Diagnosis and Management of Systemic Endemic Mycoses Causing Pulmonary Disease

Helmut J.F. Salzer, MD, MPH
Division of Clinical Infectious Diseases, Research Center Borstel
Leibniz Lung Center, Parkallee 35
DE–23845 Borstel (Germany)
E-Mail hsalzer@fz-borstel.de

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E-Mail karger@karger.com
www.karger.com/res

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Abstract
Systemic endemic mycoses cause high rates of morbidity and mortality in certain regions of the world and the real impact on global health is not well understood. Diagnosis and management remain challenging, especially in low-prevalence settings, where disease awareness is lacking. The main challenges include the variability of clinical presentation, the fastidious and slow-growing nature of the fungal pathogens, the paucity of diagnostic tests, and the lack of options and toxicity of antifungal drugs. Coccidioidomycosis and paracoccidioidomycosis are restricted to the Americas only, and while histoplasmosis and blastomycosis also occur predominantly in the Americas, these mycoses have also been reported on other continents, especially in sub-Saharan Africa. Talaromycosis is endemic in tropical and subtropical regions in South-East Asia and southern China. Systemic endemic mycoses causing pulmonary disease are usually acquired via the airborne route by inhalation of fungal spores. Infections can range from asymptomatic or mild with flu-like illnesses to severe pulmonary or disseminated diseases. Skin involvement is frequent in patients with paracoccidioidomycosis, blastomycosis, sporotrichosis, and talaromycosis and manifests as localized lesions or diffuse nodules in disseminated disease, but can also occur with other endemic mycoses. Cultural and/or characteristic histopathology from clinical samples is the diagnostic standard for endemic mycoses. Immunological assays are often not available for the diagnosis of...
most endemic mycoses and molecular amplification methods for the detection of fungal nucleic acids are not standardized at present. The first-line treatment for mild to moderate histoplasmosis, paracoccidioidomycosis, blastomycosis, sporotrichosis, and talaromycosis is itraconazole. Severe illness is treated with amphotericin B. Patients with severe coccidioidomycosis should receive fluconazole. Treatment duration depends on the specific endemic mycosis, the severity of disease, and the immune status of the patient, ranging between 6 weeks and lifelong treatment.

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Introduction

Systemic endemic mycoses include a group of dimorphic fungi that are found in distinct geographical regions. Paracoccidioidomycosis and talaromycosis are found in tropical and sub-tropical regions, while coccidioidomycosis is found in warm and dry climates of semi-deserts and blastomycosis in temperate climates. Histoplasmosis occurs under variable conditions ranging from tropical to temperate climates. The impact of climate change and changes due to migration is uncertain and the real global burden of endemic mycoses is not well understood [1]. Inhalation of fungal spores may cause infection. Clinical presentation can vary from asymptomatic to disseminated fatal disease and depends on the immune status of the host and the infectious dose from the environmental exposure. Most endemic mycoses, including histoplasmosis, coccidioidomycosis, blastomycosis, and sporotrichosis, are capable of causing large outbreaks. Diagnosis of systemic endemic mycoses causing pulmonary disease is challenging, because mycoses may resemble other diseases (e.g., pulmonary tuberculosis, bacterial or viral pneumonia, lung cancer) (Fig. 1), and physicians in low-prevalence settings may not be familiar with the disease manifestations. Establishing a diagnosis is further complicated by the difficulty in growing these organisms and by the paucity of nonculture-based diagnostic assays, specifically the lack of standardization of serological and molecular tests. Pathologists may not be familiar with the histopathological features. Furthermore, disease management is often complex, including long-term antifungal treatment, drug-drug interactions, therapeutic drug monitoring (TDM), frequent follow-ups to monitor for antifungal side effects, and disease relapse and complications.

The aim of this review is to guide physicians in the diagnosis and management of systemic endemic mycoses causing pulmonary disease. It should raise awareness about important disease characteristics (Tables 1, 2), diagnostic tests (Table 3), and antifungal treatment (Table 4).

Disease Characteristics

Histoplasmosis

Histoplasmosis caused by the dimorphic fungus *Histoplasma capsulatum* is found worldwide, but particularly in North, Central, and South America (Table 1). It has been reported from parts of southern and eastern Europe, Africa, Asia, and Australia; however, reports are usually limited to a few cases [2]. It has the potential to cause larger outbreaks [3].

Fig. 1. **a** Chest X-ray showing macronodular infiltrates in both upper lobes. **b** Corresponding CT scan of the chest showing two macronodular consolidations on the right side, smaller nodules, and traction bronchiectasis mimicking pulmonary tuberculosis in a patient with histoplasmosis.
Table 1. Disease characteristics

<table>
<thead>
<tr>
<th>Species</th>
<th>Endemic areas</th>
<th>Reservoir</th>
<th>Route of transmission</th>
<th>Populations at risk</th>
<th>Prevention</th>
<th>Commentary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Histoplasmosis</td>
<td><em>Histoplasma capsulatum sensu latu</em> – <em>Histoplasma capsulatum var. capsulatum</em> – <em>Histoplasma capsulatum var. duboisii</em> (= African histoplasmosis) – Others</td>
<td>North and Central America, Africa (Central, South, West)</td>
<td>Soil, animal droppings (bat), caves, caverns, abandoned buildings</td>
<td>Aerogenic</td>
<td>Local population, travelers to endemic regions (visiting caves, abandoned buildings, construction works)</td>
<td>Immunocompromised individuals should avoid activities with disturbing material/soil in regions of high prevalence</td>
</tr>
<tr>
<td>Paracoccidioidomycosis</td>
<td><em>Paracoccidioides brasiliensis</em>, <em>Paracoccidioides lutzii</em></td>
<td>South America (Brazil, Peru, Argentina, Colombia, Ecuador, Venezuela)</td>
<td>Soil</td>
<td>Aerogenic</td>
<td>Local population, especially smokers with COPD, workers in rural areas (e.g., farmers), few cases in travelers</td>
<td>Human infections are not contagious</td>
</tr>
<tr>
<td>Coccioidiomycosis</td>
<td><em>Coccioides immitis</em>, <em>Coccioides posadaii</em></td>
<td>Southwestern USA – Arizona (66% of cases), central and southern California (31% of cases), New Mexico, Texas, few cases from Washington, Utah – Mexico, Central and South America</td>
<td>Soil of certain arid areas</td>
<td>Aerogenic, inhalation of dust (construction, landscaping, farming, archeology, excavation, recreational pursuits) or from dust clouds (earthquakes, windstorms)</td>
<td>Persons after exposure in endemic regions (highest in dry periods following a rainy season), often associated with outdoor activities and dust; very rare cases in travelers</td>
<td>Residents can avoid activities that expose them to dust or desert soil and stay indoors during dust storms. Laboratory personnel handling the organism should practice biosafety level 3 precautions</td>
</tr>
<tr>
<td>Blastomycosis</td>
<td><em>Blastomyces dermatitidis</em>, <em>Blastomyces gilchristii</em></td>
<td>South-Eastern and South-Central states of the USA and Canadian provinces bordering the Great Lakes, and New York state and Canada along the St. Lawrence River and the Nelson River</td>
<td>Soil containing decaying vegetation or decomposed wood, associated with waterways</td>
<td>Aerogenic, skin inoculation</td>
<td>No-special population, often seen in children, can be opportunistic in immunocompromised hosts</td>
<td>Human infections are not contagious, immunocompromised individuals should avoid activities with disturbing material/soil in regions of high prevalence</td>
</tr>
<tr>
<td>Sporotrichosis</td>
<td><em>Sporothrix schenckii</em>, <em>Sporothrix brasiliensis</em>, <em>Sporothrix globosa</em>, <em>Sporothrix mexicana</em></td>
<td>Found worldwide from temperate to tropical climate, endemic in Peru</td>
<td>Soil, moss, decaying wood and vegetation</td>
<td>Skin inoculation, aerogenic</td>
<td>No-special population, higher risk for immunocompromised patients</td>
<td>Skin protection in people working in gardening or landscaping</td>
</tr>
<tr>
<td>Talaromycosis</td>
<td><em>Talaromyces marneffei</em> (formally <em>Penicillium marneffei</em>)</td>
<td>Southeast Asia, northeastern India, and southern China</td>
<td>Bamboo rats, soil in bamboo rat burrows, soil enriched with animal excreta</td>
<td>Aerogenic, skin inoculation</td>
<td>Residents and travelers in endemic regions who are immunocompromised, especially patients with advanced HIV infection</td>
<td>Transmission has been reported</td>
</tr>
</tbody>
</table>

AIDS, acquired immune deficiency syndrome; COPD, chronic obstructive pulmonary disease; HIV, human immunodeficiency syndrome.  

Fig. 2. Diffuse small nodules in both lungs on chest X-ray (a) and axial CT scan of the chest (b) mimicking mil- iary tuberculosis in a patient with histoplasmosis.
Table 2. Symptoms and radiological patterns of systemic endemic mycoses causing pulmonary disease

<table>
<thead>
<tr>
<th>Clinical presentation</th>
<th>Most frequent symptoms</th>
<th>Organ involvements</th>
<th>Chest radiological pattern</th>
<th>Commentary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Histoplasmosis</td>
<td>Acute diffuse pulmonary disease (infiltrates)</td>
<td>Pulmonary dissemination to any organ (e.g., eye)</td>
<td>Diffuse infiltrates, opacities, small or large nodules, mediastinal mass, cavities (in chronic pulmonary disease), lymph node enlargement</td>
<td>Immunosuppression as risk factor for severe disease with dissemination (e.g., advanced HIV infection)</td>
</tr>
<tr>
<td>Paracoccidioidomycosis</td>
<td>Acute/subacute form (juvenile) (5–25%)</td>
<td>Respiratory symptoms</td>
<td>Lymphatic system (lymph nodes, liver, spleen, bone marrow, skin, and mucous membranes (45–65%), organ abscess formations, fever (50–80%), pulmonary (84%), bone (5%), CNS (meningitis) (2–3%), and adrenal gland</td>
<td>More severe in immunocompromised patients; HIV-infected patients more often present with fever, lymphadenopathy, hepatosplenomegaly, and cutaneous lesions</td>
</tr>
<tr>
<td>Coccidioidomycosis</td>
<td>Primary infection: mostly with pulmonary involvement</td>
<td>Primary infection: lung, pleura, skin, and musculoskeletal</td>
<td>Primary infection: unilateral infiltrate with hilar adenopathy, parapneumonic effusion, thin-walled cavities or nodules</td>
<td>Radiographic findings may persist for years</td>
</tr>
<tr>
<td>Blastomycosis</td>
<td>Pulmonary disease (90%)</td>
<td>Mostly pulmonary, but frequently skin involvement, sometimes bone and joints, CNS, and genitourinary</td>
<td>Consolidations, interstitial infiltrations, nodules and masses, involvement of multiple or single lobes, less adenopathy</td>
<td>Residual pulmonary nodules and thin-walled cavities usually have no clinical consequences</td>
</tr>
<tr>
<td>Sporotrichosis</td>
<td>Lymphocutaneous most common</td>
<td>Skin and lymphatic, pulmonary, osteoarticular, CNS</td>
<td>Reticulonodular (miliary) pneumonia</td>
<td>More severe in immunocompromised, elderly, diabetes mellitus, pregnancy</td>
</tr>
<tr>
<td>Talaromyces</td>
<td>Localized disease: seen in non-HIV infected persons</td>
<td>Localized disease: depends on organ involved</td>
<td>Interstitial to alveolar infiltrates, reticulo-nodular pattern, nodules, miliary pattern</td>
<td>More severe in immunocompromised persons; HIV-infected persons more often present with fever, lymphadenopathy, hepatosplenomegaly, and cutaneous lesions</td>
</tr>
</tbody>
</table>

CNS, central nervous system; CPA, chronic pulmonary aspergillosis; TB, tuberculosis.

Fig. 3. Axial CT scan of the chest showing bipulmonary, solid nodules (white arrows) in a 27-year-old female biology student with cough and fever lasting for several weeks after returning from a field trip exploring bat caves in Central America. Diagnosis of pulmonary histoplasmosis was established by positive culture and Histoplasma capsulatum var. capsulatum-specific PCR from lung tissue as well as positive H. capsulatum antibody detection. Histopathology from lung tissue showed noncaseating granulomas with giant cells, but without evidence of fungi (Grocott’s methenamine silver stain). Cytology and routine microbiological cultures from bronchoalveolar lavage fluid revealed no evidence of fungi.
Table 3. Diagnostic tests to establish diagnosis of endemic mycoses and histological appearance

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Culture</th>
<th>Histopathology</th>
<th>Antigen detection</th>
<th>Serology</th>
<th>Molecular methods</th>
</tr>
</thead>
<tbody>
<tr>
<td>Histoplasmosis</td>
<td>Isolation from clinical specimens remains gold standard (caution: danger of laboratory infection by Histoplasma capsulatum in mycelial phase)</td>
<td>Tuberculosis granuloma with intracellular yeast cells (can be mistaken for trypanosoma, leishmania amastigotes, or Talaromyces marneffei yeast cells)</td>
<td>A polyclonal antibody-based antigen test in urine is commercially available in the USA; cross-reactivity with other fungal infections, including Blastomyces dermatitidis, CPA, may occur; a monoclonal antibody-based lateral flow antigen detection assay is currently under evaluation</td>
<td>Antibody detection by ID, CF, or Western blot available, high specificity, however, results may be falsely negative in immunosuppressed patients and in those who present with acute disease</td>
<td>PCR assays available in reference laboratories, not standardized</td>
</tr>
<tr>
<td>Paracoccidiomycosis</td>
<td>Cultures are diagnostic, but can take up to a month to grow</td>
<td>Tuberculosis granuloma with multipolar budding yeast cells (&quot;ship-pilot’s wheel&quot; or &quot;Mickey Mouse head&quot;)</td>
<td>Antigen detection in BAL has been described (gp43, not expressed in Paracoccidioides lutzii), but not standardized</td>
<td>DIF, CIE, ELISA, and immuno blotting; utility is hampered by cross-reactivity with other endemic fungi, inaccuracies in the diagnosis in P. lutzii infection.</td>
<td>PCR assays available in reference laboratories, but are not standardized</td>
</tr>
<tr>
<td>Coccidioidomycosis</td>
<td>Culture confirms the diagnosis; Cultures must be manipulated in a biosafety level III laboratory</td>
<td>Tuberculosis granuloma with spherules (60–100 µm with endospores of 2–5 µm)</td>
<td>Coccidioides galactomannan antigen test available in reference laboratories, low sensitivity (70%)</td>
<td>ID and CF; Most clinical infections diagnosed serologically in the setting of a compatible clinical syndrome</td>
<td>PCR assays are being evaluated</td>
</tr>
<tr>
<td>Blastomycosis</td>
<td>Culture confirms the diagnosis; diagnostic yield is high for both bronchoscopy and sputum samples, but takes 1–4 weeks</td>
<td>Tuberculosis granuloma with unipolar budding yeast cells</td>
<td>EIA for polysaccharide cell wall antigen commercially available; high sensitivity (93%) but low specificity (79%) due to cross-reactivity with other fungi</td>
<td>ID and CF have no role in diagnosis because poor sensitivity and significant cross reactivity</td>
<td>PCR assays have not been tested in large studies</td>
</tr>
<tr>
<td>Sporotrichosis</td>
<td>Isolation from clinical specimens remains gold standard; clinical specimens should be inoculated on Sabouraud agar and incubated at room temperature for 1–4 weeks</td>
<td>Necrotizing granulomas, paucity of yeasts</td>
<td>Not available</td>
<td>One EIA has been developed, but is not available</td>
<td>PCR-based assays have been developed, yet to be evaluated</td>
</tr>
<tr>
<td>Talaromyces</td>
<td>T. marneffei can be cultured from blood and other clinical samples, but can take up to 14 days for identification</td>
<td>Binary fission yeasts within histiocytes or extracellularly; T. marneffei may be confused with H. capsulatum, but has a central transverse septum unlike any other common pathogenic yeasts</td>
<td>ELAs detecting mannoprotein in the fungal cell wall in blood and urine, have high sensitivity and specificity but are not commercially available yet; over 80% of patients with disseminated talaromycosis are galactomannan antigen (“Aspergillus spp.”) positive in sera</td>
<td>Antibody detection by ID, EIA, or Western blot available; low sensitivity in HIV-infected patients</td>
<td>PCR-based assays have been developed, low sensitivities (60–70%), not standardized</td>
</tr>
</tbody>
</table>

BAL, bronchoalveolar lavage; CF, complement fixation; CIE, counterimmunoelectrophoresis; CPA, chronic pulmonary aspergillosis; DID, double immunodiffusion technique; EIA, enzyme immunoassay; ELISA, enzyme-linked immunosorbent assay; ID, immunodiffusion; PCR, polymerase chain reaction.

Fig. 4. a Chest X-ray showing bipulmonary diffuse pulmonary micronodules sparing the periphery in a 50-year-old HIV-positive male presenting with cough and dyspnea. b Corresponding axial CT scan of the chest showing diffuse, confluent perihilar pulmonary nodules. Biopsy from ulcerative lesions of the larynx and the anus demonstrated Histoplasma capsulatum.
Regardless of disease severity: Liposomal amphotericin B 3–5 mg/kg/day IV for 1–2 weeks followed by itraconazole (see above) or Deoxycholate amphotericin B 0.7–1.0 mg/kg/day IV for 1–2 weeks or until clinical improvement followed by itraconazole (see above)

Talaromycosis

<table>
<thead>
<tr>
<th>Recommended regimen</th>
<th>Duration</th>
<th>Alternative treatment</th>
<th>Commentary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regardless of disease severity: Liposomal amphotericin B 3–5 mg/kg/day IV for 1–2 weeks followed by itraconazole (see above) or Deoxycholate amphotericin B 0.7–1.0 mg/kg/day IV for 2 weeks or until clinical improvement followed by itraconazole (see above)</td>
<td>12 weeks</td>
<td>Voriconazole 400 mg b.i.d. on day 1 followed by 200 mg b.i.d. for 12 weeks or Itraconazole 200 mg p.o. t.i.d. for 3 days, followed by 200 mg p.o. b.i.d. for 12 weeks for patients unable to tolerate or have no access to amphotericin B</td>
<td>– Initial treatment with amphotericin B deoxycholate reduces mortality by 50% compared to itraconazole at 6 months in HIV-associated talaromycosis in the IVAP trial [32]</td>
</tr>
</tbody>
</table>

The clinical manifestations vary depending on the immune status of the host and the infectious dose (Table 2). The disease is usually asymptomatic or manifests as an acute respiratory illness that is self-limiting in immunocompetent persons, but it can result in severe illness with progressive pulmonary disease or disseminated infection, especially in immunocompromised persons. In most cases histoplasmosis presents with various pulmonary symptoms, often as a subacute pulmonary infection 3–21 days after exposure. Symptoms are usually mild. Fever, chills, headache, myalgia, anorexia, cough, and chest pain may occur in the more heavily exposed individuals. Pulmonary histoplasmosis is generally classified according to radiographical appearance and includes (1) acute diffuse pulmonary disease with diffuse infiltrates on chest imaging, (2) acute localized pulmonary disease with localized infiltrates and mediastinal lymphadenopathy, (3) chronic cavitary pulmonary histoplasmosis, and (4) mediastinal syndromes (e.g., mediastinitis, fibrosis), broncholithiasis, or pulmonary nodules (Fig. 1–4) [2, 4]. Disseminated histoplasmosis occurs primarily in patients with underlying immunocompromising disorders, in particular those with impairment of T-cell immunity such as in HIV infection, in patients who are treated with TNF-α inhibitors, and in patients with IFN-γ receptor deficiency [5, 6]. In endemic areas or in travelers with an appropriate travel history, pulmonary histoplasmosis should be considered as an important differential diag-

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nosis to pulmonary tuberculosis, malignancy and sarcoidosis. Extrapulmonary manifestations such as pericarditis, arthritis/arthralgia, or erythema nodosum are also reported.

Coccidioidomycosis

Pulmonary coccidioidomycosis (i.e., valley fever) refers to pulmonary infection by the dimorphic fungi Coccidioides immitis and Coccidioides posadasii (Table 1). It is endemic in the southwestern parts of the USA (California, Arizona, New Mexico, Utah, and Nevada) and parts of Central and South America (Mexico, Brazil, Argentina). Outbreaks have been reported in military trainees, in archeological workers, or have been associated with dust storms, as well as laboratory-acquired infection [7–11].

Approximately two-thirds of infected persons remain asymptomatic or develop self-limiting respiratory symptoms. When symptomatic, pulmonary involvement is common (>95% of all cases). The most common clinical manifestations are chest pain, cough, fever, weight loss, and fatigue, often associated with dermatological manifestations including erythema nodosum (Fig. 5) or erythema multiforme and rheumatological manifestations including myalgia and arthralgia. Radiological presentation can vary considerably (Table 2) (Fig. 6, 7). The disease can spread from the lungs hematogenously to bones, joints, skin, and the central nervous system. Some patients have persistent pulmonary complications including residual pulmonary nodules (coccidioidomas), fibrosis and cavities, with the concurrent risks of developing chronic pulmonary aspergillosis or pulmonary abscesses, or fistulae as long-term sequelae [7, 12, 13].

Paracoccidioidomycosis

Paracoccidioidomycosis caused by the dimorphic fungi Paracoccidioides brasiliensis and Paracoccidioides lutzii is found in certain parts of South America, especially in Brazil, but also in Argentina, Colombia, Ecua-

Fig. 5. Erythema nodosum in a patient with coccidioidomycosis.

Fig. 6. a Chest X-ray of a 30-year-old man with coccidioidomycosis showing bilateral large confluent infiltrates predominantly located in the lower lung fields. b Corresponding axial CT scan of the chest shows multiple large nodules. The patient presented with intense asthenia, cough, and chest pain. Clinical symptoms started 7 days after having participated in armadillo hunting in northeastern Brazil.
It is usually seen in individuals working in rural areas (e.g., farmers). Outbreaks of paracoccidioidomycosis have been reported [16, 17].

Infection is often asymptomatic. Symptomatic disease is divided into an acute/subacute form and a chronic form. The acute form occurs in children and young adults (juvenile form), develops more rapidly, usually within 45 days after exposure, is progressive and more severe. Patients present with infection of the lymphatic system, manifested by enlarged lymph nodes that can develop into abscesses or draining fistulae. Important differential diagnoses such as visceral leishmaniasis or tuberculosis should be considered. The disease can disseminate through the reticuloendothelial system manifested as hepatosplenomegaly and bone marrow dysfunction.

The chronic (adult) form represents reactivation of the primary infection and develops over months to years. Pulmonary involvement is the most frequent manifestation, but the disease may affect any other organs (Fig. 8-10). Patients usually present with dry cough and dyspnea and can have extensive radiographic findings varying from localized consolidations, nodules, cavities, and bilateral infiltrates to chronic findings of septal or interlobular thickening consistent with fibrosis. Hematogenous dissemination to the oropharynx area occurs over 50% of the time and is manifested as granulomatous ulcerative oropharyngeal lesions called “mulberry-like” stomatitis (Fig. 11). Infection by *P. brasiliensis* occurs mainly by inhalation. Patients often present with pulmonary symptoms associated with fever, leukocytosis with hypereosinophilia, and radiological signs of apical pleural and pulmonary lesions (Fig. 12). Enlarged lymph nodes are not a common finding, except in children. Immuno-compromised patients such as those with HIV infection, cancer, malnutrition, alcoholism, or drug abuse are at risk for the development of disseminated disease with a more rapid progression with involvement of the lung, liver, lymph nodes, and skin. Occasionally it is found in travelers [18].

**Fig. 7.** A 50-year-old female traveled for 1 week on a retreat to a lodge in the Arizona desert. Eleven days after return, she presented with cough, dyspnea, and fever. She was diagnosed as having coccidioidomycosis. Soon afterwards, she developed typical erythema nodosum lesions on her legs. Her chest X-ray showed faint reticular opacities in the right upper lobe, as well as a nodular opacity in the right apex. A CT scan shows a cavitating nodule in the right apex. Mediastinal images revealed multiple enlarged lymph nodes.

**Fig. 8.** Axial CT scans of the chest showing various types of lesions of paracoccidioidomycosis in a 42-year-old farmer presenting with fever, asthenia, severe weight loss, dysphagia, and cough. Physical examination showed diffuse enlarged lymph nodes, notably in the mid and posterior cervical chains and a small ulcerated lesion in the pharynx. Microscopy of bronchoalveolar lavage showed *Paracoccidioides brasiliensis*. a Axial CT scan of the chest shows nodules associated with ground-glass opacities and consolidations beside cavities with irregular walls. b The larger cavity on the left side shows a small round mass inside. Basal parts of the lung show peripheral confluent opacities without cavities, some displaying the reverse halo sign.
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**Fig. 9.** (a) Fistulated and enlarged cervical lymph node in a 60-year-old farmer from Brazil presenting with cough, dysphagia, and hoarseness since 6 months. Microscopy of lymph node material revealed *Paracoccidioides brasiliensis*. (b) Axial CT scan of the chest at the carina level shows nodules and consolidation with a thickened bronchovascular bundle (white arrows) in addition to areas of cicatricial emphysema.

**Fig. 10.** (a) Chest X-ray showing diffuse micronodular interstitial infiltrates predominantly in the lower fields of the lung in a 35-year-old farmer in the interior of the state of Rio de Janeiro. He presented with fever for about 40 days, asthenia, and severe weight loss. Immunodiffusion was positive for *Paracoccidioides brasiliensis*. (b) Forty days later the X-ray showed a progression of the pulmonary lesions with volumetric reduction and hypertransparent images. (c) Axial CT scan of the chest showing extensive areas of cicatricial emphysema in the left upper lobe. The patient developed respiratory insufficiency and died. (d) Postmortem biopsy revealed budding cells of *P. brasiliensis* (silver stain).
Blastomycosis

The causative pathogens for blastomycosis are the dimorphic fungi *Blastomyces dermatitidis* and *Blastomyces gilchristii*, which are found in humid soil containing decaying vegetation or decomposed wood and are associated with freshwater drainage basins [19]. It is reported mainly in North America and in Africa, but occasionally has also been reported in Central and South America, Mexico, India, and the Middle East. Blastomycosis has caused a number of outbreaks [20].

After inhalation of the fungus, the most commonly affected organ is the lung followed by the skin, genitourinary tract, and central nervous system (Fig. 13) [21]. Lung involvement is classified as acute or chronic pneumonia. Acute blastomycosis pneumonia cannot be readily distinguished from viral or bacterial pneumonia [21], and has very diverse radiological findings, which include alveolar infiltrates, consolidation with or without cavitation, military or reticulonodular patterns, and small pleural effusions. Acute pneumonia can potentially lead to acute respiratory distress syndrome with multiorgan failure and mortality rates of 50%. The clinical appearance of chronic blastomycosis pneumonia is similar to tuberculosis, lung cancer, or histoplasmosis. The radiological pattern is often described as alveola or fibronodular infiltrations, mainly with an upper lobe distribution [21]. The absence of mediastinal lymph node involvement can be helpful in distinguishing blastomycosis from histoplasmosis.

Sporotrichosis

The dimorphic fungus *Sporothrix schenckii* causes sporotrichosis, a chronic infection mainly found in
healthy individuals with outdoor activities that involve inoculation of soil through the skin or subcutaneous tissues such as gardening and landscaping [22, 23]. It is found worldwide in temperate, but also tropical and subtropical areas. Larger outbreaks of sporotrichosis have been reported [24].

Disseminated disease involving the central nervous system may occur in immunosuppressed patients (e.g. HIV/AIDS, alcoholism, diabetes) [25]. Infection is either due to inhalation of spores or through skin inoculation. The most common form is the lympho-cutaneous manifestation, which has only mild systemic involvement (Fig. 14). Pulmonary involvement usually occurs in patients with chronic obstructive pulmonary disease and alcohol use, and progresses to death if untreated. Symptoms and radiographic appearance are similar to pulmonary tuberculosis and other chronic fungal infections (Fig. 15) [26].

**Talaromycosis**

Talaromycosis is caused by the dimorphic fungus *Talaromyces marneffei* (formally *Penicillium marneffei*) and is endemic in South-East Asia, southern China and northeastern India [27]. Talaromycosis mainly affects immunocompromised patients living or traveling to these regions, in particular patients with advanced HIV infection, with hematological malignancy, and patients undergoing immunosuppressive therapy [28, 29]. Although bamboo rats are a natural reservoir, infection risk is not associated with exposure to bamboo rats but is associated with high humidity and exposure to plants and farmed animals in highland regions [30].

The infection has an insidious onset over weeks to months. The clinical symptoms range from mild to moderate infection with localized disease, to disseminated infection with multiple organ involvement, to severe disease including respiratory failure and shock [31]. The most prominent clinical features in HIV-infected patients are fever, weight loss, anemia, generalized lymphadenopathy, hepatomegaly, and splenomegaly [31]. Typical central umbilicated skin lesions are present in 70% of HIV-infected and up to 40% of non-HIV-infected patients and aid in the rapid diagnosis [32]. Besides the skin and reticuloendothelial system involvement, talaromycosis often invade the gastrointestinal tract with oropharyngeal ulcerations and diarrhea, the pulmonary system with progressive respiratory failure, and occasionally the central nervous system with meningoencephalitis. Arthritis and osteomyelitis are more commonly observed in non-HIV-infected patients. The radiological appearance is diverse and includes interstitial to alveolar infiltrates, or both (Fig. 16), and reticulonodular consolidation, with occasionally a miliary pattern similar to tuberculosis (Fig. 17) [33].

**Diagnosis**

In low-prevalence settings the diagnostic workup for endemic mycoses is challenged by the availability of diagnostic tests, and will differ widely from site to site. In addition, the positive predictive values of some nonculture-based tests will be significantly lower than in endemic set-
**Fig. 13.** a, b Chest X-rays of a 42-year-old male resident of Montreal, Canada, showing extensive consolidation mostly involving the superior segment (S6) of the right lower lobe. He was also a recreational hunter in the region of the St. Lawrence river valley. He presented with a 2-month history of cough, mild hemoptysis, and intermittent fevers. Biopsy revealed budding yeast cells, and culture from a bronchoalveolar lavage grew *Blastomyces dermatitidis*. c, d Two male patients with slowly growing, minimally painful skin lesions, unresponsive to several courses of antibacterial agents. Exposures were most like to be in rural regions of south-western Quebec (c) and central Manitoba (d), Canada. Biopsy specimens revealed noncaseating granulomatous changes, and cultures from biopsy specimens grew *Blastomyces*. There were no respiratory symptoms, but in both cases small nodular lesions were seen on pulmonary imaging, which resolved with antifungal treatment.

**Fig. 14.** Slowly progressive skin lesions in a 24-year-old male traveler returning from several months in India, where he participated in gardening activities at his residence. The initial ulcerating verrucous lesion appeared on the tip of 4th digit, followed by the appearance of popular/nodular lesions on the forearm. Culture from the fingertip ulcer grew *Sporothrix schenckii*. 
tions. As such, awareness of geographical distribution and exposure risks of endemic mycoses, along with case discussion involving an interdisciplinary team comprising infectious disease specialists, microbiologists, radiologists, and pathologists are paramount to making the diagnosis [34]. Culture of most of these organisms (particularly for coccidioides) requires biosafety level 3 laboratory precautions, and the laboratory should be alerted when infection is suspected. Table 3 summarizes diagnostic tests to establish the diagnosis of endemic mycoses.

**Fig. 15.** a) Pyogenic and ulcerated cutaneous lesion of thighs of a 24-year-old male pig caregiver in Brazil, reported onset of the disease about 4 months ago complaining of sporadic fever, cough, asthenia, and weight loss. Chest X-ray (b) and axial CT scans (c, d) show irregularly shaped thick-walled cavitations of different sizes. c) Small nodular cavities can be seen in both lungs, some partially occupied by material with soft tissue density. d) A large thick-walled cavity of the left lung with an irregular wall can be seen. e) Culture of biopsies harvested from the cutaneous lesion demonstrated growth of *Sporothrix schenckii*. 

Color version available online
Histoplasmosis

While evidence is too scarce to recommend a specific diagnostic scheme, a combination of at least two of the following diagnostic methods seems reasonable:

(a) Histology. Typically, biopsy specimens show tuberculoid granulomas with many polymorphonuclear leukocytes and histiocytes with intracellular yeast cells. Differentiation from tuberculosis or sarcoidosis may be difficult – especially in low-prevalence settings. Sensitivity and specificity of histology are highly dependent on the pathologist’s experience, but may be enhanced by fungal stains, e.g., Gomori methenamine silver and periodic acid–Schiff stains [35]. The tiny yeast forms (approx. 2 µm) are easily missed.

(b) Culture. Sensitivity depends on the clinical manifestation, the immunity status of the host, and the fungal burden – it is low in patients with acute pulmonary histoplasmosis [36]. Repeated sputum and/or bronchoalveolar lavage (BAL) and/or bone marrow aspirate for cultures and a long incubation period of cultures (up to 6 weeks) may be necessary.

(c) Antigen test. An enzyme immunoassay (EIA) for detection of *H. capsulatum* galactomannan from blood, urine, and BAL is commercially available in the USA [37]. In a multicenter study with 111 patients with proven progressive disseminated histoplasmosis, the EIA reached a sensitivity of 91% and a specificity of 99% in urine [38]. Sensitivity seems to be lower in immunocompetent hosts, probably due to a lower fungal burden. Similarly, sensitivity is lower in localized pulmonary disease. Of note, there is strong cross-reactivity with other endemic mycoses such as blastomycosis, paracoccidioidomycosis, and talaromycosis [38]. *Histoplasma* sp. contain galactomannan in the cell wall, and may give a positive result in galactomannan assays used for the diagnosis of aspergillosis.

(d) Antibody test. Histoplasma-specific antibodies can be detected either by immunodiffusion, by complement fixation or by EIA, and a commercial assay is available in the USA. Due to the time needed for the development of specific antibodies (up to 3 months) a negative test does not always exclude histoplasmosis. In contrast to antigen testing, sensitivity is higher in immunocompetent hosts, and therefore antigen and antibody are often used together to maximize overall sensitivity [38]. The histoplasmin delayed-type hypersensitivity skin test is used mainly for epidemiological studies, and is not sufficiently accurate for use in individual case diagnosis.

(e) PCR. Several protocols using a variety of molecular targets have been described in the literature, but the role for PCR in the diagnostic workup is not yet certain [34]. Fluorescence in situ hybridization (FISH) has also been described.

Coccidioidomycosis

Serology is the main method for diagnosing *Coccidioides* infection in the USA, where EIAs for specific IgM and IgG are commercially available [39]. A confirmatory immunodiffusion test should be ordered after a positive EIA due to higher specificity [40]. In contrast to most other infectious diseases, anti-coccidioidal antibodies will be positive only in the case of an ongoing or recent infection. A limitation is that antibodies will only form after a latency period of several weeks; therefore the absence of antibodies does not exclude infection in the early course of illness. Direct microscopic examination of clinical specimens and/or culture may be a faster means of diagnosing *Coccidioides* infections [39]. Fungal growth can be observed within 1 week, and identification is followed by a commercially available Genprobe with detects *C. immitis*-specific nucleic acid sequence. To assert disseminated coccidioidomycosis, it is usually necessary to visualize fungi in extrapulmonary biopsy specimens [39].

Paracoccidioidomycosis

A definite diagnosis of paracoccidioidomycosis can be made after direct microscopic examination of the characteristic yeast forms in tissue samples (sputum, ascites, bi-
opsies, scraping of skin lesion, etc.) stained with fungal stains (large yeast cells surrounded with multipolar budding daughter cells resembling a “Mickey mouse head” or a “steering-wheel”) or by culturing the organism [14]. Culture can take up to 1 month to grow; therefore direct microscopy remains the cornerstone in the diagnosis of paracoccidioides infection. Serological methods, in particular the quantitative immunodiffusion method, are widely available in the endemic regions. However, in most cases serology is not necessary for diagnosing paracoccidioidomycosis. While it can be a useful tool to monitor treatment success, so far serologic diagnosis is not standardized, and results from different laboratories may be conflicting [41]. There are no validated serological techniques for diagnosis of infection with *P. lutzii*.

**Blastomycosis**

Direct proof of *Blastomyces* infection – either by culture or visualization of the yeast forms – is necessary for a definite diagnosis of blastomycosis and the method of choice [42]. Culturing *Blastomyces* organisms from respiratory samples of affected patients has a high sensitivity of around 90%, but takes 1–4 weeks. Direct microscopic examination of typical yeast organisms with broad-based buds is characteristic of *Blastomyces*; however, microscopy has a low diagnostic yield of up to 40%. Serological tests for blastomycosis are hampered by their low sensitivities and their lack of specificity due to cross-reactivity against other endemic mycoses, in particular against histoplasmosis [43]. The utility of PCR assays for the detection of *B. dermatidis* has not yet been validated in large clinical studies. Finally, similar to histoplasmosis, a single antigen detection assay is available in the USA [44]. The assay has a high sensitivity of around 90%, but also lacks specificity due to cross-reactivity – especially with histoplasmosis.

**Sporotrichosis**

Culture is the best option in the diagnostic workup of suspected sporotrichosis [45]. Culture is very sensitive, and visible growth can be seen within 1 week. *S. schenckii* is not considered a colonizer, thus a positive clinical sample is diagnostic. While histopathology may help in showing a pyogenic and granulomatous picture, the organism can only rarely be visualized due to the paucity of organisms [45]. No validated serology or PCR is currently available.

**Talaromycosis**

*T. marneffei* can be cultured from blood and clinical samples using standard media for bacteria culture (Fig. 18). As growth may take approximately 1 week, a presumptive diagnosis can be made based on the visualization of binary fission yeasts on fungal staining of skin scraping, sputum smear, or biopsies [46]. This enables the initiation of antifungal therapy before confirmation of

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**Fig. 17.** a A 30-year-old man who presented to the Hospital for Tropical Diseases in Ho Chi Minh City in 2013 with 1 month of fever, weight loss of 12 kg, dry cough, shortness of breath, enlarged cervical lymph nodes, hepatosplenomegaly, and multiple central umbilicated nodules on his face and trunk. He was diagnosed with HIV and had a CD4 count of 12 cells/mm³. b X-ray of the chest showed a diffuse micronodular interstitial pattern consistent with miliary talaromycosis. Cultures from the lymph node, skin lesions, and blood were all positive for *Talaromyces marneffei*. c *T. marneffei* yeast cells obtained from a Giemsa-stained touch skin smear were seen under the microscope.
culture results. Rapid diagnostic assays are being developed including several monoclonal antibody-based antigen detection EIAs, which have high sensitivity and specificity, and are being evaluated as rapid diagnostic tests [47, 48]. Real-time PCR assays have been developed but sensitivities are currently insufficient (60–70%) to be clinically useful.

**Management**

For most systemic endemic mycoses causing pulmonary disease including histoplasmosis, paracoccidioidomycosis, blastomycosis, sporotrichosis, and talaromycosis, experts generally recommend antifungal treatment with itraconazole. It is the treatment of choice for mild to moderate disease manifestations (Table 4) [14, 22, 49–52]. Mild cases of histoplasmosis with symptoms less than 4 weeks usually do not require antifungal treatment, while paracoccidioidomycosis, blastomycosis, sporotrichosis, and talaromycosis should be treated when diagnosed [14, 22, 50]. Disseminated talaromycoses should be treated as soon as possible to decrease mortality, and initial therapy with amphotericin B deoxycholate has been shown to be superior to itraconazole in the IVAP trial in Vietnam [53]. For all endemic mycoses with severe disease manifestations, amphotericin B is recommended as initial therapy followed by itraconazole consolidation therapy. Generally, lipid formulations of amphotericin B are preferred due to their relatively lower toxicity (infusion related reactions, renal failure, electrolyte disturbance, and anemia). High-dose fluconazole is recommended as the treatment of choice for severe coccidioidomycosis infections, while patients with a mild disease usually recover without any antifungal treatment [39]. Little evidence exists with alternative treatment strategies and the efficacy of different antifungal drugs can differ considerably between endemic mycoses and between different manifestations within each endemic mycosis. Table 4 summarizes current antifungal treatment recommendations according to available guidelines.

**Duration of Itraconazole Treatment**

Duration of itraconazole treatment strongly depends on the specific endemic mycoses, clinical syndrome, and host immune factors (Table 4). Histoplasmosis and talarmycosis usually require a period of 2 weeks of induction therapy followed by 6–12 weeks of consolidated treatment, while paracoccidioidomycosis and sporotrichosis usually require long-term treatment of at least 12 months [14, 51, 52]. Generally, the duration should be guided by clinical improvement and radiological resolution. For immunosuppressed persons, secondary prophylaxis is recommended to prevent disease relapse. In patients with advanced HIV infection, consolidation therapy with itraconazole is recommended until the CD4+ T-cell count increases and remains above 100 cells/mm³ for at least 3–6 months on antiretroviral therapy. Strategies to mitigate the underlying cause of immunosuppression will dictate the duration of secondary prophylaxis (or consolidation therapy). In persons requiring immunosuppressive therapy, management requires a balance between strategies to mitigate immunosuppression and lifelong antifungal prophylaxis.

The treatment duration for a specific endemic mycosis will differ depending on clinical syndrome and host factors. Pulmonary histoplasmosis with its different clinical syndromes is an illustrative example. Asymptomatic patients with pulmonary nodules usually do not benefit from antifungal treatment, while symptomatic patients do. Furthermore, patients with acute diffuse pulmonary histoplasmosis often require only 6 weeks of antifungal treatment, while in patients with chronic cavitary histoplasmosis long-term treatment of at least 12 months is recommended. In AIDS patients with pulmonary histoplasmosis who do not achieve immune reconstitution even lifelong treatment may be recommended [54].

![Image](image_url)
**Dosage of Itraconazole Treatment**

The commonly recommended dosage for itraconazole consolidation treatment is 200 mg once to twice daily depending on the severity of disease (Table 4). Generally, the oral solution of itraconazole is preferred due to the improved absorption compared to capsules and tablets. However, the itraconazole solution is not well tolerated due to the osmotic effect of the co-formulated cyclodextrin [54]. Gastric acid is required for adequate absorption of the capsules and tablets, so they should be taken immediately after meals or with an acidic drink. Antacids should be avoided or taken at least 4–6 h apart from itraconazole tablets and capsules. The oral solution of itraconazole, however, should be taken on an empty stomach. It is recommended to start itraconazole treatment with a loading dose of 200 mg 3 times a day for 3 days to attain adequate drug levels more rapidly. The manufacturer labeling recommends a loading dose only for severe and life-threatening cases, but in these cases the guidelines usually recommend initial therapy with amphotericin B intravenously until clinical improvement before continuation with oral itraconazole. Because of the variable bioavailability and the potential for drug-drug interactions, TDM is recommended, especially for patients who have severe disease, critically ill patients in intensive care unit, patients on multiple drugs including rifampicin and antiretroviral therapy with nonnucleoside reverse transcriptase inhibitors and protease inhibitors, and patients with infections of the central nervous system, eyes or bones. However, TDM is not universally available and several limitations have to be considered (e.g., assays are not standardized, optimal timing of sampling, sample transportation, unclear reference values) [55].

**Amphotericin B Treatment**

Early intravenous amphotericin B treatment is recommended for most severe cases of systemic endemic mycoses (Table 4). Generally, lipid-formulated amphotericin B is preferred due to reduced toxicity. However, in many resource-constrained settings, lipid-formulated amphotericin B is not available or affordable. Deoxycholate amphotericin B still remains an effective alternative, but nephrotoxicity is common and should be closely monitored. Toxicity is significantly mitigated by daily saline and potassium supplementation. The commonly recommended duration of amphotericin B treatment is 1–2 weeks, but strongly depends on the severity of disease and the clinical condition of the patient. After clinical stabilization of the patient treatment should be changed to itraconazole.

**Follow-Up and Complications**

Azoles strongly influence the enzymatic activity of cytochrome P450 (e.g., CYP3A4), which can lead to considerable drug-drug interactions [56]. TDM can assist in detecting subtherapeutic drug concentrations due to malabsorption and drug-drug interaction and in optimizing individual dosage regimes. Treatment monitoring and patient follow-up are essential to detect antifungal side effects, drug-drug interactions, treatment failure, and pulmonary sequelae. Long-term sequelae such as chronic pulmonary aspergillosis should be considered in patients with cavitary destruction of lung parenchyma [12, 57]. Symptoms may persist for several months and a lung function test (usually showing an obstructive pattern) may help to monitor the course of disease.

**Conclusions**

This review article should guide physicians in the diagnosis and management of systemic endemic mycoses causing pulmonary disease. Several aspects have to be considered.

First, clinical presentation and radiological pattern of systemic endemic mycoses may mimic other diseases and are nonspecific. The medical history plays a central role, especially the travel history and information on risk factors for potential environmental exposures. Having a clinical suspicion is critical as it facilitates specific mycological diagnostics and communication with laboratory personnel on potential biosafety risk (in particular for Coccidioides spp.). Physicians need to be aware of basic disease manifestations and the diversity of clinical and radiological patterns.

Second, even when an endemic mycosis is suspected, diagnoses may be hampered by the lack of availability of diagnostic tests, especially in low-prevalence settings. Consultation with a mycology reference laboratory is reasonable to discuss proper sample collection and available diagnostic tests. Test results should be interpreted with consideration for their performance and for the lower positive predictive values of some of these tests in comparison to what are reported from endemic regions. Culture or histology from clinical samples (e.g., BAL, lung tissue) is the method of choice for most endemic mycoses. A combination of different diagnostic methods is reasonable, and may increase the likelihood of establishing a diagnosis.

Third, if antifungal treatment is indicated itraconazole (or fluconazole in the case of coccidioidomycoses) is the
treatment of choice in mild to moderate cases, except for talaromycosis, where amphotericin B should be the initial treatment. Early amphotericin B therapy (preferably lipid formulations) is recommended in severe cases until clinical stabilization of the patient before changing to itraconazole consolidation therapy. Drug-drug interactions, adverse events, and possible long-term sequelae should be monitored. Duration of treatment differs significantly between endemic mycoses and depends on the specific mycoses, severity of disease, clinical syndrome, and the immune status of the hosts.

In low-prevalence settings it is advisable to discuss patients with suspected endemic mycoses with an interdisciplinary team involving infectious disease specialists, microbiologists, radiologists, and pathologists.

Disclosure Statement

The authors have no conflicts of interest to declare.

References


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