STM JOURNALS

International Journal of
Fungi

ISSN: 3049-1509
Volume 3, Issue 1, 2026
January–June
DOI (Journal): 10.37591/IJF

https://journals.stmjournals.com/ijf

Research IJF

Histoplasma capsulatum (Dimorphic Fungus) in India: Biological Features, Virulence Mechanisms, and Clinical Implications of Histoplasmosis

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Abstract

Histoplasmosis is a systemic mycosis caused by the thermally dimorphic fungus Histoplasma capsulatum. Infection is acquired primarily by inhalation of infectious microconidia and may range from asymptomatic infection to severe disseminated disease. Although histoplasmosis has classically been associated with the river valleys of the Americas, it is being increasingly recognized in Asia, including India, where it frequently mimics tuberculosis, leishmaniasis, lymphoma, and leprosy, resulting in delayed diagnosis and treatment. Cutaneous and mucocutaneous manifestations are of particular importance because they may provide the earliest visible clue to systemic infection in both immunocompetent and immunocompromised patients. In India, histoplasmosis was previously considered to be limited mainly to the Gangetic belt. However, recent reports from Himachal Pradesh, Kerala, and other non-Gangetic regions suggest a wider ecological distribution and an increasing clinical burden. Adrenal involvement, progressive disseminated histoplasmosis, and mucocutaneous disease have been reported prominently in Indian cohorts, especially among people living with HIV, transplant recipients, and patients receiving corticosteroids or other immunosuppressive therapy. This review summarizes the current understanding of the biology, virulence mechanisms, epidemiology, clinical manifestations, laboratory diagnosis, and management of H. capsulatum, with special emphasis on Indian data.

Keywords: Cutaneous manifestations, *Histoplasma capsulatum*, histoplasmosis, India epidemiology, Mucocutaneous lesions, progressive disseminated histoplasmosis, thermal dimorphism

INTRODUCTION

Histoplasmosis is a systemic mycosis caused by the thermally dimorphic fungus *Histoplasma capsulatum* and is acquired primarily by inhalation of infectious microconidia. The clinical spectrum extends from asymptomatic infection to life threatening disseminated disease [1–4]. Although the disease has classically been described from the river valleys of the Americas, it is now being increasingly recognized in Asia, including India. In the Indian setting, histoplasmosis frequently mimics tuberculosis, leishmaniasis, lymphoma, or leprosy, and diagnostic delay is, therefore, common. Cutaneous and mucocutaneous lesions are especially relevant because they may be the first clue to systemic disease in both immunocompetent and immunocompromised patients [5–8].

Histoplasmosis in India was historically considered to be confined mainly to the Gangetic plains. However, published reports from Himachal Pradesh, Kerala, and several other non-Gangetic areas now indicate a broader ecological niche and

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Received Date: February 13, 2026
Accepted Date: March 25, 2026
Published Date: March 27, 2026

Citation: Atul Khajuria, Ashish Kumar, Pradeep Singh. Histoplasma Capsulatum (Dimorphic Fungus) in India: Biological Features, Virulence Mechanisms, and Clinical Implications of Histoplasmosis. International Journal of Fungi. 2026; 3(1): 38–48p.

a wider geographic distribution than previously appreciated [1, 8–11]. Indian cohorts have also shown that adrenal involvement, progressive disseminated histoplasmosis, and mucocutaneous disease are frequent and clinically important manifestations, particularly among people living with HIV, transplant recipients, and those receiving corticosteroids or other forms of immunosuppressive therapy [1, 9–10, 12–14].

In recent years, advances in antigen detection, growing awareness in non-endemic regions, and better characterization of histoplasmosis in immunocompromised hosts have improved understanding of disease burden and diagnosis [14–17]. The present review summarizes the current knowledge on *H. capsulatum* biology, virulence mechanisms, epidemiology, clinical manifestations, laboratory diagnosis, and management, with special emphasis on data from India.

METHODOLOGY

A structured literature review approach was used for this manuscript. The literature search was carried out using PubMed, Scopus, Google Scholar, and cross checking of reference lists from relevant articles. The main search terms used were *Histoplasma capsulatum*, histoplasmosis, India, progressive disseminated histoplasmosis, cutaneous histoplasmosis, mucocutaneous histoplasmosis, adrenal histoplasmosis, laboratory diagnosis, antigen detection, serology, polymerase chain reaction, and treatment. Combinations of these terms were also used to identify region specific and clinically relevant studies.

Articles published in English were included. Priority was given to original articles, case series, case reports of special relevance to India, review articles, laboratory diagnostic papers, and guideline documents. Greater emphasis was placed on studies published during the last ten years, although older landmark publications were retained where they were essential for taxonomy, pathogenesis, classical clinical descriptions, or standard management recommendations [2–4, 14–21].

Studies were excluded if they were duplicate reports, lacked adequate clinical or microbiological documentation, or were not relevant to the scope of histoplasmosis in India or to major advances in diagnosis and management. The review was narrative in design and was informed by a structured search strategy rather than a formal systematic review or meta-analysis. Therefore, PRISMA flow-based reporting was not applied. However, selection of literature was performed systematically to improve comprehensiveness and relevance.

Taxonomy, Morphology, Virulence, and Pathogenesis

H. capsulatum is a thermally dimorphic ascomycete that exists in the mycelial form in the environment at 25 to 30 degrees Celsius and converts to a budding yeast form in host tissues at 37 degrees Celsius [2–4]. In tissue sections, the organism is typically seen as a small oval yeast measuring about 2 to 5 micrometres, often showing narrow based budding and located within macrophages. A clear halo may be seen on routine stains, and organisms are highlighted more clearly by periodic acid Schiff and Gomori methenamine silver stains. In culture at 25 to 30 degrees Celsius, colonies are initially white and cottony and later become brownish. Demonstration of thermal dimorphism remains a defining microbiological feature [2–4, 10, 20].

Two pathogenic varieties have classically been described in humans. *H. capsulatum* var. capsulatum causes classical histoplasmosis, while *H. capsulatum* var. duboisii causes African histoplasmosis and is associated with larger yeast forms and more prominent cutaneous and osseous lesions [1–4, 18]. The report of an indigenous case of African histoplasmosis from Kerala highlights the need for awareness of both forms in India [11].

Infection follows inhalation of microconidia from soil enriched with bird or bat droppings such as caves, poultry environments, and old buildings [2–4, 13, 19]. After inhalation, microconidia convert

into the yeast phase in the lungs and are taken up by alveolar macrophages. Intracellular survival is facilitated by virulence mechanisms that permit adaptation to oxidative stress, iron limitation, temperature shift, and phagolysosomal conditions. Dissemination then occurs through the reticuloendothelial system. In immunocompetent hosts, cell mediated immunity usually restricts infection, whereas high inoculum exposure or impaired T cell immunity predisposes to progressive disseminated histoplasmosis with multisystem involvement [2–4, 13, 17, 21].

In India, prolonged fever, weight loss, hepatosplenomegaly, cytopenias, and bilateral adrenal enlargement are often initially attributed to tuberculosis, and this overlap contributes to diagnostic delay and inappropriate empirical therapy [1, 9, 14–15, 19].

Epidemiology with Special Reference to India

Histoplasmosis is classically endemic in the Ohio and Mississippi river valleys and in parts of Central and South America and Africa. However, reports from Southeast Asia and the Indian subcontinent indicate that the infection has a broader global distribution than was previously assumed [2–4, 13, 17, 19]. In India, older serological surveys and case reports suggested focal endemicity along the Gangetic plains, but more recent clinical series and case-based reports indicate that the disease is not restricted to that region.

A tertiary care study from North India documented multiple cases of histoplasmosis over several years, including disseminated disease and adrenal involvement, and showed that a substantial proportion of patients had initially received empirical anti tubercular treatment [1]. Reports from Himachal Pradesh and other northern areas have described disseminated and cutaneous disease in both HIV infected and apparently immunocompetent individuals, supporting the likelihood of local transmission [8, 10]. The first indigenous Indian report of African histoplasmosis from Kerala further broadened the geographic and clinical spectrum recognized in the country [11]. Reviews of Indian experience have also emphasized histoplasmosis as an important opportunistic infection in people living with HIV, transplant recipients, and those receiving prolonged steroid or other immunosuppressive therapy [13, 15, 19, 22].

Taken together, the available data suggest that histoplasmosis in India is under recognized rather than truly rare. Geographic spread appears wider than earlier believed, and the disease continues to be mistaken for tuberculosis and other chronic granulomatous disorders [1, 8–10, 12, 14–15].

Clinical Manifestations with Focus on Skin and Mucosa

The clinical spectrum of histoplasmosis extends from asymptomatic infection and mild pulmonary illness to severe progressive disseminated histoplasmosis. Major clinical syndromes include acute pulmonary histoplasmosis, chronic pulmonary histoplasmosis, mediastinal disease, primary cutaneous histoplasmosis, and progressive disseminated histoplasmosis with or without central nervous system involvement [2, 3, 9, 13–14, 18]. Major clinical forms of histoplasmosis as depicted in Table 1 in Section 7.

Cutaneous and mucosal lesions most commonly occur in disseminated disease, although primary inoculation may occasionally produce localized cutaneous lesions. In Indian reports, mucocutaneous manifestations in progressive disseminated histoplasmosis have included papules, nodules, plaques, pustules, ulcers, verrucous lesions, vegetative growths, and molluscum like papules [6–8, 12]. Oral ulcers involving the tongue, palate, buccal mucosa, and gingiva have been well documented, as have nasal masses and genital ulcers [12, 23–24]. Primary cutaneous histoplasmosis has been described rarely in immunocompetent adults after trauma, usually as a localized papule, nodule, or ulcer at the inoculation site [6, 8]. Cutaneous/Mucosal Patterns and Differentials in India as depicted in Table 2 in Section 7.

Table 1. Major clinical forms of histoplasmosis (with Indian emphasis).

Clinical form	Key features	Indian relevance/examples	Citations
Acute Pulmonary Histoplasmosis	Flu-like illness, fever, cough, chest pain, often self-limited	Likely underreported; often treated as CAP without specific testing.	[1, 3, 9]
Chronic Cavitary Pulmonary Histoplasmosis	Cavitary lesions in COPD/smokers; TB-like picture	Frequently misdiagnosed as pulmonary TB; consider when TB tests are negative or ATT fails.	[1–3, 9]
Progressive Disseminated Histoplasmosis (PDH)	Fever, weight loss, hepatosplenomegaly, cytopenias, adrenal/GI/CNS involvement	Multiple Indian series with adrenal masses, mucocutaneous lesions, and high mortality.	[1, 9–12]
Primary Cutaneous Histoplasmosis	Localized papule/nodule/ulcer at inoculation site	Reported from non-endemic regions and immunocompetent adults (e.g., Himachal Pradesh).	[6–8, 12]
Mucocutaneous Histoplasmosis (Disseminated)	Oral, nasal, pharyngeal ulcers; papulonodular skin lesions	Several Indian case reports with oral/nasal lesions and widespread skin involvement.	[8, 12, 23–24]
African Histoplasmosis (*H. capsulatum* var. duboisii)	Larger yeasts; cutaneous and bone disease	First indigenous Indian case from Kerala with cutaneous disease.	[11, 19]

Table 2. Cutaneous/mucosal patterns and differentials in India.

Pattern	Typical sites	Important differentials	Useful distinguishing points	Citations
Papulonodular Eruptions	Face, trunk, extremities	Lepromatous leprosy, papulonodular TB, leishmaniasis, deep mycoses	Biopsy with yeast-laden macrophages; PAS/GMS positive; AFB negative.	[6–8, 12]
Ulcerative/ Vegetative Plaques	Oral cavity, nasal mucosa, genitalia, limbs	TB, malignancy, GPA, mucormycosis, chromoblastomycosis	Multiple shallow ulcers with raised borders; histology shows small intracellular yeasts.	[12, 23–24]
Molluscum-like Papules	Face, trunk	Molluscum contagiosum, cryptococcosis	Umbilicated papules but without Henderson–Paterson bodies; yeasts seen on PAS/GMS.	[12, 23–24]
Erythema Nodosum-like Lesions	Legs, arms	ENL, erythema nodosum (TB, sarcoid)	Systemic symptoms with mucosal lesions; biopsy showing histoplasma rather than panniculitis alone.	[7–8, 12]
Nasal Mass/Obstruction	Nasal cavity, sinuses	NK/T cell lymphoma, invasive fungal sinusitis, rhinoscleroma	Biopsy with *H. capsulatum* yeasts; often associated PDH or HIV infection.	[7–8, 12, 23]

In India, histoplasmosis may closely mimic cutaneous tuberculosis, leprosy including erythema nodosum leprosum like lesions, leishmaniasis, deep mycoses, and other granulomatous or vasculitic conditions [6–8, 12] .For this reason, histoplasmosis should be considered in the differential diagnosis of chronic non healing ulcers, vegetative plaques, papulonodular eruptions with systemic features, molluscum like lesions in febrile adults with weight loss, and atypical leprosy like nodules that do not respond to standard therapy [6–8, 12].

Skin biopsy remains central to diagnosis. Histopathology usually shows granulomatous or mixed inflammatory infiltrates with histiocytes containing intracellular yeasts measuring 2 to 5 micrometres. Periodic acid Schiff and Gomori methenamine silver stains highlight the organisms, while Ziehl Neelsen and Fite Faraco stains are helpful in excluding mycobacterial infection and leprosy. The recognition of mucocutaneous lesions should prompt evaluation for disseminated disease, including chest imaging, abdominal imaging, adrenal assessment, bone marrow examination, and HIV testing, because cutaneous involvement frequently reflects systemic dissemination in Indian patients [1, 7–9, 12, 19, 23].

LABORATORY DIAGNOSIS OF *HISTOPLASMA CAPSULATUM*

Microbiology and Laboratory Diagnosis

The diagnosis of histoplasmosis is based on integration of clinical, radiological, histopathological, and microbiological findings. For the microbiologist, the strongest evidence is provided by demonstration of characteristic yeast forms in tissue or cytology material and by isolation of *H. capsulatum* in culture with demonstration of thermal dimorphism [2, 4, 20].

Over the last two decades, antigen detection in urine and serum has emerged as a rapid and highly sensitive tool, particularly for progressive disseminated histoplasmosis in people living with HIV. Antibody based methods and molecular assays serve complementary roles in selected settings [16–17, 20–21]. In most Indian laboratories, the practical diagnostic approach continues to rely primarily on direct microscopy, cytology, and histopathology, with culture used wherever feasible for confirmation. Antigen detection and molecular methods remain valuable but are not yet uniformly accessible across centres in India [1, 15–17, 19, 20].

Specimen Selection and Transport

Appropriate specimen selection should be guided by clinical syndrome. Pulmonary disease is best evaluated with sputum, bronchoalveolar lavage, transbronchial samples, or lung biopsy. Progressive disseminated histoplasmosis may require bone marrow aspirate or biopsy, blood, lymph node tissue, liver biopsy, skin and mucosal lesion samples, or adrenal fine needle aspiration or biopsy. Primary cutaneous disease should be sampled by deep skin biopsy taken from the active lesion edge. Central nervous system disease requires cerebrospinal fluid or, where indicated, tissue biopsy [17, 20–21].

Specimens should be separated appropriately for histology, cytology, culture, antigen testing, serology, and molecular testing where available. Prompt transport with adequate clinical details is essential to ensure proper laboratory processing and to avoid missed diagnosis in cases initially suspected to represent tuberculosis [20].

Direct Microscopy and Cytology

Fine needle aspiration cytology from adrenal lesions, lymph nodes, bone marrow, and skin or mucosal lesions is a valuable and minimally invasive diagnostic method. Smears typically show numerous small oval yeasts within macrophages, sometimes described as packed histiocytes. A common diagnostic pitfall is confusion with Leishmania amastigotes. The absence of a kinetoplast in Histoplasma and the presence of multiple small uniform yeasts within macrophages assist differentiation [20–21].

Histopathology

Histopathology often provides the first major clue in Indian patients, particularly in biopsies from skin, lymph nodes, adrenal glands, liver, and gastrointestinal lesions [1, 6–9, 11–12, 14, 20]. Routine sections may show granulomatous inflammation, mixed suppurative and granulomatous inflammation, or diffuse histiocytic infiltrates. Organisms may be subtle on haematoxylin and eosin stain and can be overlooked if special stains are not requested. Periodic acid Schiff and Gomori methenamine silver stains highlight the organisms well. In var. duboisii infection, the yeast forms are larger and thicker walled [2–4, 11, 20].

Culture

Culture remains the definitive microbiological method. Specimens should be inoculated onto routine fungal media, such as Sabouraud dextrose agar and brain heart infusion agar, and incubated at 25 to 30 degrees Celsius for up to eight weeks. Mold phase microscopy shows septate hyphae with tuberculate macroconidia and microconidia. Demonstration of mold to yeast conversion confirms dimorphism [2–4, 10, 20]. Culture sensitivity varies according to specimen type and disease burden and is highest in blood and bone marrow from patients with progressive disseminated histoplasmosis. Because culture manipulation may generate infectious aerosols, biosafety precautions are essential [20].

Antigen Detection

Antigen detection has become a central diagnostic tool in modern histoplasmosis practice, especially in progressive disseminated disease and HIV associated histoplasmosis. Urine antigen testing is generally more sensitive than serum testing in severe disease, and antigen levels may also be used for monitoring response to treatment and relapse [16–17, 21]. However, cross reactivity with other endemic mycoses should be recognized, and access to these assays remains limited in many Indian settings [15–17, 19, 21].

Antibody Detection

Complement fixation, immunodiffusion, and newer immunoassays may support diagnosis, especially in subacute and chronic pulmonary histoplasmosis. Their performance is reduced in early disease and in immunocompromised hosts, which is particularly relevant in Indian patients with progressive disseminated histoplasmosis associated with HIV infection [13, 15, 19, 21].

Molecular Methods

Polymerase chain reaction-based assays that target genes, such as Hcp100, have shown high analytical sensitivity and specificity in confirmed histoplasmosis. Loop mediated isothermal amplification has also shown promise for low resource settings. However, these methods are mainly confined to reference or research laboratories and have not yet become routine diagnostic tools in most Indian centres [17, 21].

Diagnostic Approach in India

For India, a practical diagnostic algorithm is based on high clinical suspicion, especially in tuberculosis, like illness, that is unresponsive to anti tubercular therapy, followed by tissue diagnosis using cytology or biopsy with fungal stains. Culture should be added whenever possible, and antigen detection should be used where available, particularly in HIV associated or disseminated disease. Serology and molecular assays may be used as adjunctive tests in selected cases [1, 9, 15, 17, 19–20]. Laboratory Diagnosis of Histoplasmosis as depicted in Table 3 in Section 7.

Table 3. Laboratory diagnosis of histoplasmosis.

Test	Sample	Advantages	Limitations	Role in India	Citations
Direct Microscopy (Smears, FNAC)	Bone marrow, lymph node, adrenal, skin	Rapid, low cost; shows yeast-laden macrophages	Requires expertise; low sensitivity in paucibacillary disease	First line in suspected PDH and adrenal/skin disease	[1, 6–7, 9]
Histopathology + PAS/GMS	Skin, lymph node, adrenal, GI biopsies	High yield; shows organisms and tissue response	Needs good pathology support	Cornerstone for dermatology and medicine diagnosis	[6–8, 11–12]
Culture on SDA (25–30°C)	Tissue, blood, marrow, respiratory samples	Gold standard; allows speciation and susceptibility	Slow (up to 4–8 weeks); biohazard	Essential in tertiary centres; confirmatory when TB work-up is non-diagnostic	[2, 4, 10, 12, 20]
Antigen Detection (Urine/Serum)	Urine, serum	High sensitivity in PDH; rapid	Limited availability, cost	Useful where available, especially in HIV/PDH	[13, 15, 19]
Serology (CF, ID)	Serum	Epidemiologic value; supportive evidence	Less sensitive in immunosuppressed; cross reactivity	Supportive test; not standalone for treatment decisions	[13, 15, 21]
PCR/Real-Time PCR	Tissue, blood	Rapid, specific, high sensitivity	Costly; limited availability	Reference labs and complex cases; confirmatory	[13, 17, 20–21]

CONCEPTUAL FRAMEWORK OF HISTOPLASMOSIS IN INDIA

A conceptual framework for histoplasmosis in India may be organized into five linked domains. First, environmental exposure occurs through inhalation of microconidia from soil enriched with bird or bat droppings. Second, thermal conversion to the yeast phase occurs within the host, followed by

intracellular survival in macrophages and dissemination through the reticuloendothelial system. Third, the host immune state determines the clinical phenotype, with latent or self-limited disease in immunocompetent individuals and progressive disseminated histoplasmosis in those with impaired cellular immunity. Fourth, the clinical syndrome may involve pulmonary, adrenal, gastrointestinal, central nervous system, cutaneous, or mucocutaneous disease, often overlapping with tuberculosis and other chronic granulomatous disorders in India. Fifth, outcome is determined by the timeliness of recognition, tissue-based diagnosis, access to antigen detection where available, and early initiation of antifungal therapy (Figure 1) [1–4, 9, 13–17, 19–22].

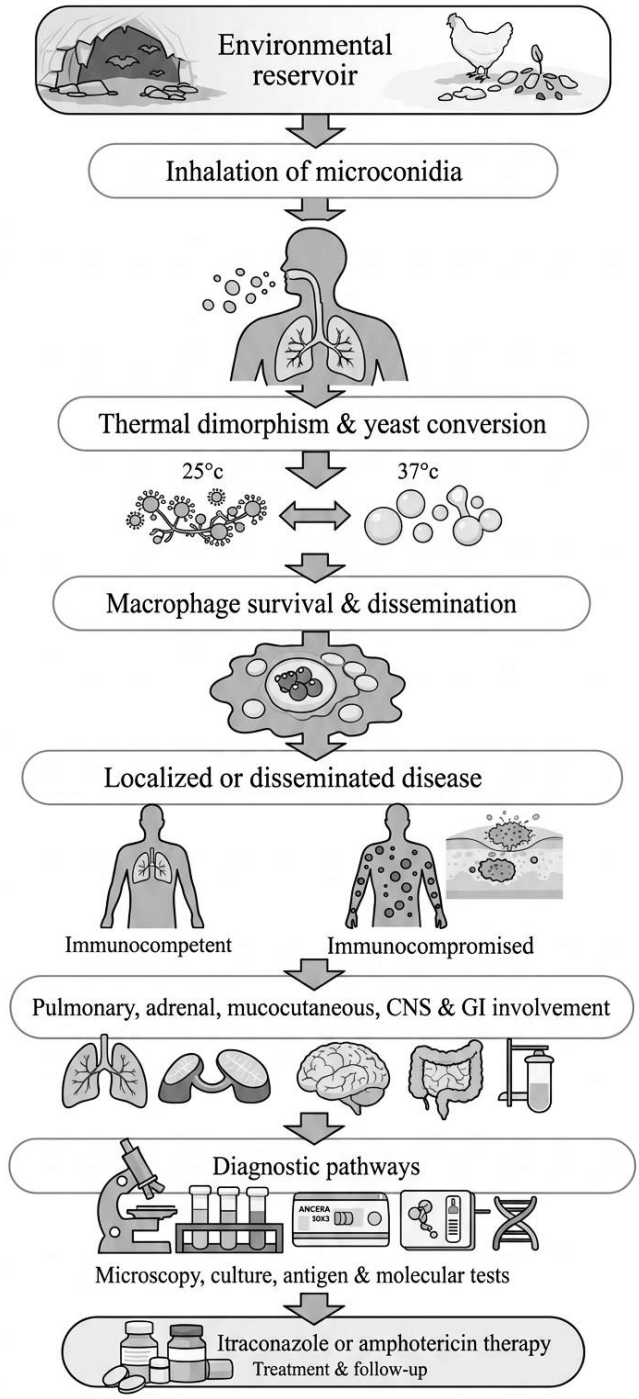

Figure 1. Conceptual framework linking exposure, pathogenesis, organ involvement, diagnosis, and management of histoplasmosis in India.

Internal Medicine Perspective: Adrenal and Disseminated Disease

For physicians, histoplasmosis remains an important mimic of tuberculosis, lymphoma, and autoimmune disease. Progressive disseminated histoplasmosis often presents with prolonged fever, weight loss, hepatosplenomegaly, lymphadenopathy, cytopenias, and adrenal enlargement [1, 2, 9, 13–15, 19, 22]. Bilateral adrenal involvement is especially notable in Indian cohorts and may occur with or without overt adrenal insufficiency. Several patients are initially treated as adrenal tuberculosis until cytology or biopsy reveals *H. capsulatum* [1, 9, 14–15, 19].

Gastrointestinal ulceration, strictures, malabsorption, and bone marrow infiltration may also occur, although these manifestations may be under recognized. Central nervous system and cardiac involvement are less common but are associated with substantial mortality and require aggressive amphotericin-based induction followed by prolonged azole therapy [9, 13–15, 18, 22, 25].

Treatment: Principles, Guidelines, and Indian Practice

Treatment is guided by disease severity, organ involvement, and immune status. Mild to moderate pulmonary or localized disease is generally treated with oral itraconazole after loading doses. Chronic pulmonary histoplasmosis usually requires prolonged therapy. Moderately severe to severe progressive disseminated histoplasmosis without central nervous system involvement is treated with intravenous amphotericin B followed by itraconazole for at least six to twelve months. Central nervous system histoplasmosis requires longer amphotericin-based induction and prolonged itraconazole continuation therapy [13–14, 18, 25].

Indian case reports and case series have broadly followed these principles [1, 7–10, 12, 14–15, 23, 26]. Primary cutaneous histoplasmosis in immunocompetent hosts has responded well to excision with itraconazole based therapy in reported cases. In disseminated disease with adrenal involvement, relapse has been observed when therapy has been shortened or when underlying immunosuppression has persisted. In HIV associated disease, prolonged suppression may be required until immune recovery occurs [13, 15, 19]. Treatment Regimens as depicted in Table 4 in Section 7.

Table 4. Treatment regimens (Indian practice).

Clinical setting	Recommended regimen	Duration	Comments	Citations
Mild to Moderate Acute Pulmonary or Localized Disease	Itraconazole 200 mg orally 2–3 times/day for 3 days (loading), then 200 mg twice/day	6–12 weeks (acute), up to 12 months (chronic pulmonary)	Monitor drug levels and liver function; interacts with rifampicin and antiretrovirals.	[1, 9, 13–15]
PDH without CNS involvement (moderate–severe)	Liposomal amphotericin B 3 mg/kg/day IV (or deoxycholate 0.7–1.0 mg/kg/day) → itraconazole 200 mg twice/day	Amphotericin B 1–2 weeks; itraconazole 6–12 months	Longer therapy in HIV, relapse or ongoing immunosuppression.	[1, 9, 13–15, 18, 22]
PDH with CNS involvement	Liposomal amphotericin B 5 mg/kg/day IV → itraconazole 200 mg 2–3 times/day	Amphotericin B 4–6 weeks; itraconazole ≥12 months	Monitor CSF, drug levels; neurology and ID input essential.	[13, 15, 18, 22, 25]
Primary Cutaneous Histoplasmosis (Immunocompetent)	Itraconazole 200 mg twice/day ± short amphotericin B; surgical excision for localized lesions	6–12 months	Favorable outcomes in Indian case reports.	[6–8, 12]
HIV-associated Severe Histoplasmosis	As PDH regimen plus ART; itraconazole prophylaxis if CD4 remains low	Induction as above; maintenance often long term	Antigen monitoring where available; high relapse risk.	[13, 15, 19]

DISCUSSION

The present review reinforces the view that histoplasmosis in India should be regarded as an under diagnosed endemic mycosis rather than as a rare-imported infection [1, 14–15, 19]. Recent literature has shown that disease burden is being increasingly recognized beyond the traditionally described Gangetic belt and that clinically important cases are now being reported from multiple non-Gangetic

regions [1, 8, 10–11, 14–15]. This trend may reflect a combination of broader ecological distribution, increased clinical suspicion, improved tissue diagnosis, and greater recognition of histoplasmosis in immunocompromised patients (Table 5) [14–15, 17, 19].

Table 5. "Red Flag" scenarios for histoplasmosis in India.

Scenario	Why consider histoplasmosis?	Initial steps	Citations
Bilateral Adrenal Masses with Fever and Weight Loss	PDH with adrenal involvement is common; often mislabelled "adrenal TB"	CT/MRI adrenals; FNAC/biopsy with PAS/GMS; fungal culture; HIV test.	[1, 9, 13, 19]
Chronic "TB-like" Illness Failing ATT	Histoplasmosis closely mimics TB clinically and radiologically	Re-evaluate with imaging, bone marrow/lymph node biopsy, fungal stains/culture.	[1, 9, 13, 15]
Papulonodular or Ulcerative Skin Lesions plus Oral/Nasal Ulcers	Classical for mucocutaneous histoplasmosis in PDH	Dermatologic biopsy; fungal stains; systemic staging for dissemination.	[6–8, 12]
HIV Positive Patient with Fever, Weight Loss, Hepatosplenomegaly, Cytopenias	PDH is an AIDS defining illness with high mortality	Antigen test (if available), bone marrow/skin biopsy, amphotericin B induction.	[13, 15, 19]
"Leprosy" or ENL-like Lesions Not Fitting Patterns or Unresponsive to MDT	Histoplasmosis can produce ENL-like nodules and plaques	Skin biopsy with fungal stains; rethink diagnosis beyond Hansen disease.	[6–8, 12]

A major challenge in India is the persistent overlap between histoplasmosis and tuberculosis. Adrenal enlargement, chronic fever, weight loss, pulmonary lesions, lymphadenopathy, and granulomatous tissue reactions often lead to presumptive anti tubercular treatment before fungal disease is considered [1, 9, 14–15, 19]. Cutaneous and mucocutaneous lesions are, therefore, of major practical importance because they may provide a visible and accessible site for biopsy. Reports from India have repeatedly shown that skin and mucosal pathology may provide the first decisive clue to progressive disseminated histoplasmosis [6–8, 10, 12, 23–24, 26].

From a diagnostic perspective, histopathology and cytology continue to serve as the backbone of diagnosis in most Indian centres [1, 6–12, 14, 20, 23, 26]. However, recent international advances have highlighted the strong performance of antigen detection for progressive disseminated histoplasmosis, particularly in HIV associated disease, and these tools are likely to become increasingly relevant in India as access improves [16–17, 21]. Molecular assays are also promising, although routine implementation remains limited [17, 21].

The review also highlights the need for multidisciplinary recognition of histoplasmosis by microbiologists, internists, dermatologists, radiologists, and pathologists. Earlier diagnosis would reduce inappropriate anti tubercular therapy, shorten time to amphotericin or itraconazole treatment, and likely improve survival in disseminated disease [1, 9, 14–15, 19]. Future Indian studies should focus on better burden estimation, antigen test availability, ecological mapping, and clinically validated diagnostic algorithms adapted to resource constrained settings.

CONCLUSION

Histoplasmosis in India is under recognized rather than rare and extends beyond the traditionally described Gangetic regions. The disease shows broad clinical diversity and frequently mimics tuberculosis, leprosy, lymphoma, and other chronic granulomatous disorders, especially in immunocompromised individuals. Recognition of mucocutaneous lesions is particularly important because these lesions may serve as the earliest visible sign of disseminated infection. In Indian practice, histopathology, cytology, and culture remain the core diagnostic tools, while antigen detection and molecular methods are emerging as important adjuncts. Early integration of clinical, radiological, histopathological, and microbiological findings is essential for timely initiation of amphotericin-based induction and itraconazole based continuation therapy, thereby improving clinical outcomes.

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