ID consultation; avoid azoles in 1st trimester, use liposomal amphotericin B if treatment needed. | Conditional<br>Very low |

## 3 Mild Acute Pulmonary Histoplasmosis

| STATEMENT | STRENGTH |
|---|---|
| **R2** — Immunocompetent patients: **suggest against** routine antifungal treatment — >75% recover fully within 2 months untreated<br>Consider treatment if prolonged illness (>1 week), progressive infiltrates, or enlarging hilar/mediastinal adenopathy. Goal is to shorten illness/reduce dissemination risk (effectiveness unproven). Itraconazole preferred if treated. | Conditional<br>Very low |

## 4 Moderate Acute Pulmonary Histoplasmosis

| STATEMENT | STRENGTH |
|---|---|
| **R3** — Immunocompetent patients: **suggest either** antifungal treatment or no treatment, weighing severity/duration of symptoms vs. drug harms<br>Favors treatment: prolonged illness, worsening symptoms, progressive infiltrates, enlarging adenopathy, more severe symptoms. Consider drug–drug interactions and cost in shared decision-making. | Conditional<br>Very low |

## 5 Immunocompromised Patients (Mild or Moderate Disease)

| STATEMENT | STRENGTH |
|---|---|
| **R4** — Moderate-to-high risk of dissemination (Table below): **suggest** antifungal treatment<br>Asymptomatic/mild disease with lesser immunocompromise may not warrant treatment. Itraconazole preferred; TDM recommended (see Section 7). | Conditional<br>Very low |

## 6 Immunocompromise Risk for Disseminated/Severe Disease

| RISK | REPRESENTATIVE CONDITIONS |
|---|---|
| High | Prednisone ≥2 mg/kg/d (≤10 kg) or ≥20 mg/d (>10 kg) ≥2 wks; primary cellular immunodeficiency (SCID, AD-HIES, IFN-γ/IL-12 defects); untreated HIV (CD4 <200); HSCT <100 d or GVHD therapy; CAR-T <90 d; solid organ transplant + rejection treatment; biologics impairing T-cell/granuloma function (e.g., TNF-α inhibitors) |
| Moderate | Prednisone 0.5–2 mg/kg/d (≤10 kg) or 5–20 mg/d (>10 kg) ≥4 wks; other primary immunodeficiency (CVID, NEMO, XHIM); HIV CD4 200–300; HSCT >100 d no GVHD; hematologic malignancy; CAR-T >90 d + resolved cytopenias; SOT on maintenance immunosuppression |
| Low | Prednisone <0.5 mg/kg/d (≤10 kg) or ≤5 mg/d (>10 kg); HIV CD4 ≥300 + undetectable VL; autoimmune/rheumatic disease not requiring biologics; general medical frailty (liver/kidney/lung disease, diabetes, malnutrition). Sickle cell disease/asplenia and antibody/complement/neutrophil deficiencies confer **no known increased risk**. |

## 7 Itraconazole Dosing & Therapeutic Drug Monitoring

| STEP | DETAIL |
|---|---|
| Adults | Original capsules/oral solution: 200 mg PO TID × 3 d, then 200 mg BID for 6–12 wks. SUBA itraconazole: 130 mg TID × 3 d, then 130 mg BID for 6–12 wks |
| Children | 5 mg/kg/dose (max 200 mg/dose) TID × 3 d, then 5 mg/kg/dose BID (max 400 mg/d) for 6–12 wks. SUBA dosing by weight is off-label; use with pharmacist input |
| TDM | Recommended for all patients on itraconazole — ~20% require dose adjustment for sub/supra-therapeutic levels; ~28% experience side effects |
| Target | Trough itraconazole component >1 mg/L and <3–4 mg/L (chromatographic assay); non-trough/random levels acceptable given long half-life. Combined hydroxy-itraconazole + itraconazole >2 mg/L may respond similarly to itraconazole alone >1 mg/L |
| Pregnancy | Avoid azoles in the 1st trimester when possible; use liposomal amphotericin B if treatment is necessary. Manage jointly with maternal-fetal medicine + infectious diseases |

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