Endemic mycoses: Overlooked causes of community acquired pneumonia

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Summary
The endemic mycoses are important but often overlooked causes for community acquired pneumonia. Delays in recognition, diagnosis and proper treatment often lead to disastrous outcomes. This topic is not usually discussed in reviews and guidelines addressing the subject of community acquired pneumonia. In this review we discuss the three major endemic mycoses in North America that present as community acquired pneumonias; Coccidioidomycosis, Histoplasmosis and Blastomycosis. We discuss their epidemiology, clinical presentations, methods of diagnosis and current treatment strategies.

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KEYWORDS
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Endemic mycosis;
Histoplasmosis;
Coccidioidomycosis;
Blastomycosis

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**Introduction**

The endemic mycoses are important but often overlooked causes for community acquired pneumonia (CAP). Of note is that they often occur outside of the traditional endemic area. For example, in a review of endemic mycoses among the elderly, one quarter of cases of coccidioidomycosis occurred outside the southwest United States.\(^1\) Not only are the endemic mycoses common causes for hospitalizations, they are often severe, fatal in nearly 10% of cases.\(^2\) Surprisingly, deaths occurred overwhelmingly (87%) in nonimmunocompromised subjects. The failure to consider and delay in testing for the endemic mycoses contributes to the poor outcome.

**Coccidioidomycosis**

**Epidemiology**

Coccidioidomycosis is a common fungal cause of community acquired pneumonia in the southwest endemic areas.\(^3\)-\(^5\) Table 1. Most infections are acquired through soil disruption and subsequent inhalation of airborne arthroconidia. As such, “haboob” sand storms near Phoenix, Arizona as well as military training exercises in California are frequent culprits of outbreaks.

**Clinical**

Coccidioidomycosis mimics bacterial causes of CAP in healthy individuals and immunocompromised patients. About 60% of people infected are asymptomatic, and of symptomatic cases 95% experience a self-limited infection that resolves after several weeks. Approximately 1% of patients will have disseminated infection with the most common extra thoracic sites being skin, soft tissue, bone, and meninges.\(^6\) Symptoms of acute infection resemble bronchitis or pneumonia and are indistinguishable from other causes of community acquired pneumonia.\(^3,4,7\) Table 1. In retrospective studies, patients with coccidioidomycosis were less likely to have cough and sputum production but more likely to have eosinophilia, pleurisy, myalgia, rash, and fatigue than patients without coccidioidomycosis.\(^4,5\) Eosinophilia occurs in a quarter of cases and may suggest coccidioidal pneumonia or prompt further testing. Although resolution is the norm, chronic progressive, often apical cavitary pneumonia resembling tuberculosis may occur, and peripheral cavities can rupture causing pneumothorax or pyopneumothorax. Pleural manifestations are more prominent in coccidioidomycosis than other endemic fungal diseases.

**Radiographic**

The radiologic findings of acute coccidioidomycosis are diverse and nonspecific. Pulmonary infiltrates are identified in the majority of patients, and pleural effusions and adenopathy are common.\(^6\) Table 1. Pulmonary nodules and cavities are identified in less than 5% of cases. Immunosuppressed patients may manifest a diffuse “miliary” pattern.\(^6\) CT scans are more sensitive, identifying effusions, hilar lymph nodes, micronodular infiltrates, and multifocal ground glass infiltrates more readily. Mediastinal and hilar adenopathy is common, but not to the degree that is seen

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Coccidioidomycosis</th>
<th>Blastomycosis</th>
<th>Histoplasmosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exposure history</td>
<td>Sand storms, construction, military exercises, often dry period following rainy seasons</td>
<td>Outdoor activity near waterways</td>
<td>Exposure to soil containing bat or bird droppings, usually unrecognized</td>
</tr>
<tr>
<td>Clinical findings</td>
<td>Respiratory symptoms, fever, fatigue, eosinophilia</td>
<td>Respiratory symptoms, skin or bone lesions</td>
<td>Respiratory symptoms, fever, arthralgia</td>
</tr>
<tr>
<td>Chest radiographs/CT</td>
<td>Focal and diffuse infiltrates, cavities, pleural effusion, adenopathy, micronodular infiltrates</td>
<td>Lobar consolidation, diffuse infiltrates, nodular infiltrates</td>
<td>Focal, diffuse or cavitary infiltrates, hilar or mediastinal lymphadenopathy</td>
</tr>
</tbody>
</table>
in some patients with acute histoplasmosis. Lymph nodes and nodules exhibit varying degrees of uptake on PET scans.

Small non-calcified nodules are common residua of acute Coccidioides that can be confused with malignancy. Nodules may evolve into thin walled cavities by shelling out the nodule contents. These cavities usually resolve but may be sanctuary for secondary infection or mycetoma, or may cause pneumothorax or hemoptysis.

**Diagnosis**

In a large proportion of community acquired pneumonia patients in the endemic area, diagnostic testing for coccidioidomycosis is not performed. In a large retrospective cohort, patients more likely to be tested for coccidioidomycosis were adults and immunosuppressed patients. Patients who experienced symptoms for >14 days, manifest a rash, or had chest pain were also more likely to be tested.

Rapid diagnosis can be achieved by cytopathologic examination of respiratory specimens in patients with lung infiltrates or cavitary disease, positive in one quarter to two-thirds of cases. Table 2: Simultaneous transbronchial biopsy may increase the diagnostic yield. Nodules may be biopsied to exclude malignancy. In many patients with negative cytopathology, culture is positive. In patients with milder illnesses, however, cytopathology and culture are performed in only 40–60% of cases, respectively.

Despite the availability of more rapid diagnostic methods, culture remains an important part of the diagnostic workup, providing the only basis for diagnosis in some cases.

Serologic tests for antibodies are the most widely used method of diagnosis and are perhaps more useful in diagnosing coccidioidal infection than the other endemic mycoses. IgM specific for the tube precipitin antigen and IgG specific for the complement fixation antigen can be assayed locally by commercially available immunodiffusion kits or enzyme-linked immunoassay (EIA). IgG antibody to the complement fixation antigen, when positive, can be quantified at reference laboratories and reported as a titer. Any positive titer is considered significant and indicative of infection. Titters are often followed in symptomatic patients or patients with chronic infection to determine treatment efficacy and resolution.

Both EIA and agar gel immunodiffusion provide results with a quick turnaround time. However, controversy arises over the accuracy of IgM antibodies determined by EIA: 100% were judged to be true positives in one but 82% were regarded as false positive in another report. An isolated positive IgM should be confirmed by additional diagnostic testing. Additionally, the antibody test may be falsely negative early in the course of infection or in immunosuppressed patients. False negative EIA was noted in 13% of healthy patients and 33% of immunosuppressed patients, declining to 5% and 17%, respectively when confirmatory tests were performed. Antibody tests may also be negative early in the disease, as noted in half of cases in one study. Thus, negative antibody tests cannot exclude coccidioidomycosis.

*Coccidioides* galactomannan antigen testing is available in select reference laboratories. Antigenemia was detected in 50% of patients with moderate and 71% with moderate to severe disease, among whom tests for antibodies were positive in 54%. Antigenemia was detected in 73% of patients with mild to moderate disease, identifying an additional 29% of cases that would have been missed if only urine was tested. Thus, the greatest sensitivity may be achieved by testing both urine and serum. Antigen also has been detected in BAL in patients with negative results in urine.

Real-time PCR targeting the internal transcribed spacer region 2 sequences exhibited a sensitivity of 100% on respiratory samples, 93% on fresh tissue and 73% on paraffin-embedded tissue, with a specificity of 98–100%. In clinical testing PCR was positive in respiratory specimens in five of nine patients, most of whom were immunosuppressed and culture positive. The relative sensitivity of real-time PCR and antigen detection remains to be determined.

**Management**

In the context of community acquired pneumonia, the decision of whether or not to treat with anti-fungal therapy is based on clinical context and severity of symptoms. When treatment is deemed necessary, azole therapy is preferred. In most cases of acute pulmonary coccidioidomycosis presenting as CAP, fluconazole or itraconazole 400 mg daily for 3–6 months is sufficient. Fluconazole is often used as itraconazole requires closer monitoring with drug levels and careful consideration of drug interactions. Longer therapy (12–18 months) is recommended for cavitary, diffuse pulmonary or disseminated disease.

Lipid formulation of amphotericin B is recommended in patients with extensive, bilateral, or "miliary" pneumonia, or disseminated disease in immunocompromised patients. Patients are frequently transitioned to fluconazole or itraconazole after a week or two and therapy continued for at least 12 months. Table 3: Concomitant steroid therapy may be appropriate if paradoxical worsening or delayed improvement occurs with anti-fungal therapy alone for severe pulmonary coccidioidomycosis. Amphotericin should be used in pregnancy due to concerns regarding the teratogenicity of azole anti-fungal agents, especially in the first trimester.

Asymptomatic pulmonary nodules and small thin walled cavities are not typically treated with antifungals. Occasionally nodules change size and extirpate their contents. However, they can be confused with malignancy when a diagnosis of coccidioidomycosis was not previously

| Table 2 Diagnostic tests in blastomycosis and coccidioidomycosis. |
|---------------------------------|------------------|------------------|
| Parameter                      | Blastomycosis    | Coccidioidomycosis |
| Cytopathology                  | 25–50            | 50                |
| Culture                        | 40–100           | 10–12,17,20,a     |
| Antibody                       | 50–100           | 12,16–18          |
| Antigenuria                    | 50–70            | 10,11,20          |
| Antigenemia                    | 70              | 10,11,45,76      |
| Antigen BAL                    | Single case      | 80                |
| PCR                            | 56–100           | 82,21             |

a Sensitivity in percent (references).
extrapulmonary dissemination occurs in up to third of cases.26,35 most commonly involving skin, bone, and the genitourinary system. Cutaneous or bone lesions in a patient with community acquired pneumonia who resides in the endemic area should raise the suspicion for blastomycosis. Dissemination to the central nervous system may also occur.36

Radiographic
No specific radiographic findings are characteristic enough to suggest the diagnosis of blastomycosis. The most common findings in acute pulmonary blastomycosis include lobar consolidation, air bronchogram, and nodular infiltrates.26,37,38 Table 1. Miliary nodules and interstitial infiltrates are common in severe cases.38 Mediastinal or hilar lymphadenopathy39 and pleural effusions are infrequent.39 Mass like lesions, often mistaken as malignancy, and cavities within areas of consolidation can be seen in chronic cases.26

Diagnosis
The diagnosis is often delayed because of failure to consider blastomycosis in patients with community acquired pneumonia.36 If suspected, the diagnosis usually can be made rapidly by microscopic visualization of the organism or detection of antigen in body fluids,26,40 (Table 2). The yield of cytopathology ranges from 38% to 97%.26,41,42 Histopathology of lung tissue biopsy specimen may provide a diagnosis in some cases with negative cytology.26,43 Definitive diagnosis requires the isolation of the organism by culture which is positive in 67–86% of cases,26,44 often within one week of incubation.

Blastomyces antigen can be detected in serum, urine and BAL fluid, often providing the initial basis for diagnosis.26,40 positive in 85%–93% of patients.26,45,46 Testing both serum and urine may improve the sensitivity for diagnosis by antigen detection. Cross reactions occur in histoplasmosis (96–100%),26,45,46 paracoccidioidomycosis (100%), and penicilliosis marneffei (70%); otherwise specificity is 98% with other mycoses (cryptococcosis, aspergillosis, coccidioidomycosis, and candidiasis).46

PCR methods are promising. Excellent sensitivity and specificity was reported using a real-time method on isolates and clinical specimen.47 This finding requires validation before the role of PCR is known.

Available tests for antibodies to Blastomyces are not used commonly because of poor sensitivity (<50%)26 and

seemed. When unclear, residual nodules frequently lead to biopsy or excision.

Blastomycosis
Epidemiology
The endemic area for blastomycosis overlaps with that of histoplasmosis, but stretches further north into Minnesota, Wisconsin, the Canadian provinces adjacent to the great lakes and the areas surrounding St. Lawrence Seaway in New York and Canada.1 Blastomycosis is less common than histoplasmosis and coccidioidomycosis.2 Recent excavation activity and residence near waterways are risk factors for blastomycosis, (Table 1).24 Point source outbreaks have been reported where most patients present with an acute illness after heavy exposure to contaminated excavation sites. The incubation period ranges from 21 to 106 days with a median of 45 days.25

Clinical
The lungs are the most commonly affected organs in blastomycosis.26,27 The majority of infected individuals are either asymptomatic or manifest a mild self-limited illness.26 Also, most patients are otherwise healthy.26 Acute pulmonary blastomycosis is commonly seen in the setting of an outbreak following heavy, point source exposure. Symptoms are abrupt and include cough productive of purulent sputum, fever, night sweats, dyspnea, chest pain, weight loss, myalgia and occasionally hemoptysis, (Table 1). The illness is often confused with bacterial community acquired pneumonia, and the diagnosis is suspected only after failure to respond to antibacterial therapy.28,29 In one series, diagnosis took more than 30 days in 43% of the cases, with only one quarter diagnosed within a week of presentation.30 The illness may rapidly progresses to acute respiratory distress syndrome (ARDS) and shock in about 10% of cases26,31 with up to 60% mortality.28 Delays in considering and testing for blastomycosis contribute to this poor outcome. Severe pulmonary blastomycosis is more common in young immunocompromised patients32,33 and those with diabetes mellitus.28

Chronic pulmonary blastomycosis is usually gradual in onset, and symptoms include cough productive of purulent sputum, fever, night sweats, malaise, and weight loss.34 The illness can be mistaken for tuberculosis or lung cancer, and is progressive if untreated.34

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Coccidioidomyces23,49</th>
<th>Blastomycosis27,49</th>
<th>Histoplasmosis49,69</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe (ICU)</td>
<td>Lipid amphotericin B 1–2 week then fluconazole or itraconazole</td>
<td>Lipid amphotericin B, 1–2 week then fluconazole</td>
<td>Lipid amphotericin B 1–2 week then itraconazole</td>
</tr>
<tr>
<td>Moderately severe (hospitalize)</td>
<td>Lipid amphotericin B 1–2 week then fluconazole or itraconazole</td>
<td>Lipid amphotericin B 1–2 week then fluconazole</td>
<td>Lipid amphotericin B 1–2 week then itraconazole</td>
</tr>
<tr>
<td>Mild (not hospitalize)</td>
<td>Fluconazole or itraconazole</td>
<td>Itraconazole</td>
<td>Itraconazole</td>
</tr>
</tbody>
</table>

a Consider systemic corticosteroids in patients with ARDS.
specificity, however accuracy may be improved using certain *Blastomyces* antigens.46

**Management**

Treatment is recommended unless clinical resolution has occurred before the diagnosis is made.27,49 A lipid formulation of Amphotericin B is recommended for patients with severe or CNS disease, (Table 3). Amphotericin B is usually administered until there is clinical improvement (1–2 weeks) except in patients with CNS diseases, in which 4–6 weeks is recommended. Itraconazole is administered for 6–12 months after discontinuation of amphotericin B. Itraconazole is the treatment of choice for non-severe cases.50 The recommended dose is 200 mg three times a day for three days followed by 200 mg twice a day for at least six months. A Longer treatment is recommended for immunosuppressed patients, those with bone disease, and those who relapse. Fluconazole is less effective and is not recommended except in patients who do not tolerate itraconazole, and then should be administered at high doses (800 mg/day). Voriconazole has been used51 but its role remains unclear. Corticosteroids may be useful adjuncts to anti-fungal therapy in patients with ARDS.52,53

**Histoplasmosis**

**Epidemiology**

Histoplasmosis is a community acquired infection, most often presenting as pneumonia. Most cases are first treated with antibiotics and the diagnosis is not suspected until they fail to improve. Except in outbreak settings where multiple individuals become ill following a shared activity and present acutely with diffuse pulmonary infiltrates, a history of exposure to sites likely to harbor *Histoplasma* mold is uncommon. Some epidemiologic clues are listed in Table 1.

**Clinical**

There are no unique clinical findings to alert the physician to suspect histoplasmosis. Patients present with cough, chest pain, fever, sweats and malaise, usually occurring between one and three weeks following a high-inoculum exposure,54,55 described as the “epidemic” type of acute pulmonary histoplasmosis, Table 1.56 Severe cases may culminate in respiratory failure28,57 and death.57 Low-level exposure causes mild flu-like illness often lasting for more than a month, referred to herein as subacute pulmonary histoplasmosis.58,59 Although self-limited, patients often undergo unneeded invasive procedures, receive repeated courses of antibiotic therapy, and miss school or work, at a substantial cost.

Patients with underlying obstructive lung disease typically experience chronic pulmonary symptoms accompanied by progressive lung infiltrates with cavitation, termed chronic pulmonary histoplasmosis.55 Cavitation and chronicity may suggest anaerobic infection, for which repeated courses antibiotics are prescribed without clinical benefit before histoplasmosis is suspected.

**Radiographic**

Chest radiographs or CT scans in acute pulmonary histoplasmosis show diffuse reticulonodular or miliary infiltrates, at times accompanied by mediastinal or hilar lymphadenopathy, at times accompanied by mediastinal or hilar lymphadenopathy, at times accompanied by mediastinal or hilar lymphadenopathy.56 Table 4. Similar findings may be seen in patients with progressive disseminated histoplasmosis,60 which should be suspected in the absence of an acute exposure or the presence of immunosuppression. Findings in subacute pulmonary histoplasmosis include hilar or mediastinal lymphadenopathy with localized or patchy infiltrates.55 With healing infiltrates may regress into nodules, which eventually calcify but may cavitate. Imaging studies in chronic pulmonary histoplasmosis show changes of underlying emphysema, upper lobes infiltrates, pleural thickening, volume loss and cavitation, resembling those seen in tuberculosis.55

**Diagnosis**

Demonstration of yeast by cytology or histopathology may provide a rapid diagnosis with high specificity but with lower sensitivity than antigen or antibody detection. Isolation of the organism by culture may provide the only laboratory basis for diagnosis in some patients, but requires at least one week and often up to four weeks to detect positive results. The role of PCR remains to be determined. Good sensitivity and specificity was reported,47 but only six

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Acute pulmonary histoplasmosis</th>
<th>Subacute pulmonary histoplasmosis</th>
<th>Chronic pulmonary histoplasmosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Culture</td>
<td>8/196,4</td>
<td>14/2664</td>
<td>11/2667</td>
</tr>
<tr>
<td>Antibody</td>
<td>39/4164</td>
<td>67/6662</td>
<td>14/1462</td>
</tr>
<tr>
<td>Antigenemia</td>
<td>151/17667</td>
<td>14/1567</td>
<td></td>
</tr>
<tr>
<td>Antigenuria</td>
<td>5/276</td>
<td>22/656</td>
<td>2/275</td>
</tr>
<tr>
<td>Antigen BAL</td>
<td>3/47</td>
<td>2/275</td>
<td>5/57</td>
</tr>
</tbody>
</table>

Table 4: Diagnostic tests in histoplasmosis.
BAL specimens and five other respiratory specimens were tested, of which four BALs were negative. Other studies have shown that PCR was not sensitive when testing BAL and that PCR was less sensitive than pathology when applied to tissues.

Acute pulmonary histoplasmosis: Antigen detection is the most sensitive diagnostic test in acute pulmonary histoplasmosis (Table 4). Both urine and serum must be tested to achieve the highest sensitivity: 38% of cases would have been missed by testing urine only, based on findings in one study. The sensitivity of cytopathology of respiratory specimens is uncertain, but probably low, based upon a review of the findings in published studies. Serologic tests for anti-Histoplasma antibodies are positive in about two-thirds of cases, but not during the first three weeks of infection, based on one report, when diagnosis is often most valuable. Respiratory cultures are positive less than half of cases.

Subacute pulmonary histoplasmosis: As most patients have been ill for more than a month before testing is performed, and antibody tests are usually positive. Accordingly, agar gel immunodiffusion and/or complement fixing antibodies are positive in 95% of cases. The complement fixation test is positive at titers of at least 1:8 in 90%, M bands in three quarters, and H bands in one quarter of patients. CF titers of 1:8 or 1:16 are less than 10%, M bands in three quarters, and H bands in one quarter of patients. CF titers of 1:8 or 1:16 are less than 10%, M bands in three quarters, and H bands in one quarter of patients.

Tests for antigenuria are positive in about one-third of cases, histopathology or cytology in 10–40%, and culture in 10–50%, if invasive procedures are performed. However, the diagnosis can usually be made by serology, avoiding biopsies.

Chronic pulmonary histoplasmosis: Culture of respiratory specimens, antigen testing of BAL or bronchial washings, and tests for antibodies are most useful. Cultures were positive in 65–85% of cases. Culture of sputum when cultures of BAL and/or bronchial washings are negative. Antibody tests are positive in over 90% of cases in most series. Antigen was detected in the urine of 14% of cases in one report and 80% in another, using a more sensitive assay. Detection of high levels of antigenuria, however, suggests concurrent progressive disseminated histoplasmosis.

Management

Lipid amphotericin B and itraconazole are preferred for treatment of histoplasmosis. Liposomal amphotericin B was superior to the deoxycholate formulation for treatment of progressive disseminated histoplasmosis in patients with the acquired immunodeficiency syndrome. Several studies have established effectiveness of itraconazole for treatment of mild to moderately severe histoplasmosis, reviewed elsewhere. Itraconazole blood level monitoring is recommended as levels are highly variable. Drug interactions must also be considered.

Acute pulmonary histoplasmosis: Although most patients recover without therapy, the clinical findings may be severe, recovery may be slow, and death may occur. Accordingly, most patients should be treated. The anecdotal experience supports treatment efficacy for acute pulmonary histoplasmosis. Lipid amphotericin B is recommended in those who are hypoxic, accompanied by corticosteroids for the first week or two. Patients with milder illnesses may be treated with itraconazole alone, 200 mg once or twice daily. The optimal duration of therapy is unknown, but a six to 12 week course is recommended.

Subacute pulmonary histoplasmosis: Most patients with have mild symptoms and have improved by the time the diagnosis is established. Thus, anti-fungal therapy is usually unnecessary. Itraconazole 200 mg once or twice daily given for up to 12 weeks may be helpful in those who remain symptomatic for more than one month.

Chronic pulmonary histoplasmosis: Treatment is indicated in all patients with chronic pulmonary histoplasmosis. Treatment reduces symptoms, eradicates the organism from respiratory specimens, and reduces pulmonary infiltrates. Itraconazole 200 mg once or twice daily is recommended for at least 12 months, and until the chest imaging shows no further improvement. Relapse occurs in about 15% of cases followed for 1–2 years.

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Conflict of interest statement

Dr. L.J. Wheat is an employee of MiraVista Diagnostics, the laboratory that provides the Histoplasma, Blastomyces and Coccidioidomyces antigens.

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