Chapter 38: Fungal Infections, Invasive

HISTOPLASMOSIS

- *Histoplasmosis* is caused by inhalation of dust-borne microconidia of the dimorphic fungus *Histoplasma capsulatum*. In the United States, most disease is localized along the Ohio and Mississippi river valleys.

Clinical Presentation and Diagnosis

- In the vast majority of patients, low-inoculum exposure to *H. capsulatum* results in mild or asymptomatic pulmonary histoplasmosis. The course of disease is generally benign, and symptoms usually abate within a few weeks of onset. Patients exposed to a higher inoculum during a primary infection or reinfection may experience an acute, self-limited illness with flu-like pulmonary symptoms, including fever, chills, headache, myalgia, and nonproductive cough.
- Chronic pulmonary histoplasmosis generally presents as an opportunistic infection imposed on a preexisting structural abnormality, such as lesions resulting from emphysema. Patients demonstrate chronic pulmonary symptoms and apical lung lesions that progress with inflammation, calcified granulomas, and fibrosis. Progression of disease over a period of years, seen in 25%–30% of patients, is associated with cavitation, bronchopleural fistulas, extension to the other lung, pulmonary insufficiency, and often death.
- In patients exposed to a large inoculum and in immunocompromised hosts, progressive illness, disseminated histoplasmosis, occurs. The clinical severity of the diverse forms of disseminated histoplasmosis (**Table 38-1**) generally parallels the degree of macrophage parasitization observed.
- Acute (infantile) disseminated histoplasmosis is seen in infants and young children and (rarely) in adults with Hodgkin disease or other lymphoproliferative disorders. It is characterized by unrelenting fever; anemia; leukopenia or thrombocytopenia; enlargement of the liver, spleen, and visceral lymph nodes; and GI symptoms, particularly nausea, vomiting, and diarrhea.
- If untreated it is uniformly fatal in 1-2 months. A less severe “subacute” form of the disease, which occurs in both infants and immunocompetent adults, is characterized by focal destructive lesions in various organs, weight loss, weakness, fever, and malaise.
- Most adults with disseminated histoplasmosis demonstrate a mild, chronic form of the disease. Untreated patients are often ill for 10–20 years, with long asymptomatic periods interrupted by relapses characterized by weight loss, weakness, and fatigue.
- Adult patients with acquired immunodeficiency syndrome (AIDS) demonstrate an acute form of disseminated disease that resembles the syndrome seen in infants and children. Progressive disseminated histoplasmosis can occur as the direct result of initial infection or because of reactivation of dormant foci.
- In most patients, serologic evidence (complement fixation test or immunodiffusion testing) remains the primary method in the diagnosis of histoplasmosis. Detection of histoplasma antigen by enzyme immunoassay (EIA) in the urine, blood, or bronchoalveolar lavage fluid of infected patients provides rapid diagnostic information and is particularly useful in patients who are severely ill.

TABLE 38-1

Clinical Manifestations and Therapy of Histoplasmosis

Type of Diseaseand Common Clinical	ApproximateFrequency (%)[a]	Therapy/Comments

Manifestations		
Nonimmunosuppressed Host		
Acute pulmonary histoplasmosis		
Asymptomatic or mild-to-moderate disease	50–99	*Asymptomatic, mild, or symptoms <4 weeks:* No therapy generally required; itraconazole (200 mg three times daily for 3 days and then 200 mg once or twice daily for 6–12 weeks) is recommended for patients who continue to have symptoms for 11 months *Symptoms >4 weeks:* Itraconazole 200 mg once daily × 6–12 weeks[b]
Self-limited disease	1–50	Amphotericin B[c] 0.3–0.5 mg/kg/day IV × 2–4 weeks (total dose 500 mg) or ketoconazole 400 mg orally daily × 3–6 months can be beneficial in patients with severe hypoxia following inhalation of large inocula; antifungal therapy generally not useful for arthritis or pericarditis; NSAIDs or corticosteroids can be useful in some cases
Mediastinal granulomas	1–50	Most lesions resolve spontaneously; surgery or antifungal therapy with amphotericin B 40–50 mg/day IV × 2–3 weeks or itraconazole 400 mg/day orally × 6–12 months can be beneficial in some severe cases; mild-to-moderate disease can be treated with itraconazole for 6–12 months
Moderately severe to severe diffuse pulmonary disease		Lipid amphotericin B 3–5 mg/kg/day IV followed by itraconazole 200 mg twice daily for 3 days then twice daily for a total of 12 weeks of therapy; alternatively, in patients at low risk for nephrotoxicity, amphotericin B deoxycholate 0.7–1 mg/kg/day IV can be utilized; methylprednisolone (0.5–1 mg/kg daily IV) during the first 1–2 weeks of antifungal therapy is recommended for patients who develop respiratory complications, including hypoxemia or significant respiratory distress
Inflammatory/fibrotic disease	0.02	*Fibrosing mediastinitis:* The benefit of antifungal therapy (itraconazole 200 mg orally twice daily × 3 months) is controversial but should be considered, especially in patients with elevated ESR or CF titers ≤1:32; surgery can be of benefit if disease is detected early; late disease cannot respond to therapy *Sarcoid-like:* NSAIDs or corticosteroids[d] can be of benefit for some patients *Pericarditis:* Severe disease: Prednisone (0.5–1.0 mg/kg daily [maximum, 80 mg daily] in tapering doses over 1–2 weeks) or pericardial drainage procedure
Chronic cavitary pulmonary histoplasmosis	0.05	Antifungal therapy generally recommended for all patients to halt further lung destruction and reduce mortality *Mild–moderate disease:* Itraconazole 200 mg three times daily for 3 days and then one or two times daily for at least 1 year; some clinicians recommend therapy for 18–24 months due to the high rate of relapse; itraconazole plasma concentrations should be obtained after the patient has been receiving this agent for at least 2 weeks *Severe disease:* Amphotericin B 0.7 mg/kg/day for a minimum total dose of 25–35 mg/kg is effective in 59%–100% of cases and should be used in patients who require hospitalization or are unable to take itraconazole because of drug interactions, allergies, failure to absorb drug, or failure to improve clinically after a minimum of 12 weeks of itraconazole therapy

Histoplasma endocarditis		Amphotericin B (lipid formulations may be preferred, due to their lower rate of renal toxicity) plus a valve replacement is recommended; if the valve cannot be replaced, lifelong suppression with itraconazole is recommended
CNS histoplasmosis		Amphotericin B should be used as initial therapy (lipid formulations at 5 mg/kg/day IV, for a total dosage of 175 mg/kg may be preferred, due to their lower rate of renal toxicity) for 4–6 weeks, followed by an oral azole (fluconazole or itraconazole 200 mg two or three times daily) for at least a year; some patients may require lifelong therapy; response to therapy should be monitored by repeat lumbar punctures to assess *Histoplasma* antigen levels, WBC, and CF antibody titers; blood levels of itraconazole should be obtained to ensure adequate drug exposure
Immunosuppressed Host		
Disseminated histoplasmosis	0.02–0.05	Untreated mortality 83%–93%; relapse 5%–23% in non-AIDS patients; therapy is recommended for all patients
Acute (infantile)		*Nonimmunosuppressed patients:* Ketoconazole 400 mg/day orally or
Subacute		*Immunosuppressed patients (non-AIDS) or endocarditis or CNS disease:* Deoxycholate amphotericin B >35 mg/day IV × 3 months followed by fluconazole or itraconazole 200 mg orally twice daily × 12 months
Progressive histoplasmosis (immunocompetent patients and immunosuppressed patients without AIDS)		*Moderately severe to severe:* Liposomal amphotericin B (3 mg/kg daily) IV, amphotericin B lipid complex (ABLC, 5 mg/kg daily) IV, or deoxycholate amphotericin B (0.7–1 mg/kg daily) for 1–2 weeks IV, followed by itraconazole (200 mg twice daily for at least 12 months)
Progressive disease of AIDS	25–50[e]	Deoxycholate amphotericin B 15–30 mg/day IV (1–2 g over 4–10 weeks)[f] or itraconazole 200 mg orally three times daily for 3 days then twice daily for 12 weeks, followed by lifelong suppressive therapy with itraconazole 200–400 mg orally daily; although patients receiving secondary prophylaxis (chronic maintenance therapy) might be at low risk for recurrence of systemic mycosis when their $CD4^+$ T-lymphocyte counts increase to >100 cells/μL (0.1×10^9/L) in response to HAART, the number of patients who have been evaluated is insufficient to warrant a recommendation to discontinue prophylaxis

[a]As a percentage of all patients presenting with histoplasmosis.

[b]Itraconazole plasma concentrations should be measured during the second week of therapy to ensure that detectable concentrations have been achieved. If the concentration is below 1 mcg/mL (mg/L; 1.4 μmol/L), the dose may be insufficient or drug interactions can be impairing absorption or accelerating metabolism, requiring a change in dosage. If plasma concentrations are greater than 10 mcg/mL (mg/L; 14 μmol/L), the dosage can be reduced.

[c]Deoxycholate amphotericin B.

[d]Effectiveness of corticosteroids is controversial.

[e]As a percentage of AIDS patients presenting with histoplasmosis as the initial manifestation of their disease.

[f]Liposomal amphotericin B (AmBisome) may be more appropriate for disseminated disease.

AIDS, acquired immunodeficiency syndrome; CF, complement fixation; ESR, erythrocyte sedimentation rate; HAART, highly active antiretroviral therapy; NSAIDs, nonsteroidal anti-inflammatory drugs; PO, orally.

Treatment

- The goals of therapy are resolution of clinical abnormalities, prevention of relapse, and eradication of infection whenever possible, although chronic suppression of infection can be adequate in immunosuppressed patients, including those with HIV disease.
- Recommended therapy for the treatment of histoplasmosis is summarized in **Table 38-1**.
- Patients with mild, self-limited disease, chronic disseminated disease, or chronic pulmonary histoplasmosis who have no underlying immunosuppression usually can be treated with either oral **itraconazole** or IV **amphotericin B**.
- In AIDS patients, intensive 12-week primary antifungal therapy (induction and consolidation therapy) is followed by lifelong suppressive (maintenance) therapy with itraconazole. Amphotericin B dosages of 50 mg/day (up to 1 mg/kg per day) should be administered IV to a cumulative dose of 15–35 mg/kg (1–2 g) in patients who require hospitalization.
- Amphotericin B can be replaced with itraconazole 200 mg orally twice daily when the patient no longer requires hospitalization or IV therapy to complete a 12-week total course of induction therapy. In patients who do not require hospitalization, itraconazole therapy for 12 weeks can be used.
- Response to therapy should be measured by resolution of radiologic, serologic, and microbiologic parameters and improvement in signs and symptoms of infection.
- After the initial course of therapy for histoplasmosis is completed, lifelong suppressive therapy with oral azoles or amphotericin B (1–1.5 mg/kg weekly or biweekly) is recommended, because of the frequent recurrence of infection.
- Relapse rates in AIDS patients not receiving preventive maintenance are 50%–90%.

BLASTOMYCOSIS

- North American *blastomycosis* is a systemic fungal infection caused by *Blastomyces dermatitidis*. Pulmonary disease can be acute or chronic and can mimic infection with tuberculosis, pyogenic bacteria, other fungi, or malignancy.

Clinical Presentation and Diagnosis

- Acute pulmonary blastomycosis is generally an asymptomatic or self-limited disease characterized by fever, shaking chills, and a productive, purulent cough, with or without hemoptysis in immunocompetent individuals.
- Sporadic pulmonary blastomycosis may present as a more chronic or subacute disease, with low-grade fever, night sweats, weight loss, and a productive cough resembling that of TB rather than bacterial pneumonia. Chronic pulmonary blastomycosis is characterized by fever, malaise, weight loss, night sweats, chest pain, and productive cough.
- The simplest and most successful method of diagnosing blastomycosis is by direct microscopic visualization of the large, multinucleated yeast with single, broad-based buds in sputum or other respiratory specimens, following digestion of cells and debris with 10% potassium hydroxide. Histopathologic examination of tissue biopsies and culture of secretions should be used to identify *B. dermatitidis*, although it can require up to

30 days to isolate and identify a small inoculum.

Treatment

- In the immunocompetent host, acute pulmonary blastomycosis can be mild and self-limited and may not require treatment. However, consideration should be given to treating all infected individuals to prevent extrapulmonary dissemination. All individuals with moderate-to-severe pneumonia, disseminated infection, or those who are immunocompromised require antifungal therapy (**Table 38-2**).
- Some authors recommend azole therapy for the treatment of self-limited pulmonary disease, with the hope of preventing late extrapulmonary disease.
- **Itraconazole**, 200–400 mg/day, demonstrated 90% efficacy as a first-line agent in the treatment of non-life-threatening, non-CNS blastomycosis and 95% success rate for compliant patients who completed at least 2 months of therapy.
- All patients with disseminated blastomycosis, as well as those with extrapulmonary disease, require therapy.

TABLE 38-2

Therapy of Blastomycosis

Type of Disease	Preferred Treatment
Pulmonary[a]	
Moderately severe to severe disease	Lipid formulation of amphotericin B 3–5 mg/kg IV daily or amphotericin B[b] 0.7–1 mg/kg IV daily (total dose 1.5–2.5 g) × 1–2 weeks or until improvement is noted, followed by itraconazole[c,d] 200 mg orally three times daily for 3 days, then 200 mg twice daily, × total of 6–12 months
Mild-to-moderate disease	Itraconazole[b,d] 200 mg orally three times daily for 3 days, then 200 mg twice daily, for a total of 6 months[b]
CNS Disease	*Induction:* Lipid formulation of amphotericin B 5 mg/kg IV daily × 4–6 weeks, followed by an oral azole as consolidation therapy *Consolidation:* Fluconazole[d] 800 mg orally daily, or itraconazole[d] 200 mg two or three times orally daily, or voriconazole[d] 200–400 mg orally twice daily, for ≥12 months and until resolution of CSF abnormalities
Disseminated or Extrapulmonary Disease	
Moderately severe to severe disease	Lipid formulation of amphotericin B 3–5 mg/kg IV daily or amphotericin B[b] 0.7–1 mg/kg IV daily × 1–2 weeks or until improvement is noted, followed by itraconazole[c,d] 200 mg orally three times daily for 3 days, then 200 mg twice daily × 6–12 months; treat osteoarticular disease with 12 months of antifungal therapy Most clinicians prefer to step-down to itraconazole[d] therapy once the patient's condition improves
Mild to moderate	Itraconazole[c,d] 200 mg orally three times daily for 3 days, then 200 mg once or twice daily × ≥12 months; treat osteoarticular disease with 12 months of antifungal therapy
Immunocompromised Host (Including Patients with AIDS, Transplants, or Receiving Chronic Glucocorticoid Therapy)	
Acute disease	Lipid formulation of amphotericin B 3–5 mg/kg IV daily or amphotericin B[a] 0.7–1 mg/kg IV daily × 1–2 weeks or until improvement is noted, then give suppressive therapy for a total of at least 12 months of therapy
Suppressive therapy	Itraconazole[c,d] 200 mg orally three times daily for 3 days, then 200 mg twice daily for a total of at least 12 months of therapy; lifelong suppressive therapy with oral itraconazole[d] 200 mg daily may be required for immunosuppressed patients in whom immunosuppression cannot be reversed, and in patients who experience relapse despite appropriate therapy

[a]In the immunocompetent host, acute pulmonary blastomycosis can be mild and self-limited and may not require treatment.

[b]Desoxycholate amphotericin B.

[c]Serum levels of itraconazole should be determined after the patient has received itraconazole for ≥2 weeks to ensure adequate drug exposure.

[d]Azoles should not be used during pregnancy.

COCCIDIOIDOMYCOSIS

- *Coccidioidomycosis* is caused by infection with *Coccidioides immitis*. The endemic regions encompass the semiarid areas of the southwestern United States from California to Texas, known as the Lower Sonoran Zone. It encompasses a spectrum of illnesses ranging from primary uncomplicated respiratory tract infection that resolves spontaneously to progressive pulmonary or disseminated infection.

Clinical Presentation and Diagnosis

- Approximately 60% of infected patients have an asymptomatic, self-limited infection without clinical or radiological manifestations. The remaining 40% of patients exhibit nonspecific symptoms that are often indistinguishable from ordinary upper respiratory infections, including fever, cough, headache, sore throat, myalgias, and fatigue that occur 1–3 weeks after exposure to the pathogen. A fine, diffuse rash may appear during the first few days of illness.
- Chronic, persistent pneumonia or persistent pulmonary coccidioidomycosis (primary disease lasting >6 weeks) is complicated by hemoptysis, pulmonary scarring, and the formation of cavities or bronchopleural fistulas.
- Disseminated infection occurs in less than 1% of infected patients. Dissemination may occur to the skin, lymph nodes, bone, meninges, spleen, liver, kidney, and adrenal gland. CNS infection occurs in ~16% of patients with disseminated infection.
- The diagnoses of coccidioidomycosis generally includes identification or recovery of *Coccidioides* spp. from clinical specimens and detection of specific anticoccidioidal antibodies in serum or other body fluids.

Treatment

- Desired outcomes of treatment are resolution of signs and symptoms of infection, reduction of serum concentrations of anticoccidioidal antibodies, and return of function of involved organs.
- Therapy of coccidioidomycosis is difficult, and the results are unpredictable. Only 5% of infected persons require therapy.
- Azole antifungals, primarily fluconazole and itraconazole, have replaced amphotericin B as initial therapy for most chronic pulmonary or disseminated infections. Specific antifungals (and their usual dosages) for the treatment of coccidioidomycosis include **amphotericin B** IV (0.5–1.5 mg/kg/day), **ketoconazole** (400 mg orally daily), IV or oral **fluconazole** (usually 400–800 mg daily, although dosages as high as 1200 mg/day have been used without complications), and **itraconazole** (200–300 mg orally twice daily as either capsules or solution). If itraconazole is used, measurement of serum concentrations may be helpful to ascertain whether oral bioavailability is adequate.
- Therapy often ranges from many months to years in duration, and in some patients, lifelong suppressive therapy is needed to prevent relapses.
- Amphotericin B is generally preferred as initial therapy in patients with rapidly progressive disease, whereas azoles are generally preferred in patients with subacute or chronic presentations. Lipid formulations of amphotericin B have not been extensively studied for coccidioidomycosis but can offer a means of giving more drugs with less toxicity.
- Patients with disease outside the lungs should be treated with 400 mg/day of an oral azole. For meningeal disease, fluconazole 400 mg/day orally should be used; however, some clinicians initiate therapy with 800 or 1000 mg/day, and itraconazole doses of 400–600 mg/day are comparable.

CRYPTOCOCCOSIS

- *Cryptococcosis* is a noncontagious, systemic mycotic infection caused by the ubiquitous encapsulated soil yeast *Cryptococcus neoformans*.

Clinical Presentation and Diagnosis

- Primary cryptococcosis in humans almost always occurs in the lungs. Symptomatic infections are usually manifested by cough, rales, and shortness of breath that generally resolve spontaneously. Infection is acquired by inhalation of the organism.

- Disease may remain localized in the lungs or disseminate to other tissues, particularly the CNS, although the skin can also be affected.
- In the non-AIDS patient, the symptoms of cryptococcal meningitis are nonspecific. Symptomatic infections usually are manifested by cough, rales, and shortness of breath that generally resolve spontaneously. Headache, fever, nausea, vomiting, mental status changes, and neck stiffness are generally observed. In AIDS patients, fever and headache are common, but meningismus and photophobia are much less common than in non-AIDS patients.
- Examination of cerebrospinal fluid (CSF) in patients with cryptococcal meningitis generally reveals an elevated opening pressure, CSF pleocytosis (usually lymphocytes), leukocytosis, a decreased CSF glucose, an elevated CSF protein, and a positive cryptococcal antigen by latex agglutination.
- *C. neoformans* can be detected in ~60% of patients by India ink smear of CSF and cultured in more than 96% of patients.

Treatment

- Treatment of cryptococcosis is detailed in **Table 38-3**. For asymptomatic, immunocompetent persons with isolated pulmonary disease and no evidence of CNS disease, careful observation may be warranted. With symptomatic infection, **fluconazole** for 6–12 months is warranted.
- The use of intrathecal **amphotericin B** is not recommended for the treatment of cryptococcal meningitis except in very ill patients or in those with recurrent or progressive disease despite aggressive IV amphotericin B therapy. The dosage of amphotericin B employed is usually 0.5 mg administered via the lumbar, cisternal, or intraventricular (via an Ommaya reservoir) route two or three times weekly.
- Amphotericin B with **flucytosine** is the initial treatment of choice for acute therapy of cryptococcal meningitis in AIDS patients, although 1 week of amphotericin B plus flucytosine and 2 weeks of fluconazole plus flucytosine were effective as induction therapy for cryptococcal meningitis in resource limited settings. After the initially successful 2-week induction period, consolidation therapy with fluconazole can be administered for 8 weeks or until CSF cultures are negative.
- Immunocompromised patients with CNS infection require more prolonged therapy; treatment regimens are based on those used in the HIV-infected population and follow induction therapy with amphotericin B and consolidation therapy with 6–12 months of suppressive therapy with fluconazole.
- Relapse of *C. neoformans* meningitis occurs in ~50% of AIDS patients after completion of primary therapy. After the completion of induction/consolidation phases of therapy, long-term chronic suppression with fluconazole (200 mg orally daily) should be continued for a minimum of 1 year.

TABLE 38-3

Therapy of Cryptococcosis[a,b]

Type of Disease and Common Clinical Manifestations	Therapy/Comments
Nonimmunocompromised Patients (Non–HIV-Infected, Nontransplant)	
Meningoencephalitis *without* neurological complications, in patients in whom CSF yeast cultures are negative after 2 weeks of therapy	*Induction:* Amphotericin B[c] IV 0.7–1 mg/kg/day *plus* flucytosine 100 mg/kg/day orally in four divided doses × ≥4 weeks A lipid formulation of amphotericin B may be substituted for amphotericin B in the second 2 weeks
Follow all regimens with suppressive therapy	*Consolidation:* Fluconazole 400–800 mg orally daily × 8 weeks *Maintenance:* Fluconazole 200 mg orally daily × 6–12 months
Meningoencephalitis *with* neurological complications	*Induction:* Same as for patients without neurologic complications, but consider

	extending the induction therapy for a total of 6 weeks; a lipid formulation of amphotericin B may be given for the last 4 weeks of the prolonged induction period *Consolidation:* Fluconazole 400 mg orally daily × 8 weeks
Mild-to-moderate pulmonary disease (nonmeningeal disease)	Fluconazole 400 mg orally daily × 6–12 months
Severe pulmonary cryptococcosis	*Same as CNS disease × 12 months*
Cryptococcemia (nonmeningeal, nonpulmonary disease)	*Same as CNS disease × 12 months*
Immunocompromised Patients	
Severe pulmonary cryptococcosis	*Same as CNS disease × 12 months*
HIV-Infected Patients	
Primary therapy; induction and consolidation[d]	*Preferred regimen*: *Induction:* Amphotericin B[e] IV 0.7–1 mg/kg IV daily *plus* flucytosine 100 mg/kg/day orally in four divided doses for ≥2 weeks
Follow all regimens with suppressive therapy	*Consolidation:* Fluconazole 400 mg (6 mg/kg) orally daily × ≥8 weeks Liposomal amphotericin B 3–4 mg/kg IV daily, or amphotericin B lipid complex (ABLC) 5 mg/kg IV daily, for ≥2 weeks can be substituted for amphotericin B[e] in patients with or at risk for renal dysfunction *Alternative regimens, in order of preference:* Amphotericin B[e] IV 0.7–1 mg/kg IV daily × 4–6 weeks *or* liposomal amphotericin B 3–4 mg/kg IV daily[f] × 4–6 weeks *or* ABLC 5 mg/kg IV daily × 4–6 weeks *or* Amphotericin B[e] IV 0.7 mg/kg IV daily, *plus* fluconazole 800 mg (12 mg/kg) orally daily × 2 weeks, followed by fluconazole 800 mg (12 mg/kg) orally daily × ≥8weeks *or* Fluconazole ≥800 mg (1200 mg/day is preferred) orally daily *plus* flucytosine 100 mg/kg/day orally in four divided doses × 6 weeks *or* Fluconazole 800–1200 mg/day orally daily × 10–12 weeks (a dosage ≥1200 mg/day is preferred when fluconazole is used alone)[g] *or* Itraconazole 200 mg orally twice daily × 10–12 weeks (use of itraconazole, which produces minimal concentrations of active drug in the CSF, is discouraged)[h]
Suppressive/Maintenance therapy[i]	Preferred: Fluconazole 200 mg orally daily × ≥1 year *or* Itraconazole[h] 200 mg orally twice daily × ≥1 year *or*

	Amphotericin B[i] IV 1 mg/kg weekly × ≥1 year
Organ Transplant Recipients	
Mild-to-moderate non-CNS disease or mild-to-moderate symptoms without diffuse pulmonary infiltrates	Fluconazole 400 mg (6 mg/kg) orally daily × 6–12 months
CNS disease, moderately severe or severe CNS disease or disseminated disease without CNS disease, or severe pulmonary disease without evidence of extrapulmonary or disseminated disease	*Induction:* Liposomal amphotericin B 3–4 mg/kg IV daily,[f] or ABLC 5 mg/kg IV daily *plus* flucytosine 100 mg/kg/day orally in four divided doses × ≥2 weeks If induction therapy does not include flucytosine, consider a lipid formulation of amphotericin B for ≥4–6 weeks of induction therapy; consider the use of a lipid formulation of amphotericin B[j] lipid formulation (6 mg/kg IV daily) in patients with a high-fungal burden disease or relapse of disease *Consolidation:* Fluconazole 400–800 mg (6–12 mg/kg) per day orally for 8 weeks *Maintenance:* Fluconazole 200–400 mg per day orally for 6–12 months

[a]When more than one therapy is listed, they are listed in order of preference.

[b]See the text for definitions of induction, consolidation, suppressive/maintenance therapy, and prophylactic therapy.

[c]Deoxycholate amphotericin B.

[d]Initiate HAART therapy 2–10 weeks after commencement of initial antifungal treatment.

[e]In patients with significant renal disease, lipid formulations of amphotericin B can be substituted for deoxycholate amphotericin B during the induction.

[f]Liposomal amphotericin B has been given safely up to 6 mg/kg daily; could be considered in treatment failure or in patients with a high-fungal burden.

[g]Or until cerebrospinal fluid (CSF) cultures are negative.

[h]Drug level monitoring is strongly advised.

[i]Consider discontinuing suppressive therapy during HAART in patients with a CD4 cell count ≥100 cells/μL (0.1×10^9/L) and an undetectable or very low HIV RNA level sustained for ≥3months (with a minimum of 12 months of antifungal therapy). Consider reinstitution of maintenance therapy if the CD4 cell count decreases to <100 cells/μL (0.1×10^9/L).

[j]Use is discouraged except in azole intolerant patients, since it is less effective than azole therapy, and is associated with a risk of IV catheter-related infections.

HIV, human immunodeficiency virus; IT, intrathecal.

CANDIDA INFECTIONS

- Eight species of *Candida* are regarded as clinically important pathogens in human disease: *C. albicans, C. tropicalis, C. parapsilosis, C. krusei, C. stellatoidea, C. guilliermondii, C. lusitaniae*, and *C. glabrata. C. albicans* is a normal commensal of the skin, female genital tract, and entire GI tract of humans.

Hematogenous Candidiasis

- Dissemination of *C. albicans* can result in infection in single or multiple organs, particularly the kidney, brain, myocardium, skin, eye, bone, and

joints.

- *Candida* is generally acquired via the gastrointestinal (GI) tract, although organisms may also enter the bloodstream via indwelling IV catheters.
- Immunosuppressed patients, including those with lymphoreticular or hematologic malignancies, diabetes, immunodeficiency diseases, or those receiving immunosuppressive therapy with high-dose corticosteroids, immunosuppressants, antineoplastic agents, or broad-spectrum antimicrobial agents are at high risk for invasive fungal infections.
- Major risk factors for hematogenous candidiasis include the use of central venous catheters, total parenteral nutrition, receipt of multiple antibiotics, extensive surgery and burns, renal failure and hemodialysis, mechanical ventilation, and prior fungal colonization.
- Treatment of candidiasis is presented in **Table 38-4**.

TABLE 38-4

Antifungal Therapy of Invasive Candidiasis

Type of Disease and Common Clinical Manifestations	Therapy/Comments
Prophylaxis of Candidemia	
Non-neutropenic patients[a]	Not recommended except for severely ill/high-risk patients in whom fluconazole IV/oral 400 mg daily should be used
Neutropenic patients[a]	The optimal duration of therapy is unclear but at a minimum should include the period at risk for neutropenia: fluconazole IV/oral 400 mg daily *or* itraconazole solution 2.5 mg/kg every 12 hours orally *or* micafungin 50 mg (1 mg/kg in patients under 50 kg) IV daily
Solid-organ transplantation, liver transplantation	*Patients with two or more key risk factors*[b]: Amphotericin B IV 10–20 mg daily *or* liposomal amphotericin B (AmBisome) 1 mg/kg/day *or* fluconazole 400 mg orally daily
Empirical (Preemptive) Antifungal Therapy	
Suspected disseminated candidiasis in febrile non-neutropenic patients	None recommended; data are lacking defining subsets of patients who are appropriate for therapy
Initial Antifungal Therapy (Documented Candidemia with Unknown *Candida* Species)	
Febrile neutropenic patients with prolonged fever despite 4–6 days of empirical antibacterial therapy	*Treatment duration:* Until resolution of neutropenia An echinocandin[c] is a reasonable alternative; voriconazole can be used in selected situations (see the text)
Less critically ill patients with no recent azole exposure	An echinocandin[c] or fluconazole (loading dose of 800 mg [12 mg/kg], then 400 mg [6 mg/kg] daily)

Additional mold coverage is desired	Voriconazole
Antifungal Therapy of Documented Candidemia and Acute Hematogenously Disseminated Candidiasis, Unknown Species	
Nonimmunocompromised host[d]	*Treatment duration:* 2 weeks after the last positive blood culture and resolution of signs and symptoms of infection *Remove existing central venous catheters when feasible plus fluconazole (loading dose of 800 mg [12 mg/kg], then 400 mg [6 mg/kg] daily) or an echinocandin*[d]
Patients with recent azole exposure, moderately severe or severe illness, or who are at high risk of infection due to *C. glabrata* or *C. krusei*	An echinocandin[c] Transition from an echinocandin to fluconazole is recommended for patients who are clinically stable and have isolates (eg, *C. albicans*) likely to be susceptible to fluconazole
Patients who are less critically ill and who have had no recent azole exposure	Fluconazole
Antifungal Therapy of Specific Pathogens	
C. albicans, C. tropicalis, and *C. parapsilosis*	Fluconazole IV/oral 6 mg/kg/day *or* an echinocandin[c] or amphotericin B IV 0.7 mg/kg/day *plus* fluconazole IV/orally 800 mg/day; amphotericin B deoxycholate 0.5–1 mg/kg daily or a lipid formulation of amphotericin B (3–5 mg/kg daily) are alternatives in patients who are intolerant to other antifungals; transition from amphotericin B deoxycholate or a lipid formulation of amphotericin B to fluconazole is recommended in patients who are clinically stable and whose isolates are likely to be susceptible to fluconazole (eg, *C. albicans*); voriconazole (400 mg [6 mg/kg] twice daily × two doses then 200 mg [3 mg/kg] twice daily thereafter) is efficacious, but offers little advantage over fluconazole; it may be utilized as step-down oral therapy for selected cases of candidiasis due to *C. krusei* or voriconazole-susceptible *C. glabrata* *Patients intolerant or refractory to other therapy*[e]: Amphotericin B lipid complex IV 5 mg/kg/day Liposomal amphotericin B IV 3–5 mg/kg/day Amphotericin B colloid dispersion IV 2–6 mg/kg/day
C. krusei	Amphotericin B IV ≤1 mg/kg/day *or* an echinocandin[c]
C. lusitaniae	Fluconazole IV/orally 6 mg/kg/day
C. glabrata	An echinocandin[c] (transition to fluconazole or voriconazole therapy is not recommended without confirmation of isolate susceptibility)
Neutropenic host[f]	*Treatment duration:* Until resolution of neutropenia *Remove existing central venous catheters when feasible, plus:* Amphotericin B IV 0.7–1 mg/kg/day (total dosages 0.5–1 g) *or patients failing therapy with traditional amphotericin B:* Lipid formulation of amphotericin B IV 3–5 mg/kg/day

Chronic disseminated candidiasis (hepatosplenic candidiasis)	*Treatment duration:* Until calcification or resolution of lesions *Stable patients:* Fluconazole IV/orally 6 mg/kg/day *Acutely ill or refractory patients:* Amphotericin B IV 0.6–0.7 mg/kg/day
Urinary candidiasis	*Asymptomatic disease:* Generally no therapy is required *Symptomatic or high-risk patients*[g]: Removal of urinary tract instruments, stents, and Foley catheters, +7–14 days therapy with fluconazole 200 mg orally daily *or* amphotericin B IV 0.3–1 mg/kg/day

[a]Patients at significant risk for invasive candidiasis include those receiving standard chemotherapy for acute myelogenous leukemia, allogeneic bone marrow transplants, or high-risk autologous bone marrow transplants. However, among these populations, chemotherapy or bone marrow transplant protocols do not all produce equivalent risk, and local experience should be used to determine the relevance of prophylaxis.

[b]Risk factors include retransplantation, creatinine of more than 2 mg/dL (177 µmol/L), choledochojejunostomy, intraoperative use of 40 units or more of blood products, and fungal colonization detected within the first 3 days after transplantation.

[c]Echinocandin = caspofungin 70 mg loading dose, then 50 mg IV daily maintenance dose, or micafungin 100 mg daily, or anidulafungin 200 mg loading dose, then 100 mg daily maintenance dose.

[d]Therapy is generally the same for acquired immunodeficiency syndrome (AIDS)/non-AIDS patients except where indicated and should be continued for 2 weeks after the last positive blood culture and resolution of signs and symptoms of infection. All patients should receive an ophthalmologic examination. Amphotericin B can be switched to fluconazole (IV or oral) for the completion of therapy. Susceptibility testing of the infecting isolate is a useful adjunct to species identification during selection of a therapeutic approach because it can be used to identify isolates that are unlikely to respond to fluconazole or amphotericin B. However, this is not currently available at most institutions.

[e]Often defined as failure of ≥500 mg amphotericin B, initial renal insufficiency (creatinine ≥2.5 mg/dL [221 µmol/L] or creatinine clearance <25 mL/min [0.42 mL/sec]), a significant increase in creatinine (to 2.5 mg/dL [221 µmol/L] for adults or 1.5 mg/dL [133 µmol/L] for children), or severe acute administration-related toxicity.

[f]Patients who are neutropenic at the time of developing candidemia should receive a recombinant cytokine (granulocyte colony–stimulating factor or granulocyte–monocyte colony-stimulating factor) that accelerates recovery from neutropenia.

[g]Patients at high risk for dissemination include neutropenic patients, low-birth-weight infants, patients with renal allografts, and patients who will undergo urologic manipulation.

ASPERGILLUS INFECTIONS

- *Aspergillus fumigatus* is the most commonly observed pathogen, followed by *Aspergillus flavus.*
- Invasive aspergillosis commonly affects immunocompromised patients and patients with acute myeloid leukemia (AML) and those who undergo allogeneic HSCT who have prolonged durations (more than 10 days) of neutropenia. Aspergillosis is generally acquired by inhalation of airborne conidia that are small enough (2.5–3 mm) to reach the alveoli or the paranasal sinuses.
- Superficial or locally invasive infections of the ear, skin, or appendages can often be managed with topical antifungal therapy.

Allergic Bronchopulmonary Aspergillosis

- Allergic manifestations of *Aspergillus* range in severity from mild asthma to allergic bronchopulmonary aspergillosis characterized by severe asthma with wheezing, fever, malaise, weight loss, chest pain, and a cough productive of blood-streaked sputum.

- Therapy is aimed at minimizing the quantity of antigenic material released in the tracheobronchial tree.
- Antifungal therapy is generally not indicated in the management of allergic manifestations of aspergillosis, although some patients have demonstrated a decrease in their glucocorticoid dose following therapy with itraconazole.

Aspergilloma

- In the nonimmunocompromised host, *Aspergillus* infections of the sinuses most commonly occur as saprophytic colonization (aspergillomas, or "fungus balls") of previously abnormal sinus tissue. Treatment consists of removal of the aspergilloma. Therapy with glucocorticoids and surgery is generally successful.
- Although IV **amphotericin B** is generally not useful in eradicating aspergillomas, intracavitary instillation of amphotericin B has been used successfully in a limited number of patients.

Invasive Aspergillosis

- Patients with invasive aspergillosis generally have blunted or nonspecific signs and symptoms of infection due to impaired inflammatory responses. Patients often present with classic signs and symptoms of acute pulmonary embolus: pleuritic chest pain, fever, hemoptysis, and friction rubs.
- Demonstration of *Aspergillus* by repeated culture and microscopic examination of tissue provides the most firm diagnosis.

Treatment

- **Voriconazole** is the drug of choice for primary therapy of most patients with invasive aspergillosis as it provided improved survival and fewer side effects.
- In patients who cannot tolerate voriconazole, amphotericin B can be used. Full doses (1–1.5 mg/kg/day) are generally recommended, with response measured by defervescence and radiographic clearing. The lipid-based formulations may be preferred as initial therapy in patients with marginal renal function or in patients receiving other nephrotoxic drugs. The optimal duration of treatment is unknown.
- **Caspofungin** is indicated for treatment of invasive aspergillosis in patients who are refractory to or intolerant of other therapies such as amphotericin B.
- The use of prophylactic antifungal therapy to prevent primary infection or reactivation of aspergillosis during subsequent courses of chemotherapy is controversial.

See Chapter 139, Invasive Fungal Infections, authored by Peggy L. Carver, for a more detailed discussion of this topic.