only one site or multiple anatomic foci. When it occurs, clinical dissemination is usually evident within the first few months after primary pulmonary infection.

Coccidioidal meningitis, if untreated, is uniformly fatal. Patients usually present with a persistent headache, which is sometimes accompanied by lethargy and confusion. Nuchal rigidity, if present, is not severe. Examination of cerebrospinal fluid (CSF) demonstrates lymphocytic pleocytosis with profound hypoglycorrhachia and elevated protein levels. CSF eosinophilia is occasionally documented. With or without appropriate therapy, patients may develop hydrocephalus, which presents clinically as a marked decline in mental status, often with gait disturbances.

DIAGNOSIS

As mentioned above, coccidioidomycosis is often misdiagnosed as community-acquired bacterial pneumonia. Clues that suggest a diagnosis of coccidioidomycosis include peripheral-blood eosinophilia, hilar or mediastinal adenopathy on radiographic imaging, marked fatigue, and failure to improve with antibiotic therapy.

Serology plays an important role in establishing a diagnosis of coccidioidomycosis. Several techniques are available, including the traditional tube-precipitin (TP) and complement-fixation (CF) assays, immunodiffusion (IDTP and IDCF), and enzyme immunoassay (EIA) to detect IgM and IgG antibodies. TP and IgM antibodies are found in serum soon after infection and persist for weeks. They are not useful for gauging disease progression and are not found in the CSF. The CF and IgG antibodies occur later in the course of the disease and persist longer than TP and IgM antibodies. Rising CF titers are associated with clinical progression, and the presence of CF antibody in CSF is indicative of coccidioidal meningitis. Antibodies disappear over time in persons whose clinical illness resolves.

Because of its commercial availability, the coccidioidal EIA is frequently used as a screening tool for coccidioidal serology. There has been concern that the IgM EIA is occasionally falsely positive, particularly in asymptomatic individuals. In addition, while the sensitivity and specificity of the IgG EIA appear to be higher than those of the CF and IDCF assays, the optical density obtained in the EIA does not correlate with the serologic titer of either of the latter tests.

Coccidioides grows within 3–7 days at 37°C on a variety of artificial media, including blood agar. Therefore, it is always useful to obtain samples of sputum or other respiratory fluids and tissues for culture in suspected cases of coccidioidomycosis. The clinical laboratory should be alerted to the possibility of this diagnosis, since *Coccidioides* poses a significant laboratory hazard if it is inadvertently inhaled. The organism can also be identified directly. While treatment of samples with potassium hydroxide is rarely fruitful in establishing the diagnosis, examination of sputum or other respiratory fluids after Papanicolaou or Gomori methenamine silver staining reveals spherules in a significant proportion of patients with pulmonary coccidioidomycosis. For fixed tissues (e.g., those obtained from biopsy specimens), spherules with surrounding inflammation can be demonstrated with hematoxylin-eosin or Gomori methenamine silver staining.

A commercially available test for coccidioidal antigenuria and antigenemia has been developed and appears to be particularly useful in immunosuppressed patients with severe or disseminated disease. False-positive results may occur in cases of histoplasmosis or blastomycosis. Some laboratories offer genomic detection by polymerase chain reaction.

TREATMENT COCCIDIOIDOMYCOSIS

Currently, two main classes of antifungal agents are useful for the treatment of coccidioidomycosis (Table 237-1). While once prescribed routinely, amphotericin B in all its formulations is now reserved for only the most severe cases of dissemination and for intrathecal or intraventricular administration to patients with coccidioidal meningitis in whom triazole antifungal therapy has failed. The original formulation of amphotericin B, which is dispersed with deoxycholate, is usually administered intravenously in doses of 0.7–1.0 mg/kg either daily or three times per week. The newer lipid-based formulations—amphotericin B lipid complex (ABLC), amphotericin B colloidal dispersion (ABCD), and amphotericin B liposomal complex (L-AmB)—are associated with less renal toxicity. The lipid dispersions are administered intravenously at doses of 5 mg/kg daily or three times per week.

TABLE 237-1 CLINICAL PRESENTATIONS OF COCCIDIOIDOMYCOSIS, THEIR FREQUENCY, AND RECOMMENDED INITIAL THERAPY FOR THE IMMUNOCOMPETENT HOST

Clinical Presentation	Frequency, %	Recommended Therapy
Asymptomatic infection	60	None
Primary pneumonia (focal)	40	In most cases, none[a]
Diffuse pneumonia	<1	Amphotericin B followed by prolonged oral triazole therapy
Pulmonary sequelae	5	
Nodule	—	None
Cavity	—	In most cases, none[b]
Chronic pneumonia	—	Prolonged triazole therapy
Disseminated disease	≤1	
Skin, bone, joint, soft tissue disease	—	Prolonged triazole therapy[c]
Meningitis	—	Lifelong triazole therapy[d]

[a]Treatment is indicated for hosts with depressed cellular immunity as well as for those with prolonged symptoms and signs of increased severity, including night sweats for >3 weeks, weight loss of >10%, a complement-fixation titer of >1:16, and extensive pulmonary involvement on chest radiography. [b]Treatment (usually with the oral triazoles fluconazole and itraconazole) is recommended for persistent symptoms. [c]In severe cases, some clinicians would use amphotericin B as initial therapy. [d]Intraventricular or intrathecal amphotericin B is recommended in cases of triazole failure. Hydrocephalus may occur, requiring a CSF shunt.

Note: See text for dosages and durations.

Triazole antifungals are the principal drugs now used to treat most cases of coccidioidomycosis. Clinical trials have demonstrated the usefulness of both fluconazole and itraconazole. Evidence indicates that itraconazole may be more efficacious against bone and joint disease. Because of its demonstrated penetration into CSF, fluconazole is the azole of choice for the treatment of coccidioidal meningitis, but itraconazole also is effective. For both drugs, a minimal oral adult dosage of 400 mg/d should be used. The maximal dose of itraconazole is 200 mg three times daily, but higher doses of fluconazole may be given. Two newer triazole antifungals, posaconazole and voriconazole, are now available. Data suggest that both drugs may be useful against infections, including meningitis, in which prior fluconazole therapy has failed. High-dose triazole therapy may be teratogenic during the first trimester of pregnancy; thus, amphotericin B should be considered as therapy for coccidioidomycosis in pregnant women during this period.

Most patients with focal primary pulmonary coccidioidomycosis require no therapy. Patients for whom antifungal therapy should be considered include those with underlying cellular immunodeficiencies and those with prolonged symptoms and signs of extensive disease. Specific criteria include symptoms persisting for ≥2 months, night sweats occurring for >3 weeks, weight loss of >10%, a serum CF antibody titer of >1:16, and extensive pulmonary involvement apparent on chest radiography.

Diffuse pulmonary coccidioidomycosis represents a special situation. Because most patients with this form of disease are profoundly hypoxemic and critically ill, many clinicians favor beginning therapy with amphotericin B and switching to an oral triazole antifungal once clinical improvement occurs.

The nodules that may follow primary pulmonary coccidioidomycosis do not require treatment. As noted above, these nodules are not easily distinguished from pulmonary malignancies by means of radiographic imaging. Close clinical follow-up and biopsy may be required to distinguish between these two entities. Most pulmonary cavities do not require therapy. Antifungal treatment should be considered in