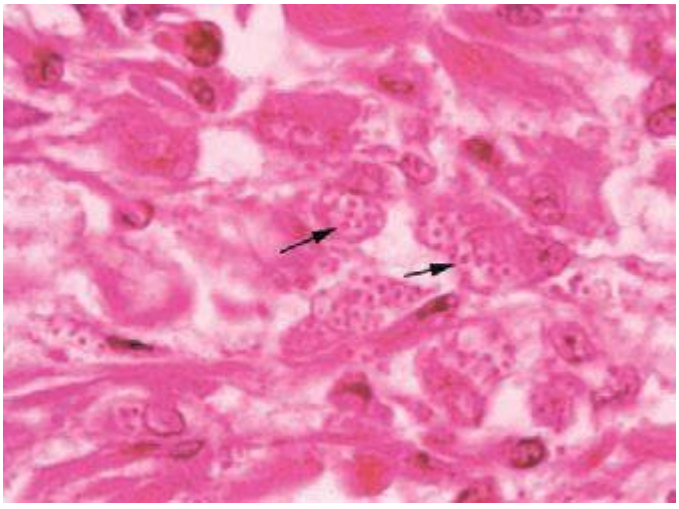

FIGURE 236-3 **Intracellular yeasts (*arrows*) of *H. capsulatum*** in a liver biopsy specimen (hematoxylin and eosin stain).

CLINICAL MANIFESTATIONS

The clinical spectrum of histoplasmosis ranges from asymptomatic infection to life-threatening illness. The attack rate and the extent and severity of the disease depend on the intensity of exposure, the immune status of the exposed individual, and the underlying lung architecture of the host.

In immunocompetent individuals with low-level exposure, most *Histoplasma* infections are either asymptomatic or mild and self-limited. Of adults residing in endemic areas, 50–80% have skin-test and/or radiographic evidence of previous infection without clinical manifestations. When symptoms do develop, they usually appear 1–4 weeks after exposure. Heavy exposure leads to a flulike illness with fever, chills, sweats, headache, myalgia, anorexia, cough, dyspnea, and chest pain. Chest radiographs usually show signs of pneumonitis with prominent hilar or mediastinal adenopathy. Pulmonary infiltrates may be focal with light exposure or diffuse with heavy exposure. Rheumatologic symptoms of arthralgia or arthritis, often associated with erythema nodosum, occur in 5–10% of patients with acute histoplasmosis. Pericarditis may also develop. These manifestations represent inflammatory responses to the acute infection rather than its direct effects. Hilar or mediastinal lymph nodes may undergo necrosis and coalesce to form large mediastinal masses that can cause compression of great vessels, proximal airways, and the esophagus. These necrotic lymph nodes may also rupture and create fistulas between mediastinal structures (e.g., bronchoesophageal fistulas).

PDH is typically seen in immunocompromised individuals, who account for ~70% of cases. Common risk factors include AIDS (CD4+ T cell count, <200/μL), extremes of age, immunosuppressive medications administered for prevention or treatment of rejection following transplantation (e.g., prednisone, mycophenolate, calcineurin inhibitors, and biologic response modifiers), and methotrexate, anti-TNF-α agents, or other biologic response modifiers given for inflammatory arthritis or Crohn's disease.

The spectrum of PDH ranges from an acute, rapidly fatal course—with diffuse interstitial or reticulonodular lung infiltrates causing respiratory failure, shock, coagulopathy, and multiorgan failure—to a more subacute course with a focal organ distribution. Common manifestations include fever and weight loss. Hepatosplenomegaly also is common. Other findings may include meningitis or focal brain lesions, ulcerations of the oral mucosa, gastrointestinal ulcerations, and adrenal insufficiency. Prompt recognition of this devastating illness is of paramount importance in patients with more severe manifestations or with underlying immunosuppression, especially AIDS (Chap. 226).

Chronic cavitary histoplasmosis is seen in smokers who have structural lung disease (e.g., bullous emphysema). This chronic illness is characterized by productive cough, dyspnea, low-grade fever, night sweats, and weight loss. Chest radiographs usually show upper-lobe infiltrates, cavitation, and pleural thickening—findings resembling those of tuberculosis. Without treatment, the course is slowly progressive.

Fibrosing mediastinitis is an uncommon and serious complication of histoplasmosis. In certain patients, acute infection is followed for unknown reasons by progressive fibrosis around the hilar and mediastinal lymph nodes. Involvement may be unilateral or bilateral; bilateral involvement carries a worse prognosis. Major manifestations include superior vena cava syndrome, obstruction of pulmonary vessels, and airway obstruction. Patients may experience recurrent pneumonia, hemoptysis, or respiratory failure. Fibrosing mediastinitis is fatal in up to one-third of cases.

In healed histoplasmosis, calcified mediastinal nodes or lung parenchyma may erode through the walls of the airways and cause hemoptysis. This condition is called *broncholithiasis*.

The clinical features and management of histoplasmosis caused by the genetically different clades in Central and South America are similar to those of the disease in North America. African histoplasmosis caused by var. *duboisii* is clinically distinct and is characterized by frequent skin and bone involvement.

DIAGNOSIS

Fungal culture remains the gold standard diagnostic test for histoplasmosis. However, culture results may not be known for up to 1 month, and cultures are often negative in less severe cases. Cultures are positive in ~75% of cases of PDH and chronic pulmonary histoplasmosis. Cultures of bronchoalveolar lavage (BAL) fluid are positive in about half of cases that include acute pulmonary histoplasmosis causing diffuse infiltrates with hypoxemia. In PDH, the culture yield is highest for BAL fluid, bone marrow aspirate, and blood. Cultures of sputum or bronchial washings are usually positive in chronic pulmonary histoplasmosis. Cultures are typically negative, however, in other forms of histoplasmosis.

Fungal stains of cytopathology or biopsy materials showing structures resembling *Histoplasma* yeasts are helpful in the diagnosis of PDH, yielding positive results in about half of cases. Yeasts can be seen in BAL fluid (Fig. 236-2) from patients with diffuse pulmonary infiltrates, in bone marrow biopsy samples, and in biopsy specimens of other involved organs (e.g., the adrenal glands). Occasionally, yeasts are seen in blood smears from patients with severe PDH. However, artifacts and other fungal elements sometimes stain positive and may be misidentified as *Histoplasma* yeasts.

The detection of *Histoplasma* antigen in body fluids is extremely useful in the diagnosis of PDH and acute diffuse pulmonary histoplasmosis. The sensitivity of this technique is >95% in patients with PDH and >80% in patients with acute pulmonary histoplasmosis if both urine and serum are tested. Antigen level correlates with severity of illness in PDH and can be used to follow disease progression as levels predictably decrease with effective therapy. An increase in antigen levels also predicts relapse. Antigen can be detected in cerebrospinal fluid from patients with meningitis and in BAL fluid from those with pneumonia. Cross-reactivity occurs with African histoplasmosis, blastomycosis, coccidioidomycosis, paracoccidioidomycosis, and *Penicillium marneffei* infection.

Serologic tests, including immunodiffusion and complement fixation, are useful for the diagnosis of histoplasmosis in immunocompetent patients. Serum antibody titers may rise fourfold in patients with acute histoplasmosis. Serologic tests are especially useful for the diagnosis of chronic pulmonary histoplasmosis. The limitations of serology, however, include insensitivity early in the course of infection (at least 1 month is required for the production of antibodies), insensitivity in immunosuppressed patients, and persistence of detectable antibody for several years after infection. Positive results from past infection may lead to a misdiagnosis of active histoplasmosis in a patient with another disease process.

TREATMENT HISTOPLASMOSIS

Treatment recommendations for histoplasmosis are summarized in Table 236-1. Treatment is indicated for all patients with PDH or chronic pulmonary histoplasmosis as well as for symptomatic