Chapter 144: Invasive Fungal Infections

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CHAPTER SUMMARY FROM THE PHARMACOTHERAPY HANDBOOK

For the Chapter in the Schwinghammer Handbook, please go to Chapter 39, Fungal Infections, Invasive.

KEY CONCEPTS

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1. Systemic mycoses can be caused by pathogenic fungi and include histoplasmosis, coccidioidomycosis, cryptococcosis, blastomycosis, paracoccidioidomycosis, and sporotrichosis, or infections by opportunistic fungi such as *Candida albicans*, *Aspergillus* species, *Trichosporon*, *Candida glabrata*, *Fusarium*, *Alternaria*, and *Mucor*.

2. The diagnosis of fungal infection is accomplished by careful evaluation of clinical symptoms, results of serologic tests, and histopathologic examination and culture of clinical specimens. Rapid, accurate diagnostic laboratory tests are currently under development.

3. Histoplasmosis is caused by *Histoplasma capsulatum* and is endemic in parts of the central United States along the Ohio and Mississippi River valleys, and in Central and South America. Although most patients experience asymptomatic infection, some can experience chronic, disseminated disease.

4. Asymptomatic patients with histoplasmosis are not treated, while patients with evident disease are treated with either oral itraconazole or an IV amphotericin B lipid formulation.

5. Blastomycosis is caused by *Blastomyces dermatitidis*. 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 persons with moderate-to-severe pneumonia, disseminated infection, or those who are immunocompromised require antifungal therapy.

6. Coccidioidomycosis is caused by *Coccidioides immitis* and *Coccidioides posadasii* and is endemic in some parts of the southwestern United States. It can cause nonspecific symptoms, acute pneumonia, or chronic pulmonary or disseminated disease. Primary pulmonary disease (unless severe) frequently is not treated, whereas disseminated and meningeal disease is treated with fluconazole.

7. Cryptococcosis is caused by *Cryptococcus neoformans*, which occurs primarily in immunocompromised patients, and *Cryptococcus gattii*, which occurs primarily in nonimmunocompromised patients. Patients with acute meningitis are treated with lipid formulations of amphotericin B with flucytosine. Patients infected with human immunodeficiency virus (HIV) often require long- term suppressive therapy with fluconazole or itraconazole.

8. A variety of *Candida* species (including *C. albicans*, *C. glabrata*, *Candida tropicalis*, *Candida parapsilosis*, and *Candida krusei*) can cause diseases such as mucocutaneous, oral, esophageal, vaginal, and hematogenous candidiasis, as well as candiduria. Candidemia can be treated with a variety of antifungal agents; the optimal choice depends on previous patient exposure to antifungal agents, potential drug interactions and toxicities of each agent, and local epidemiology of intensive care unit (ICU) or hematology–oncology centers.

9. Aspergillosis can be caused by a variety of *Aspergillus* species that can cause superficial infections, pneumonia, allergic bronchopulmonary aspergillosis (BPA), or invasive infection. Voriconazole has emerged as the drug of choice of most clinicians for primary therapy of most patients with invasive aspergillosis (IA). Combination therapy may be considered in cases of severe infection, especially in patients with persistent neutropenia.

BEYOND THE BOOK

BEYOND THE BOOK

Watch the following two videos, which provide a brief (9:48) overview of the epidemiology, diagnosis, and treatment of candidemia

Candida: Systemic Candidiasis Treatment & Prevention. https://tinyurl.com/u22fqmt

INTRODUCTION

Advances in medical technology including organ and bone marrow transplantation, cytotoxic chemotherapy, the widespread use of indwelling IV catheters, and the increased use of potent broad- spectrum antimicrobial agents all have contributed to the dramatic increase in the incidence of fungal infections worldwide.[1-3] Problems remain in the diagnosis, prevention, and treatment of fungal infections.[1,4-6] The Infectious Diseases Society of America (IDSA) publishes guidelines regarding the prophylaxis and treatment of many commonly encountered fungal infections.[7-12]

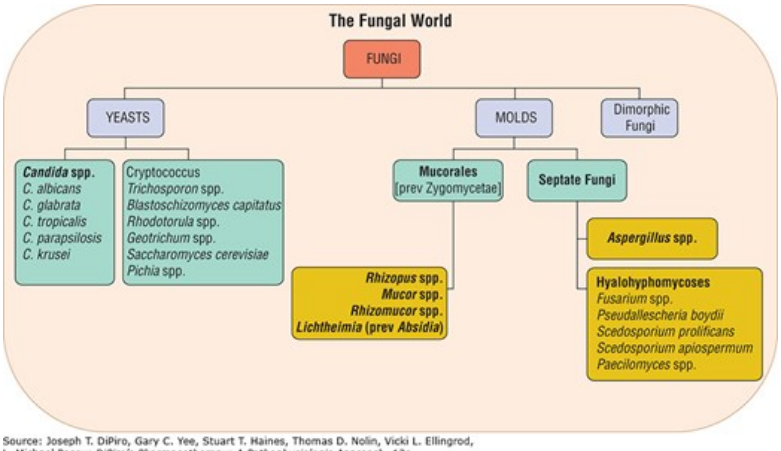
MYCOLOGY

Fungi are eukaryotic organisms with a defined nucleus enclosed by a nuclear membrane; a cytoplasmic membrane containing lipids, glycoproteins, and sterols, mitochondria, golgi apparatus, and ribosomes bound to endoplasmic reticulum; and a cytoskeleton with microtubules, microfilaments, and intermediate filaments. Fungi have rigid cell walls composed of chitin, cellulose, or both that stain with Gomori methenamine silver or periodic acid–Schiff reagent. Most fungi, except *Candida* species, are too weakly gram-positive to be seen well on Gram stain. *Cryptococcus neoformans* has a polysaccharide capsule surrounding the cell wall.[1]

Morphologically, pathogenic fungi can be grouped as either filamentous molds or unicellular yeasts (Fig. 144-1). *Molds* grow as multicellular branching, threadlike filaments (hyphae) that are either septate (divided by transverse walls) or coenocytic (multinucleate without crosswalls). Yeasts are oval or spherically shaped unicellular forms that generally produce pasty or mucoid colonies on agar medium similar to those observed with bacterial cultures. Yeasts have rigid cell walls and reproduce by budding, a process in which daughter cells arise from pinching off a portion of the parent cell.

FIGURE 144-1

Morphologically, pathogenic fungi can be grouped as either filamentous molds or unicellular yeasts. Molds grow as multicellular branching, thread-like filaments (hyphae) that are either septate (divided by transverse walls) or coenocytic (multinucleate without crosswalls).



Many pathogenic fungi, including the etiological agents of histoplasmosis, coccidioidomycosis, blastomycosis, paracoccidioidomycosis, and sporotrichosis, are termed *dimorphic fungi*. These pathogens can exist as either a yeast or a mold, depending on the pathogen, ambient CO_2, the production of host 17-beta-estradiol, the site of growth (in the host or in the laboratory setting), and temperature. Temperature shifts provoke reversible conversions between the hyphal (22-25^{o}C) and yeast (37^{o}C) phases. Dimorphic fungi can infect humans with either normal or impaired host immune defenses. Usually, yeasts are the parasitic form that invades human or animal host tissue, whereas molds are the free-living form found in the environment.[13]

Clinical Versus Microbial Resistance

Host factors contribute greatly to clinical outcome. A patient may respond clinically to treatment with an antifungal agent despite resistance to that

agent in vitro because the patient's own immune system may eradicate the infection, or the agent may reach the site of infection in high concentrations. Thus, in vitro susceptibility does *not* necessarily equate with in vivo clinical success, and in vitro resistance might *not* always correlate with treatment failure.[6]

It is important to distinguish between clinical resistance and microbial resistance. *Clinical resistance* refers to failure of an antifungal agent in the treatment of a fungal infection that arises from factors other than microbial resistance, such as failure of the antifungal agent to reach the site of infection or inability of a patient's immune system to eradicate a fungus whose growth is retarded by an antifungal agent.[14]

Microbial resistance can refer to *primary* or *secondary* resistance, as determined by in vitro susceptibility testing using standardized methodology. *Primary* or *intrinsic resistance* refers to resistance recorded prior to drug exposure in vitro or in vivo. *Secondary* or *acquired resistance* develops on exposure to an antifungal agent and can be either reversible, owing to transient adaptation, or acquired as a result of one or more genetic alterations.[14]

Susceptibility Testing of Antifungal Agents

Most laboratories do not routinely perform susceptibility tests on fungal isolates, but standardized methods for performing these tests are being developed and are now available for testing selected yeasts. As the prevalence of nosocomial and community-acquired fungal infections become more prominent, the need for in vitro susceptibility testing increases. Susceptibility testing is occasionally indicated, for example, in a patient with prolonged fungemia with a presumed susceptible isolate, and is most helpful in dealing with infections caused by non-*albicans* species of *Candida*.[5-7]

Clinical breakpoints (CBPs) are antimicrobial concentrations (MICs) obtained from susceptibility testing, which are used to define isolates as susceptible, intermediate, or resistant. No CBPs have been established for posaconazole, isavuconazole, or amphotericin B versus *Candida*, or for antifungal agents and filamentous fungi such as *Aspergillus*.[6] CBPs can be used to differentiate strains for which there is a high likelihood of treatment success (organisms that are clinically susceptible [S]), from those for which treatment is more likely to fail (clinically resistant [R]) (Tables 144-1–144-3). A clinically intermediate (I) or susceptible dose-dependent (SDD) category can be assigned to pathogens for which the level of antimicrobial agent activity is associated with uncertain therapeutic effect, implying that infections due to the isolate may be appropriately treated in body sites where the drugs are physically concentrated or when a high dosage of drug can be used. Although CBPs are designed to guide therapy, they do not distinguish between fungal isolates with or without resistance mechanisms, nor do they always allow for early detection of resistant isolates.[6] Table 144-3 shows the currently approved interpretive CBPs for *Candida* species.

TABLE 144-1

General Patterns of In Vitro Susceptibility of *Candida* Species

Patterns of Susceptibility							
	Azoles					Echinocandins	Amphotericin B
***Candida* species**	**Fluconazole**	**Itraconazole**	**Voriconazole**	**Posaconazole**	**Isavuconazole**	**Caspofungin Anidulafungin Micafungin**	
C. albicans	Yes	Yes	Yes	Yes	Yes	Yes	Yes
C. tropicalis	Yes	Yes	Yes	Yes	Yes	Yes	Yes
C. parapsilosis	Yes	Yes	Yes	Yes	Yes	Yes[a]	Yes
C. glabrata	Variable[b]	Variable[b]	Variable[b]	Variable[b]	Variable[b]	Yes	Yes
C. krusei	No	Yes	Yes	Yes	Yes	Yes	Yes
C. lusitaniae	Yes	Yes	Yes	Yes	Yes	Yes	Variable[c]

[a]Most isolates of *C. parapsilosis* have reduced susceptibility to echinocandins.

[b]Approximately 15% of *C. glabrata* isolates are resistant to fluconazole; *C. glabrata* generally exhibits cross-resistance across the azole class.[15]

[c]Although frank resistance to amphotericin B is not observed in all isolates, it is well described for isolates of *C. lusitaniae.*

Data from Reference 7.

TABLE 144-2

General Patterns of In Vitro Susceptibility of Non-*Candida* Fungal Pathogens

Patterns of Susceptibility							
	Azoles					Echinocandins	Amphotericin B
Pathogen	**Fluconazole**	**Itraconazole**	**Voriconazole**	**Posaconazole**	**Isavuconazole**	**Caspofungin Anidulafungin Micafungin**	**Yes**
Aspergillus fumigatus/flavus	No	Yes	Yes	Yes	Yes	Yes	Yes
Aspergillus terreus	No	Yes	Yes	Yes	Yes	Yes	No
Fusarium	No	No	Variable	Variable	Variable	No	Variable
Scedosporium	No	No	Yes	Variable	Variable	No	No
Lomentospora	No	No	Variable	No	No	No	No
Mucorales[a]	No	No	No	Variable	Variable	No	Yes
Cryptococcus	Yes	Yes	Yes	Yes	Yes	No	Yes
Histoplasma	Yes	Yes	Yes	Yes	Yes	No[b]	Yes
Coccidioides	Yes	Yes	Yes	Yes	Yes	No[b]	Yes

[a]Includes *Rhizopus*, *Mucor*, and *Absidia* species.

[b]While the echinocandins display activity against the mycelial forms of endemic fungi such as *Histoplasma* spp., *Blastomyces* spp., and *Coccidioides* spp., they display significantly higher MIC values against the yeast forms of these organisms, and should not be used to treat these infections.

Data from References 9, 10, 12, and 16.

TABLE 144-3

Clinical Breakpoints for *Candida* Species and Azole Antifungals

Drug[a]	Species	Interpretive Clinical Breakpoints (mg/L)			
		S	I	SDD	R
Fluconazole	*C. albicans*	≤2	---	4	≥8
	C. glabrata	---	---	≤32	≥64
	C. krusei	---	---	---	---
	C. parapsilosis	≤2	---	4	≥8
	C. tropicalis	≤2	---	4	≥8
Voriconazole	*C. albicans*	≤0.12	0.25-0.5	---	≥1
	C. glabrata	---	---	---	---
	C. krusei	≤0.5	1	---	≥2
	C. parapsilosis	≤0.12	0.25-0.5	---	≥1
	C. tropicalis	≤0.12	0.25-0.5	---	≥1

[a]Clinical breakpoints have not been established for isavuconazole by CLSI.

S, susceptible; I, intermediate; SDD, susceptible-dose dependent; R, resistant; ---, not defined or not applicable.

Data from Reference 6.

Resistance to Antifungal Agents

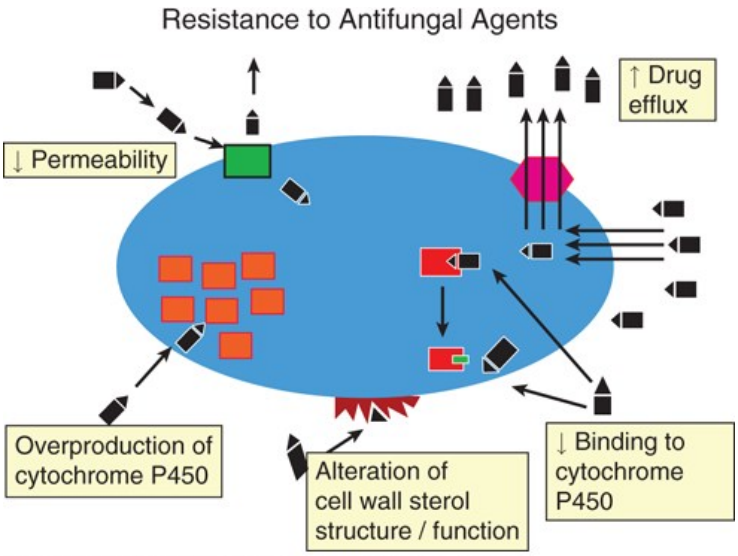
Understanding mechanisms of resistance is an important process in the optimization of antifungal therapy. The most exhaustive and definitive accounts of antifungal resistance have been described in *Candida* species, in particular *C. albicans* and, to a lesser extent, *C. glabrata*, *C. tropicalis*, and *Candida krusei*, as well as in a few *C. neoformans* isolates.[14] *C. glabrata* isolates are increasingly resistant to both azole and echinocandin antifungal agents.

There are four different mechanisms that result in azole resistance: (a) mutations or upregulation of *ERG11* (an enzyme involved in the ergosterol biosynthesis pathway), (b) expression of multidrug efflux transport pumps that decrease antifungal drug accumulation within the fungal cell, (c) alteration of the structure or concentration of antifungal drug target proteins, and (d) alteration of membrane sterol proteins (Fig. 144-2). Although detailed analysis of each of the elucidated mechanism of resistance is beyond the scope of this chapter, interested readers are referred to a publication that has comprehensively summarized this topic.[14]

FIGURE 144-2

Mechanisms of azole resistance. Four different mechanisms result in azole resistance: (a) mutations or upregulation of *ERG11*, the target enzyme of azoles, (b) expression of multidrug efflux transport pumps that decrease antifungal drug accumulation within the fungal cell, (c) alteration of the

structure or concentration of antifungal drug target proteins, and (d) alteration of membrane sterol proteins.



Source: Joseph T. DiPiro, Gary C. Yee, Stuart T. Haines, Thomas D. Nolin, Vicki L. Ellingrod, L. Michael Posey: *DiPiro's Pharmacotherapy: A Pathophysiologic Approach, 12e*

The most commonly reported mechanisms of azole resistance among *C. albicans* isolates include reduced permeability of the fungal cell membrane to azoles, modification or overproduction of the target fungal enzymes (cytochrome P450, CYP) resulting in decreased binding of the azole to the target site, alterations in sterol synthesis, and activation of efflux pumps capable of actively pumping azoles from the target pathogen. Fluconazole resistance is observed most frequently in *C. glabrata*, which is often resistant, and in *C. krusei*, for which fluconazole resistance is universal.[5,14] With the increase in echinocandin use, there has been an increase in the number of reports of echinocandin-resistant isolates from patients failing therapy. Echinocandin exposure and previous episodes of *C. glabrata* are predictors of FKS gene mutations in *Candida*.[17,18]

Although, to date, the rate of amphotericin B resistance remains low, the exact incidence remains difficult to quantify and the response to antifungal agents difficult to characterize.[6] As such, no consensus for therapy has been formulated at this time, although clinicians should keep in mind that *C. glabrata, Candida guilliermondii, C. krusei*, and *Candida lusitaniae* may have a higher propensity to developing resistance than other species.

Acquired resistance of *Aspergillus* species during long-term azole exposure, while still relatively uncommon, is emerging, and varies widely between geographic centers. Acquisition of primary-resistant isolates is also increasing, due to the agricultural use of azoles.[19] Cross-resistance of azole-resistant strains of *Aspergillus* to amphotericin B has not been described. Azole resistance among *Aspergillus* spp. (specifically *Aspergillus fumigatus*) is predominantly mediated by specific point mutations in TR/L98H in the CYP51A gene promoter region, causing amino acid changes and tandem repeats, and often results in cross-resistance with azole antifungals.[19]

EPIDEMIOLOGY AND PATHOGENESIS

Systemic mycoses caused by primary or pathogenic fungi include histoplasmosis, coccidioidomycosis, cryptococcosis, blastomycosis, paracoccidioidomycosis, and sporotrichosis. Primary pathogens can cause disease in both healthy and immunocompromised individuals, although disease generally is more severe or disseminated in the immunocompromised host.[1] *Candida* species are commensals in humans, and most infections are iatrogenic.[20] Mycoses caused by opportunistic fungi such as *Aspergillus* species, *Fusarium*, *Alternaria*, and *Mucor* are found only in the immunocompromised host.[1]

Most fungal infections are acquired as a result of accidental inhalation of airborne conidia. For example, *Histoplasma capsulatum* is found in soil contaminated by bat, chicken, or starling excreta, and *C. neoformans* is associated with pigeon droppings. Although some fungi, including *C. neoformans*, and *Aspergillus* species, are ubiquitous pathogens with worldwide distribution, other fungi have regional distributions associated with specific geographic environments.[1]

Invasive fungal infections (IFIs) are a major cause of morbidity and mortality in the immunocompromised patient.[21,22] Patients with decreased neutrophil counts or decreased neutrophil function are at higher risk of infections, particularly infections caused by *Candida* and *Aspergillus* species. In patients with hematologic malignancies and following hematopoietic stem cell transplantation (HSCT), there has been a shift in the most commonly encountered IFIs from *Candida* spp. to *Aspergillus* spp.[23,24]

Nosocomially acquired fungal infections can arise from either exogenous or endogenous flora. Endogenous flora can include normal commensal organisms of the skin, GI, genitourinary, or respiratory tract. *C. albicans* is found as a normal commensal of the GI tract in 20% to 30% of humans. A complex interplay of host and pathogen factors influences the acquisition and development of fungal infections. Intact skin or mucosal surfaces serve as primary barriers to infection. Alterations in the balance of normal flora caused by the use of antibiotics or alterations in nutritional status can allow the proliferation of fungi such as *Candida*, increasing the likelihood of systemic invasion and infection.[20] *Candida* species are the fourth most commonly isolated bloodstream isolate.[25]

Diagnosis and Rapid Diagnostic Tests

2 The diagnosis of IFIs is accomplished by careful evaluation of clinical symptoms, results of serologic tests, and histopathologic examination and culture of clinical specimens. While direct microscopy, culture and histological techniques constitute the “gold standard” for diagnosis, obtaining biopsies from sterile body sites for these studies is a highly invasive approach that may not be possible in severely ill patients. Also, histopathology lacks sensitivity and selectivity, as several filamentous fungi may exhibit undistinguishable morphologies. Further, the finding of a positive culture from a sterile site may indicate transient colonization and not true infection, especially for opportunistic fungi. Fungi may require special laboratory conditions, with additional time (up to 4 days) required in order to obtain species identification and the results of susceptibility testing. Some species, such as *C. glabrata*, tend to grow more slowly; initial identification of yeast from blood averages 100 hours (~4 days) in most institutions.[27] Several rapid, accurate diagnostic laboratory tests, including matrix-assisted laser desorption ionization time-of-flight mass spectrometry (MALDI-TOF), peptide nucleic acid (PNA) in situ hybridization (PNA-FISH), PCR, galactomannan, and T2 magnetic resonance assays, have the potential to enhance sensitivity and speed of diagnosis of IFIs.[28,29]

New laboratory methods that allow for early differentiation of IFIs due to *Aspergillus* species versus zygomycetes and other molds would be helpful in allowing clinicians in the earlier initiation of appropriate antifungal therapy. These underscore the need for rapid diagnosis and identification of clinically significant isolates to species level, and the need for susceptibility testing.[28]

Risk Factors for Fungal Infections

Increasing use of aggressive and intensive cancer chemotherapeutic regimens, immunosuppressive therapy for autoimmune disorders, and transplantation have led to an increase in the number of susceptible hosts, contributing to the changing epidemiology of fungal infections. Infection epidemiology can drastically vary depending on patients’ underlying concomitant conditions, comorbidities, confounding risk factors, and geographical area.[20]

A clinical indicator for a patient’s immunologic status is the quantitation of absolute neutrophil count (ANC). Neutropenia, defined as an ANC ≤ 500/mm^3 (0.5 × 10^9/L), dramatically escalates the risk of acquiring and opportunistic infection. Major risk factors for *Candida* bloodstream infections (BSIs) in ICU patients include the use of central venous catheters (CVCs), receipt of multiple antibiotics or parenteral nutrition (PN), extensive surgery and burns, renal failure and hemodialysis, mechanical ventilation, and prior fungal colonization.[26]

TREATMENT

Invasive Mycoses

Strategies for the prevention or treatment of invasive mycoses can be classified broadly as prophylaxis, early empirical therapy, empirical therapy, and secondary prophylaxis or suppression. In patients undergoing cytotoxic chemotherapy, antifungal therapy is directed primarily at the prevention or treatment of infections caused by *Candida* and *Aspergillus* species.

Prophylactic therapy with oral or IV antifungal agents is administered prior to and throughout periods of granulocytopenia (absolute neutrophil count < 1,000 cells/μL [1×10^9/L]) or other immunosuppressive events (such as development of graft-versus-host disease [GvHD] in hematopoietic stem cell transplant recipients). The potential benefits of prophylactic therapy must be weighed against the potential risks inherent in each regimen, including safety, efficacy, cost, the prevalence of infection, and the potential consequences (eg, resistance) of widespread use.[23,24]

Empirical therapy is the administration of systemic antifungal agents in patients with signs and symptoms of fungal infection, but without confirmation of infection. For example, empirical therapy with systemic antifungal agents is administered to granulocytopenic patients with persistent or recurrent fever despite the administration of appropriate antimicrobial therapy.[30,31]

Secondary prophylaxis (or *suppressive therapy*) is the administration of systemic antifungal agents (generally prior to and throughout the period of granulocytopenia) to prevent relapse of documented IFI.[32]

HISTOPLASMOSIS

In humans, histoplasmosis is caused by inhalation of dust-borne microconidia of the dimorphic fungus *H. capsulatum*. Although there exist two dimorphic varieties of *H. capsulatum*, the small-celled (2-5 μm) form (var. *capsulatum*) occurs globally, whereas the large-celled (8-15 μm) form (var. *duboisii*) is confined to the African continent and Madagascar. In tissues stained by conventional techniques, *H. capsulatum* appears as an oval or round, narrow-pore, budding, unencapsulated yeast.[33]

Epidemiology

Although histoplasmosis is found worldwide, certain areas of North, Central, and South America are recognized as highly endemic areas. In the United States, most disease is localized along the Ohio and Mississippi River valleys, where more than 90% of residents may be affected. However, due to differences in reporting requirements, variable diagnostic methodologies and capabilities, and a lack of adequate surveillance, particularly in low-resource settings, infections occur in other areas. Infections have been increasingly identified in some classically "non-endemic" areas of the United States, including the Rocky Mountain states (Montana and Idaho), the southeast (Florida and South Carolina), and the North Central states of Minnesota and North Dakota. Additional cases are being reported in Africa, Asia, and worldwide, in patients with HIV or those receiving immunosuppressive agents.[34]

Precise reasons for this endemic distribution pattern are unknown but are thought to include moderate climate, humidity, and soil characteristics. *H. capsulatum* is found in nitrogen-enriched soils, particularly those heavily contaminated by avian or bat guano, which accelerates sporulation. Blackbird or pigeon roosts, chicken coops, and sites frequented by bats, such as caves, attics, or old buildings, serve as "microfoci" of infections; once contaminated, soils yield *Histoplasma* for many years. Although birds are not infected because of their high body temperature, bats (mammals) may be infected and can pass yeast forms in their feces, allowing the spread of *H. capsulatum* to new habitats. Air currents carry the spores for great distances, exposing individuals who were unaware of contact with the contaminated site.[33]

Pathophysiology

At ambient temperatures, *H. capsulatum* grows as a mold. The mycelial phase consists of septate branching hyphae with terminal micro- and macroconidia that range in size from 2 to 14 μm in diameter. When soil is disturbed, these conidia become aerosolized and reach the bronchioles or alveoli.[33]

Animal studies demonstrate that within 2 to 3 days after reaching lung tissue, the conidia germinate, releasing yeast forms that begin multiplying by binary fission. During the next 9 to 15 days, organisms are ingested but not destroyed by large numbers of macrophages that are recruited to the infected site, resulting in small infiltrates. Infected macrophages migrate to the mediastinal lymph nodes and other sites within the mononuclear phagocyte system, particularly the spleen and liver. At this time, the onset of specific T-cell immunity in the nonimmune host activates the macrophages, rendering them capable of fungicidal activity. Tissue granulomas form, many of which develop central caseation and necrosis over the next 2 to 4 months. Over a period of several years, these foci become encapsulated and calcified, often with viable yeast trapped within the necrotic tissue.[33]

Cellular immunity, as measured by histoplasmin skin-test reactivity, wanes in the absence of occasional reexposure. Although exposure to heavy inocula can overcome these immune mechanisms, resulting in severe disease, reinfection occurs frequently in endemic areas. In the immune individual, the reactions of acquired immunity begin 24 to 48 hours after the appearance of yeast forms, resulting in milder forms of illness and little proliferation of organisms. Although viable organisms can be found within granulomas years after initial infection, the organisms appear to have little ability to proliferate within the fibrous capsules, except in immunocompromised patients.[33]

Clinical Presentation

The outcome of infection with *H. capsulatum* depends on a complex interplay of host, pathogen, and environmental factors.[10,33] Host factors include the degree of immunosuppression and the presence of immunity (from prior infection). Environmental factors include inoculum size, exposure within an enclosed area, and duration of exposure. Hematogenous dissemination from the lungs to other tissues probably occurs in all infected individuals during the first 2 weeks of infection before specific immunity has developed but is nonprogressive in most cases, which leads to the development of calcified granulomas of the liver and/or spleen. Progressive pulmonary infection is common in patients with underlying centrilobular emphysema.

Acute and chronic manifestations of histoplasmosis appear to result from unusual inflammatory or fibrotic responses to the pathogen, including pericarditis and rheumatologic syndromes during the first year after exposure, with chronic mediastinal inflammation or fibrosis, broncholithiasis, and enlarging parenchymal granulomas later in the course of disease.

In the vast majority of patients, low-inoculum exposure to *H. capsulatum* results in mild or asymptomatic pulmonary histoplasmosis. However, in Africa, infection with *H. capsulatum* var. *duboisii* results primarily in skin and soft tissue infection and only rarely in pulmonary disease.[34] The course of disease generally is benign, and symptoms usually abate within a few weeks of onset. Patients exposed to a higher inoculum during an acute primary infection or reinfection can experience an acute, self-limited illness with flu-like pulmonary symptoms, including fever, chills, headache, myalgia, and a nonproductive cough. Patients with diffuse pulmonary histoplasmosis can have diffused radiographic involvement, become hypoxic, and require ventilatory support. A low percentage of patients present with arthritis, erythema nodosum, pericarditis, or mediastinal granuloma.

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. Patients with early, non-cavitary disease often recover without treatment. Progression of disease over a period of years, seen in 25% to 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, successful containment of the organism within macrophages may not occur, resulting in a progressive illness characterized by yeast-filled phagocytic cells and an inability to produce granulomas. This disease, termed *disseminated histoplasmosis*, is characterized by persistent parasitization of macrophages. The clinical severity of the diverse forms of disseminated histoplasmosis (Table 144-4) generally parallels the degree of macrophage parasitization observed.

TABLE 144-4

Clinical Manifestations and Therapy of Histoplasmosis

Type of Disease and Common Clinical Manifestations	Therapy/Comments
Acute pulmonary histoplasmosis	
Asymptomatic or mild-to-moderate disease	*Asymptomatic, mild, or symptoms <4 weeks:* No therapy is generally required. Itraconazole[a] orally (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 greater than 1 month[a]
Moderately severe to severe diffuse pulmonary disease	Lipid amphotericin B 3-5 mg/kg/day IV for 1-2 weeks followed by itraconazole[a] orally 200 mg orally three times daily for 3 days then twice daily for a total of 12 weeks of therapy; 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
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 for 4-6 weeks, followed by itraconazole[a] orally 200 mg orally 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 CSF antibody titers
Progressive histoplasmosis	*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[a] orally (200 mg orally twice daily for at least 12 months) *Mild to moderate:* Itraconazole[a] orally (200 mg orally twice daily for at least 12 months). Immunosuppressed patients may require lifelong suppressive therapy with itraconazole[a] orally 200 mg daily

[a]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.

Data from References 10 and 33.

Acute (infantile) disseminated histoplasmosis is characterized by massive involvement of the mononuclear phagocyte system by yeast-engorged macrophages. Typically, this severe type of infection is seen in infants and young children and (rarely) in adults with Hodgkin's disease or other lymphoproliferative disorders. In infants or children, acute disseminated histoplasmosis 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. The chest roentgenogram often demonstrates remnants of the initiating acute pulmonary lesion. Untreated disease is uniformly fatal in 1 to 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. Untreated disease is fatal in approximately 10 months.

Most adults with disseminated histoplasmosis demonstrate a mild, chronic form of the disease. Untreated patients often are ill for 10 to 20 years, demonstrating long asymptomatic periods interrupted by relapses of clinical illness characterized primarily by weight loss, weakness, and fatigue. Chronic disseminated histoplasmosis can be seen in patients with lymphoreticular neoplasms (Hodgkin's disease) and patients undergoing

immunosuppressant chemotherapy for organ transplantation or for rheumatic diseases. Although CNS involvement occurs in 10% to 20% of patients with severe underlying immunosuppressive conditions, focal organ involvement is uncommon. The disease is characterized by the development of focal granulomatous lesions, often with bone marrow involvement resulting in thrombocytopenia, anemia, and leukemia. Fever, hepatosplenomegaly, and GI ulceration are common.

Histoplasmosis in HIV-Infected Patients

Adult patients with AIDS demonstrate an acute form of disseminated disease that resembles the syndrome seen in infants and children. Progressive disseminated histoplasmosis (PDH), which is defined as a clinical illness that does not improve after at least 3 weeks of observation and that is associated with physical or radiographic findings and/or laboratory evidence of involvement of extrapulmonary tissues, can occur as the direct result of initial infection or because of the reactivation of dormant foci. In endemic areas, 50% of AIDS patients demonstrate PDH as the first manifestation of their disease. PDH is characterized by fever (75% of patients), weight loss, chills, night sweats, enlargement of the spleen, liver, or lymph nodes, and anemia. Pulmonary symptoms occur in only one-third of patients and do not always correlate with the presence of infiltrates on chest roentgenogram. A clinical syndrome resembling septicemia is seen in approximately 25% to 50% of patients.[10]

Diagnosis

The diagnosis of histoplasmosis is made on the basis of histopathology, cultures, antigen detection, and serologic tests for *Histoplasma*-specific antibodies. Detection of single, ovoid cells 2 to 5 µm in diameter with narrow-based budding by direct examination or by histologic study of blood smears or tissues should raise strong suspicion of infection with *H. capsulatum* because colonization does not occur as with *Aspergillus* or *Candida* infection. In patients with acute self-limited histoplasmosis, extensive testing to verify the diagnosis may not be necessary.[33]

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. The highest sensitivity is obtained by testing both urine and serum.[33] *Histoplasma* EIA has also been used to monitor the course of therapy and to detect relapses in patients with AIDS, and the clearance of antigen from serum and urine correlates with clinical efficacy during maintenance therapy.[33]

Treatment

Table 144-4 summarizes the recommended therapy for the treatment of histoplasmosis. In general, asymptomatic or mildly ill patients and patients with sarcoid-like disease do not benefit from antifungal therapy. In the vast majority of patients, low-inoculum exposure to *H. capsulatum* results in *mild* or *asymptomatic* pulmonary histoplasmosis. The course of disease generally is benign, and symptoms usually abate within a few weeks of onset. Therapy can be helpful in symptomatic patients whose conditions have not improved during the first month of infection. Fever persisting more than 3 weeks can indicate that the patient is developing progressive disseminated disease, which can be aborted by antifungal therapy. Whether antifungal therapy hastens recovery or prevents complications is unknown because it has never been studied in prospective trials. 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.[10] Such patients may also require longer durations of therapy and lifelong suppressive therapy if immunosuppression cannot be reduced.

Fluconazole remains a second-line agent for the treatment of histoplasmosis due to inferior outcomes as compared to itraconazole in patients with and without AIDS. Clinical data regarding the use of newer azoles are limited. *Histoplasma* isolates from patients who have relapsed following therapy with fluconazole retain susceptibility to itraconazole, posaconazole, and isavuconazole, but not voriconazole. Voriconazole was clinically inferior to itraconazole as an initial or step-down therapeutic regimen.[35,36] While both have activity against *Histoplasma*, posaconazole appears to be more active than itraconazole in the immune compromised and non-immune compromised mouse model of infection. Both agents have been used successfully in a few patients. Of note, the echinocandins have no activity against *Histoplasma*.

In regions experiencing high rates of histoplasmosis (>5 cases/100 patient-years), itraconazole 200 mg/day orally is recommended as prophylactic therapy in HIV-infected patients. Fluconazole is not an acceptable alternative because of its inferior activity against *H. capsulatum* and its lower efficacy for the treatment of histoplasmosis.[10]

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 greater than 100 cells/μL (0.1×10^9/L) in response to highly active antiretroviral therapy (HAART), the number of patients who have been evaluated is insufficient to warrant a recommendation to discontinue prophylaxis.

Evaluation of Therapeutic Outcomes

Response to therapy should be measured by resolution of radiologic, serologic, and microbiologic parameters and by improvement in signs and symptoms of infection. Although investigators are limited by the lack of standardized criteria to quantify the extent of infection, degree of immunosuppression, or treatment response, response rates (based on resolution or improvement in presenting signs and symptoms) of greater than 80% have been reported in case series in AIDS patients receiving varied dosages of amphotericin B. Rapid responses are reported, with the resolution of symptoms in 25% and 75% of patients by days 3 and 7 of therapy, respectively.

After the initial course of therapy for histoplasmosis is complete, lifelong suppressive therapy in some patients with oral azoles is recommended because of the frequent recurrence of infection. Relapse rates in AIDS patients not receiving maintenance therapy range from 50% to 90%.[10] Antigen testing can be useful for monitoring therapy since concentrations decrease with therapy and increase with relapse.

BLASTOMYCOSIS

Blastomycosis is a systemic fungal infection primarily caused by the *Blastomyces dermatitidis* complex, a dimorphic fungus that infects primarily the lungs. Patients, however, can present with a variety of pulmonary and extrapulmonary clinical manifestations. Pulmonary disease can be acute or chronic and can mimic infection with tuberculosis, pyogenic bacteria, other fungi, or malignancy. Blastomycosis can disseminate to virtually every other body organ, and approximately 40% of patients with blastomycosis present with skin, bone and joint, or genitourinary tract involvement without any evidence of pulmonary disease.[8,37]

Pulmonary infection probably occurs by inhalation of conidia, which convert to the yeast form in the lung. A vigorous inflammatory response ensues, with neutrophilic recruitment to the lungs followed by the development of cell-mediated immunity and the formation of non-caseating granulomas.

Epidemiology

The *Blastomyces dermatitidis* complex includes *B. dermatitidis* and *B. gilchristii*, although they are often referred to solely as *B. dermatitidis*. *B. dermatitidis* has been isolated from soil containing decayed vegetation, decomposed wood, and pigeon manure, frequently in association with warm, moist soil of wooded areas near fresh water. *B. dermatitidis* is endemic to the southeastern and south central states of the United States (especially those bordering on the Mississippi and Ohio River basins) and the Midwestern states and Canadian provinces bordering the Great Lakes and St. Lawrence River. Infection due to other rarer species occurs outside this endemic region, such as *B. helicus* in the western United States.[8,37] Although initial review of sporadic cases suggested that males with outdoor occupations that exposed them to soil were at greatest risk for blastomycosis, there is no sex, age, or occupational predilection for blastomycosis.[8,37]

Pathophysiology and Clinical Presentation

Colonization does not occur with *Blastomyces.*[8,37] *Pulmonary blastomycosis* is the most common manifestation, and can range from asymptomatic infection to acute pneumonia with or without respiratory failure to chronic disease. Typical symptoms of acute pulmonary infection include fever, shaking chills, and productive, purulent cough, with or without hemoptysis. The clinical presentation can be difficult to differentiate from other respiratory infections, including bacterial pneumonia, on the basis of clinical symptoms alone. Development of the acute respiratory distress syndrome (ARDS) is associated with high mortality.

Sporadic pulmonary blastomycosis can present as a more chronic or subacute disease, with low-grade fever, night sweats, weight loss, and productive cough that resembles tuberculosis rather than bacterial pneumonia. *Chronic pulmonary blastomycosis* is characterized by fever, malaise, weight loss, night sweats, chest pain, and productive cough. Patients often are thought to have tuberculosis and frequently have evidence of disseminated disease that can appear 1 to 3 years after the primary pneumonia has resolved. Reactivation of disease can occur in the lungs or as the focus of new infection in other organs.

In approximately 15% to 50% of patients, dissemination occurs, with the most common sites including the skin and bony skeleton, although less commonly the prostate, oropharyngeal mucosa, and abdominal viscera are involved. CNS disease, while exceedingly uncommon, is associated with the highest mortality rate.

Laboratory and Diagnostic Tests

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 staining.[8,37] Culture growth is slow and can require up to 30 days to isolate and identify a small inoculum.

No reliable skin test exists to determine the incidence and prevalence of disease in endemic populations, and reliable serologic diagnosis of blastomycosis is not available. Quantitative antigen testing is available, with highest sensitivity from urine samples, although cross-reactivity with other endemic fungi (including *H. capsulatum*) results in a low specificity.[37]

Treatment

Non-HIV-Infected Patient

5 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.

In patients with mild-to-moderate pulmonary blastomycosis, itraconazole is effective; however, in patients with moderately severe to severe pulmonary disease, the clinical presentation of the patient, the immune competence of the patient, and the toxicity of the antifungal agents are the main determinants of the choice of antifungal therapy (Table 144-5). In the case of disease limited to the lungs, cure might have occurred without treatment before the diagnosis is made. Regardless of whether or not the patient receives treatment, however, he or she must be followed carefully for many years for evidence of reactivation or progressive disease.[8,37]

TABLE 144-5

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] 200 mg orally three times daily for 3 days, then 200 mg twice daily, × total of 6-12 months
Mild-to-moderate disease	Itraconazole[c] 200 mg orally three times daily for 3 days, then 200 mg twice daily, for a total of 6 months
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 800 mg orally daily, or itraconazole[c] 200 mg two or three times orally daily, or voriconazole 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] 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[c] therapy once the patient's condition improves
Mild to moderate	Itraconazole[b,c] 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,b] 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] 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[c] 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.

AIDS, acquired immunodeficiency syndrome.

Data from Reference 8.

Some authors recommend azole therapy for the treatment of self-limited pulmonary disease, with the hope of preventing late extrapulmonary disease;

however, data supporting the efficacy of these regimens are lacking.[8,37] Itraconazole 200 to 400 mg/day demonstrated 90% efficacy as a first-line agent in the treatment of non-life-threatening non-CNS blastomycosis, and for compliant patients who completed at least 2 months of therapy, a success rate of 95% was noted. No therapeutic advantage was noted with the higher (400 mg) dosage as compared with patients treated with 200 mg.[38]

All patients with disseminated blastomycosis, as well as those with extrapulmonary disease, require therapy. Amphotericin B is recommended for patients with overwhelming or life-threatening disease, CNS infection, and treatment failures.[8,37] Lipid preparations of amphotericin B have largely replaced conventional amphotericin B for treatment of blastomycosis, despite their higher cost, due to their decreased renal toxicity. Surgery has only a limited role in the treatment of blastomycosis.

HIV-Infected Patient

For unclear reasons, blastomycosis is an uncommon opportunistic disease among immunocompromised individuals, including AIDS patients; however, blastomycosis can occur as a late (CD4 lymphocytes < 200 cells/mm^3 [0.2×10^9/L]) and frequently fatal complication of HIV infection. In this population, overwhelming disseminated disease with frequent involvement of the CNS is common.[8,37] Following induction therapy with amphotericin B (total cumulative dose of 1 g), HIV-infected patients should receive chronic suppressive therapy with an oral azole antifungal for at least a year and until they are on effective antiretroviral therapy with a CD4+ T-cell count > 150 cells/µL (0.15×10^9/L).[8,37]

COCCIDIOIDOMYCOSIS

Epidemiology

Coccidioidomycosis is caused by infection with *Coccidioides immitis* and *Coccidioides posadasii,* dimorphic fungi found in the southwestern and western United States, as well as in parts of Mexico and South America. In North America, the endemic regions encompass the semiarid areas of the southwestern United States from California to Texas known as the Lower Sonoran Zone, where there is scant annual rainfall, hot summers, and sandy, alkaline soil. *Coccidioides* grows in the soil as a mold, and mycelia proliferate during the rainy season. During the dry season, resistant arthroconidia form and become airborne when the soil is disturbed.

Although generally considered to be a regional disease, coccidioidomycosis has increased in importance in recent years because of the increased tourism and population in endemic areas, the increased use of immunosuppressive therapy in transplantation and oncology, and the AIDS epidemic. Although there is no racial, hormonal, or immunologic predisposition for acquiring primary disease, these factors affect the risk of subsequent dissemination of disease (Table 144-6).[39]

TABLE 144-6

Factors for Severe, Disseminated Infection with Coccidioidomycosis

Race (Filipino and African American ancestry)
Pregnancy (especially when infection is acquired or reactivated in the second or third trimester)
Male gender
Neonates
Compromised cellular immune system, including • AIDS patients • Patients receiving corticosteroids, immunosuppressive agents, or chemotherapy

AIDS, acquired immune deficiency syndrome.

Data from Reference 39.

Pathophysiology

When individuals come in contact with contaminated soil during ranching, dust storms, or proximity to construction sites or archeological excavations, arthroconidia are inhaled into the respiratory tree, where they transform into spherules, which reproduce by cleavage of the cytoplasm to produce endospores. The endospores are released when the spherules reach maturity. Similar to histoplasmosis, an acute inflammatory response in the tissue leads to infiltration of mononuclear cells, ultimately resulting in granuloma formation.[39]

Clinical Presentation

Coccidioidomycosis encompasses a spectrum of illnesses ranging from primary uncomplicated respiratory tract infection that resolves spontaneously to progressive pulmonary or disseminated infection.[39] Initial or primary infection almost always involves the lungs. Although approximately one-third of the population in endemic areas is infected, the average incidence of symptomatic disease is only approximately 0.43%.

Signs and Symptoms

Primary Coccidioidomycosis ("*Valley Fever*"): Approximately 60% of infected patients have an asymptomatic, self-limited infection without clinical or radiological manifestations. Most of the remaining 40% of patients exhibit non-specific symptoms that are often indistinguishable from ordinary upper respiratory infections, including fever, cough, headache, sore throat, myalgias, and fatigue that occur 1 to 3 weeks after exposure to the pathogen. More commonly, a diffuse, mild erythroderma or maculopapular rash is observed. Patients can have pleuritic chest pain and peripheral eosinophilia.

A fine, diffuse rash can appear during the first few days of the illness. Primary pneumonia can be the first manifestation of disease, characterized by a productive cough that can be blood-streaked, as well as single or multiple soft or dense homogeneous hilar or basal infiltrates on chest roentgenogram. *Chronic, persistent pneumonia, or persistent pulmonary coccidioidomycosis* (primary disease lasting more than 6 weeks) is complicated by hemoptysis, pulmonary scarring, and the formation of cavities or bronchopleural fistulas.

Necrosis of pulmonary tissue with drainage and cavity formation occurs commonly. Most parenchymal cavities close spontaneously or form dense nodular scar tissue that can become superinfected with bacteria or spherules of *Coccidioides.* These patients often have persistent cough, fevers, and weight loss.

Disseminated disease occurs in less than 1% of infected patients. The most common sites for dissemination are the skin, lymph nodes, bone, and meninges, although spleen, liver, kidney, and adrenal gland also can be involved. Occasionally, miliary coccidioidomycosis occurs with rapid, widespread dissemination, often in concert with positive blood cultures for *Coccidioides.* Patients with AIDS frequently present with miliary disease. Coccidioidomycosis in AIDS patients appears to be caused by reactivation of disease in most patients. Dissemination also is more likely if infection occurs during pregnancy, especially during the third trimester or in the immediate postpartum period.[39]

CNS infection occurs in approximately 16% of patients with disseminated coccidioidomycosis. Patients can present with meningeal disease without previous symptoms of primary pulmonary infection, although disease usually occurs within 6 months of the primary infection. The signs and symptoms are often subtle and non-specific, including headache, weakness, changes in mental status (lethargy and confusion), neck stiffness, low-grade fever, weight loss, and occasionally, hydrocephalus. Space-occupying lesions are rare, and the main areas of involvement are the basilar meninges.

The diagnoses of coccidioidomycosis generally utilizes identification or recovery of *Coccidioides* spp. from clinical specimens and detection of specific anticoccidioidal antibodies in serum or other body fluids.

Treatment

Goals of Therapy

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. It would also be desirable to prevent relapse of illness on discontinuation of therapy, although current therapy is often unable to achieve this goal.

General Approach

Therapy for coccidioidomycosis is difficult, and the results are unpredictable. Guidelines[11] are available for treatment of this disease; however, optimal treatment for many forms of this disease still generates debate. The efficacy of antifungal therapy for coccidioidomycosis often is less certain than that for other fungal etiologies, such as blastomycosis, histoplasmosis, or cryptococcus, even when in vitro susceptibilities and the sites of infections are similar. The refractoriness of coccidioidomycosis can relate to the ability of *Coccidioides* spherules to release hundreds of endospores, maximally challenging host defenses.[39] Fortunately, only approximately 5% of infected patients require therapy.

Specific Agents Used for the Treatment of Coccidioidomycosis

Although there is continued disagreement among experts in endemic areas whether antifungal therapy in patients with uncomplicated early coccidioidal infection might shorten the course of illness or reduce the development of more serious complications, prospective randomized trials addressing this question are lacking. The excellent tolerability of oral azoles has lowered the threshold for deciding to treat primary infection, and clinicians should treat patients with significantly debilitating illness, those with extensive pulmonary disease, and with who are frail due to advanced age, concurrent diabetes or comorbidities.[11]

Azole antifungals, primarily fluconazole and itraconazole, have replaced amphotericin B as initial therapy for most chronic pulmonary or disseminated infections. Amphotericin B is now usually reserved for patients with respiratory failure because of infection with *Coccidioides* species, those with rapidly progressive coccidioidal infections, or women during pregnancy. Therapy often ranges from many months to years in duration, and in some patients, lifelong suppressive therapy is needed to prevent relapses. Specific antifungals (and their usual dosages) for the treatment of coccidioidomycosis include IV lipid formulations of amphotericin B (3-5 mg/kg/day), IV or oral fluconazole (usually 400-800 mg/day, although dosages as high as 1,200 mg/day have been used without complications), and itraconazole (200-300 mg orally twice daily or three times daily, as capsules or solution).[39] If itraconazole is used, measurement of serum concentrations can be helpful to ascertain whether oral bioavailability is adequate.

Given the efficacy and superior tolerability profile of the triazole antifungals, amphotericin B products are generally only recommended for patients refractory to or intolerant of other agents, or in those with rapid deterioration. Compared to amphotericin B deoxycholate, the lipid formulations of amphotericin B have not been studied extensively in coccidioidal infection but can offer a means of giving more drug with less toxicity. Fluconazole probably is the most frequently used medicine given its tolerability, although high relapse rates have been reported in some studies. Itraconazole therapy resulted in superior response in patients with skeletal infection, and relapse rates in the overall study population were lower with itraconazole therapy than with fluconazole.[39,40] Posaconazole was effective treatment in patients with refractory infections. Its efficacy relative to other triazole antifungals is unknown.

Combination therapy with members of different classes of antifungal agents has not been evaluated in patients, and there is a hypothetical risk of antagonism. However, some clinicians feel that outcome in severe cases is improved when amphotericin B is combined with an azole antifungal. If the patient improves, the dosage of amphotericin B can be slowly decreased while the dosage of azole is maintained.[39]

Primary Respiratory Infection

Although most patients with symptomatic primary pulmonary disease recover without therapy, management should include follow-up visits for 1 to 2 years to document resolution of disease or to identify as early as possible evidence of pulmonary or extrapulmonary complications.

Patients with a large inoculum, severe infection, or concurrent risk factors (eg, HIV infection, organ transplant, pregnancy, or high doses of corticosteroids) probably should be treated, particularly those with high CF titers, in whom incipient or occult dissemination is likely. Because some racial or ethnic populations have a higher risk of dissemination, some clinicians advocate their inclusion in the high-risk group. Common indicators that are used to judge the severity of infection include weight loss (greater than 10%), intense night sweats persisting more than 3 weeks, infiltrates involving more than one-half of one lung or portions of both lungs, prominent or persistent hilar adenopathy, CF antibody titers of greater than 1:16, failure to develop dermal sensitivity to coccidioidal antigens, inability to work, or symptoms that persist for more than 2 months.[39]

Commonly prescribed therapies include currently available oral azole antifungals at their recommended doses for courses of therapy ranging from 3 to 6 months.[39] In patients with diffuse pneumonia with bilateral reticulonodular or miliary infiltrates, therapy usually is initiated with amphotericin B;

several weeks of therapy are required to produce clear evidence of improvement. Consolidation therapy with oral azoles can be considered at that time. The total duration of therapy should be at least 1 year, and in patients with underlying immunodeficiency, oral azole therapy should be continued as secondary prophylaxis.

Infections of the Pulmonary Cavity

Many pulmonary infections that are caused by *Coccidioides* are benign in their course and do not require intervention. In the absence of controlled clinical trials, evidence of the benefit of antifungal therapy is lacking, and asymptomatic infections generally are left untreated. Symptomatic patients can benefit from oral azole therapy, although recurrence of symptoms can be seen in some patients once therapy is discontinued. Surgical resection of localized cavities provides resolution of the problem in patients in whom the risks of surgery are not too high.[39]

Extrapulmonary (Disseminated) Disease

Nonmeningeal Disease

Almost all patients with disease located outside the lungs should receive antifungal therapy, which is usually initiated with 400 mg/day of an oral azole. Amphotericin B is an alternative therapy and can be necessary in patients with worsening lesions or with disease in particularly critical locations such as the vertebral column. Approximately 50% to 75% of patients treated with amphotericin B for nonmeningeal disease achieve a sustained remission, and therapy usually is curative in patients with infections localized strictly to skin and soft tissues without extensive abscess formation or tissue damage. The efficacy of local injection into joints or the peritoneum, as well as intra-articular or intradermal administration, remains poorly studied. Amphotericin B appears to be most efficacious when cell-mediated immunity is intact (as evidenced by a positive coccidioidin or spherulin skin test or low CF antibody titer). However, controlled trials that document these clinical impressions are lacking.[39]

Meningeal Disease

Fluconazole has become the drug of choice for the treatment of coccidioidal meningitis. A minimum dose of 400 mg/day orally leads to a clinical response in most patients and obviates the need for intrathecal amphotericin B. Some clinicians will initiate therapy with 800 or 1,000 mg/day, and itraconazole dosages of 400 to 600 mg/day are comparably effective. It is also clear, however, that fluconazole only leads to remission rather than cure of the infections; thus suppressive therapy must be continued for life. Ketoconazole cannot be recommended routinely for the treatment of coccidioidal meningitis because of its poor CNS penetration following oral administration. Patients who do not respond to fluconazole or itraconazole therapy are candidates for intrathecal amphotericin B therapy with or without continuation of azole therapy. The intrathecal dose of amphotericin B ranges from 0.01 to 1.5 mg given at intervals ranging from daily to weekly. Therapy is initiated with a low dosage and is titrated upward as patient tolerance develops.[39]

CRYPTOCOCCOSIS

Epidemiology

Cryptococcosis is a noncontagious, systemic mycotic infection caused by the ubiquitous encapsulated soil yeast *Cryptococcus*, which is found in soil, particularly in pigeon droppings, although disease occurs throughout the world, even in areas where pigeons are absent. Infections caused by *C. neoformans* var. *grubii* (serotype A) are seen worldwide among immunocompromised hosts, followed by *C. neoformans* var. *neoformans* (serotype D). On the other hand, *Cryptococcus gattii* (serotypes B and C) is geographically more restricted and in contrast to *C. neoformans*, rarely infects immunosuppressed patients, is not associated with HIV infection, and the infections are more difficult to treat. *C. gattii* is not associated with birds; its main reservoir was thought to be limited to certain species of eucalyptus tree. Until recently, it was most common in tropical and subtropical areas, such as Australia, South America, Southeast Asia, and central Africa, with the highest incidence in Papua New Guinea and Northern Australia, although infections occur in non-tropical areas such as North America and Europe. *C. gattii* emerged on Vancouver Island, British Columbia, Canada, in 1999, and subsequently spread to the Vancouver lower mainland, Washington state, and Oregon.[41,42]

Infection is acquired by inhalation of the organism. Immunocompromised patients are at elevated risk, including those with malignancies, diabetes mellitus, chronic renal failure, and organ transplants and those receiving immunosuppressive agents. In most developed countries, widespread use of

HAART has significantly decreased the incidence of cryptococcosis; however, the incidence and mortality of this infection are still extremely high in areas with limited access to HAART and a high incidence of HIV.[9,42]

Disease can remain localized in the lungs or can disseminate to other tissues, particularly the CNS, although the skin also can be affected. Hematogenous spread generally occurs in the immunocompromised host, although it also has been seen in individuals with intact immune systems.

Clinical Presentation

Primary cryptococcosis in humans almost always occurs in the lungs, although the pulmonary focus usually produces a subclinical infection. Symptomatic infections usually are manifested by cough, rales, and shortness of breath that generally resolve spontaneously. Cryptococcus can present as part of an immune reconstitution inflammatory syndrome (IRIS), a paradoxical worsening of preexisting infectious processes following the initiation of HAART in HIV-infected individuals. The symptoms of cryptococcal meningitis are nonspecific. Headache, fever, nausea, vomiting, mental status changes, and neck stiffness are generally observed. Less common symptoms include visual disturbances (photophobia and blurred vision), papilledema, seizures, and aphasia. Intracerebral mass lesions (cryptococcomas) are more common in *C. gattii* than in *C. neoformans*, presumably due to their different host immune responses.[42]

Laboratory Tests

With cryptococcal meningitis, the CSF opening pressure is elevated. There is a CSF pleocytosis (usually lymphocytes), leukocytosis, a decreased glucose concentration, and an elevated CSF protein concentration. There is also a positive cryptococcal antigen (detected by LA). The test is rapid, specific, and extremely sensitive, but false-negative results can occur. False-positive tests can result from cross-reactivity with rheumatoid factor and *Trichosporon beigelii. C. neoformans* can be detected in approximately 60% of patients by India ink smear of CSF, and it can be cultured in more than 96% of patients. Occasionally, large volumes of CSF are required to confirm the diagnosis.

The CSF parameters in patients with AIDS are similar to those seen in non-AIDS patients, with the exception of a decreased inflammatory response to the pathogen, resulting in a strikingly low number of leukocytes in CSF and extraordinarily high cryptococcal antigen titers.[42]

Treatment

The choice of treatment for disease caused by *C. neoformans* depends on both the anatomic sites of involvement and the host's immune status, and thus, treatment recommendations are divided into three specific risk groups: (a) HIV-infected individuals, (b) transplant recipients, and (c) non–HIV-infected and nontransplant hosts (Table 144-7).[9] The management of cryptococcosis includes systemic antifungal therapy, control of elevated intracranial pressure (ICP), and supportive care. When possible, immune defects should be addressed. Although no randomized clinical trials have been performed to address this, outcomes of treatment for CNS cryptococcosis (without mass lesions or hydrocephalus) appear to be similar for disease due to either *C. neoformans* or *C. gattii*.[41]

TABLE 144-7

Therapy of Cryptococcosis[a,b]

Type of Disease and Common Clinical Manifestations	Therapy/Comments
Non-immunocompromised Patients (Non–HIV-Infected, Nontransplant)	
Meningoencephalitis *without* neurological complications, in patients in whom CSF yeast cultures are negative after 2 weeks of	*Induction:* Amphotericin B[c,d] IV 0.7-1 mg/kg/day *plus* flucytosine 100 mg/kg/day orally in four divided doses × ≥4 weeks

therapy	
Meningoencephalitis with neurological complications	*Induction:* Same as for patients without neurologic complications, but consider extending the induction therapy for a total of 6 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
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 (non-meningeal, non-pulmonary disease)	*Same as CNS disease × 12 months*
HIV-infected Patients	
Primary therapy; induction and consolidation[e]	*Preferred regimen: Induction:* Amphotericin B[c,d] IV 0.7-1 mg/kg IV daily *plus* flucytosine 100 mg/kg/day orally in four divided doses for ≥2 weeks. Alternative regimens, in order of preference: Amphotericin B[c,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[c] 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 × ≥8 weeks *or* Fluconazole ≥800 mg (1,200 mg/day is preferred) orally daily *plus* flucytosine 100 mg/kg/day orally in four divided doses × 6 weeks *or* Fluconazole 800-1,200 mg/day orally daily × 10-1 2 weeks (a dosage ≥1,200 mg/day is preferred when fluconazole is used alone)[g]
Follow all regimens with suppressive therapy	*Consolidation:* Fluconazole 400 mg (6 mg/kg) orally daily × ≥8 weeks *Maintenance:* Fluconazole 200 mg orally daily × ≥ 1 year[h,i]
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 lipid formulation (6 mg/kg IV daily) in patients with a high-fungal burden disease or relapse of disease
Follow all regimens with	*Consolidation:* Fluconazole 400-800 mg (6-12 mg/kg) per day orally for 8 weeks

suppressive therapy	*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]In patients with, or at risk of renal disease, lipid formulations of amphotericin B can be substituted for deoxycholate amphotericin B. Doses are liposomal amphotericin B 3-4 mg/kg IV daily, or amphotericin B lipid complex (ABLC) 5 mg/kg IV daily.

[e]Initiate HAART therapy 2-10 weeks after commencement of initial antifungal treatment.

[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]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).

[i]Drug level monitoring is strongly advised.

HIV, human immunodeficiency virus; IT, intrathecal.

Data from Reference 9.

Non-immunocompromised Patients

Prior to the introduction of amphotericin B, cryptococcal meningitis was an almost uniformly fatal disease; approximately 86% of patients died within 1 year. The use of large (1-1.5 mg/kg) daily doses of amphotericin B resulted in cure rates of approximately 64%. When amphotericin B is combined with flucytosine, a smaller dose of amphotericin B can be employed because of the in vitro and in vivo synergy between the two antifungal agents.[43] Resistance develops to flucytosine in up to 30% of patients treated with flucytosine alone, limiting its usefulness as monotherapy.[42] Combination therapy with amphotericin B and flucytosine has become standard therapy, will sterilize the CSF within 2 weeks of treatment in 60% to 90% of patients, and most immunocompetent patients will be treated successfully with 6 weeks of combination therapy.[43] Lipid formulations of amphotericin B are preferred because they increase the likelihood of completing the full course of therapy.[42] However, because of the need for prolonged IV therapy and the potential for renal and hematologic toxicity with this regimen, alternative regimens utilizing shorter (2 weeks) courses of amphotericin B followed by consolidation therapy with fluconazole for 8 weeks, then maintenance therapy with a lower dosage of fluconazole for 6 to 12 months has been advocated.[9]

For asymptomatic, immunocompetent hosts with isolated mild-to-moderate pulmonary disease and no evidence of CNS disease, careful observation can be warranted; in the case of symptomatic infection, fluconazole for 6 to 12 months is warranted. Patients with severe pulmonary disease should be treated with the same regimens as for CNS disease. Additionally, patients with non-CNS, non-pulmonary cryptococcosis, such as cryptococcemia, usually have disseminated disease and treatment regimens similar to those as for CNS disease are recommended.[9]

Despite low CSF concentrations of amphotericin B (2%-3% of those observed in plasma), the use of intrathecal amphotericin B is not recommended for the treatment of cryptococcal meningitis except in very ill patients or in patients with recurrent or progressive disease despite aggressive therapy with IV amphotericin B.[9]

The recommended management of raised ICP in cryptococcal meningitis (without hydrocephalus, a mass lesion, or a shift on computed tomography

[CT] scan) has been repeated CSF removal by spinal tap. Those who do not respond and have ongoing raised ICP should have ophthalmologic monitoring for possible vision loss, and should be considered for ventriculoperitoneal shunt surgery. Neither corticosteroids (in the absence of IRIS) nor acetazolamide is recommended for management of raised ICP. Symptomatic, medically refractory mass lesions that may be compressing vital structures should be considered for surgical therapy.[9]

Immunocompromised Patients

Immunocompromised hosts with isolated severe pulmonary and extrapulmonary disease (including cryptococcemia) without CNS disease should be treated similar to non-immunocompromised patients with CNS disease. Induction regimens as short as 2 weeks in HIV-infected patients with CNS disease are effective. However, continuation of combination induction therapy is recommended in patients who have not improved or are deteriorating, or in those with anticipated/proven persistent positive CSF cultures. Non-HIV immunocompromised patients with CNS infection, such as solid organ transplant recipients, are generally managed with regimens similar to those recommended for patients with HIV.[9]

Organ Transplant Recipients

Cryptococcosis has been documented in an average of 2.8% of solid-organ transplant recipients. The median time to disease onset is 21 months after transplantation; 68.5% of the cases occur greater than 1 year after transplantation.

Induction therapy for solid organ transplant recipients with cryptococcal meningoencephalitis consists of liposomal amphotericin B or amphotericin B lipid complex (ABLC) plus flucytosine for at least 2 weeks. Fluconazole consolidation therapy should be administered for 8 weeks, and maintenance therapy should be continued for at least 6 to 12 months. Immunosuppressive management should include sequential or stepwise reduction of immunosuppressants, with consideration of lowering the corticosteroid dose first. Amphotericin B should be used with caution in transplant recipients and is not recommended as first-line therapy in this patient population due to the risk of nephrotoxicity in this population that frequently has reduced renal function. If used, the tolerated dosage of amphotericin B is uncertain, but 0.7 mg/kg daily is suggested with frequent renal function monitoring. Regardless of the agent utilized, all antifungal dosages need to be carefully monitored.[9]

HIV-Infected Patients

Primary antifungal prophylaxis for cryptococcosis is not routinely recommended in HIV-infected patients in the United States and Europe. However, in areas with limited HAART availability, high levels of antiretroviral drug resistance, and a high burden of disease, clinicians may wish to consider the use of either prophylactic therapy or a preemptive strategy with serum cryptococcal antigen testing for asymptomatic antigenemia.[9]

Early studies confirmed the benefit of early high-dose amphotericin B use, the usefulness of flucytosine added to amphotericin B for induction therapy, and the slight superiority of fluconazole over itraconazole for consolidation therapy.[43]

Amphotericin B formulations combined with flucytosine during the 2-week induction phase of therapy is the initial treatment of choice, as this regimen has been repeatedly validated in clinical trials.[44-46] Amphotericin B plus fluconazole and flucytosine plus fluconazole are non-preferred alternatives. In patients who cannot tolerate flucytosine, amphotericin B alone for 4 to 6 weeks is an alternative. After the initially successful 2-week induction period, consolidation therapy with fluconazole can be administered for 8 weeks. In patients in whom fluconazole cannot be given, itraconazole is an acceptable, albeit less effective, alternative.[9]

In HIV-infected patients, mortality is highly associated with elevated ICP (CSF opening pressure greater than 250 mm H_2O [2.5 kPa]). At the initiation of antifungal therapy, lumbar drainage should remove enough CSF to normalize the opening pressure. Patients initially should undergo daily lumbar punctures to maintain CSF opening pressure in the normal range. When the CSF pressure is normal for several days, the procedure can be suspended.[9] Adjunctive steroid treatment is not recommended.[47] Similarly, neither mannitol nor acetazolamide therapy provides any clear benefit in the management of elevated ICP.[9]

Suppressive (Maintenance) Therapy for Cryptococcal Meningitis in HIV-Infected Patients

Relapse of *C. neoformans* meningitis occurs in approximately 50% of AIDS patients after completion of primary therapy. Persistence of asymptomatic

urinary *C. neoformans* has been documented in a high percentage of AIDS patients despite seemingly adequate courses of therapy for primary meningeal disease. The prostate appears to act as a sequestered reservoir of infection in these patients, resulting in systemic relapse.

Patients appear to be at low risk for recurrence of cryptococcosis when they have successfully completed a course of initial therapy for cryptococcosis, remain asymptomatic with regard to signs and symptoms of cryptococcosis, have received antifungal therapy for greater than 3 of the previous 6 months, have a serum cryptococcal antigen titer less than 1:512, or have a sustained increase (eg, greater than 6 months) in their $CD4^+$ T-lymphocyte counts to greater than 100 to 200 cells/μL (0.1×10^9-0.2×10^9/L) and an HIV viral load of less than 50 copies/mL (50×10^3/L).

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. Maintenance therapy can be discontinued after 1 year in patients who have successfully completed primary therapy, are free of symptoms and signs of active cryptococcosis, and have been receiving HAART with a sustained CD4 cell count greater than 100 cells/mL (0.100×10^6/L) and an undetectable viral load sustained for at least 3 months.[9,43] One consideration regarding the initiation of HAART involves concern for immune reconstitution inflammatory syndrome (IRIS) in patients with AIDS not on antiretroviral therapy. In such patients, initiation of HAART may provoke an exuberant inflammatory response resulting in new/worsened symptoms, including possibly increasing intracranial pressure. Therefore, the initiation of HAART should be withheld during the induction phase of treatment, and started 2 to 10 weeks after the start of antifungal therapy. Corticosteroids may be necessary for major complications.[9,42]

CANDIDA INFECTIONS

Candida species are yeasts that exist primarily as small (4-6 μm), unicellular, thin-walled, ovoid cells that reproduce by budding. On agar medium, they form smooth, white, creamy colonies resembling staphylococci. Although there are more than 150 species of *Candida*, eight species—*C. albicans*, *C. tropicalis*, *Candida parapsilosis*, *C. krusei*, *Candida dublinensis*, *C. guilliermondii*, *C. lusitaniae*, and *C. glabrata*—are regarded as clinically important pathogens in human disease. Yeast forms, hyphae, and pseudohyphae can be found in clinical specimens.[48]

Pathophysiology

C. albicans is a normal commensal of the skin, female genital tract, and entire GI tract of humans. Therefore, the mere presence of hyphae or pseudohyphae in a clinical specimen is insufficient for the diagnosis of invasive disease. The majority of infections with *C. albicans* are acquired endogenously, although human-to-human transmission also can occur. Although the term *fungemia* refers to the presence of fungi in the blood, the most commonly isolated organism is *C. albicans*. Candidiasis can cause mucocutaneous or systemic infection, including endocarditis, peritonitis, arthritis, and infection of the CNS (mucocutaneous infections caused by *Candida* are discussed in further detail in Chapter 143).

Adherence of *C. albicans* is important in the pathogenesis of oral candidiasis and subsequent colonization of the GI tract. Because evidence suggests that the GI tract is often the portal of entry for *Candida* in disseminated disease, factors that alter the adherence of *Candida* are crucial in the development of local and systemic infection. *C. tropicalis* adheres to intravascular catheters at a higher rate than *C. albicans*, a factor that may help to account for the increased incidence of systemic infections caused by this pathogen.

CANDIDEMIA AND ACUTE HEMATOGENOUSLY DISSEMINATED CANDIDIASIS

Epidemiology

Candidemia is the fourth most common BSI in US hospitals.[25] It is associated with high mortality, increased length of hospital stay, and significant economic burden.[49] Although patients with neutropenia are at high risk for IFIs, the use of antifungal prophylaxis and prompt initiation of antifungal therapy in persistently febrile patients with neutropenia who do not respond to antibiotics has resulted in a reduction in the frequency of *Candida* BSIs in this population.[7]

The most commonly encountered clinical species of *Candida* include *C. albicans*, *C. glabrata, C. tropicalis, C. parapsilosis, C. lusitaniae, C. krusei,* and *C. guilliermondii*. While *C. albicans* is still the most common species of *Candida* causing candidemia, its relative frequency is decreasing, while the frequency of the other, non-*albicans* species, especially *C. glabrata*, has increased.[15] The change in species is of concern clinically, as certain

pathogens, such as *C. krusei* and *C. glabrata*, are intrinsically more resistant to commonly used triazole drugs.[15] Although risk factors for the development of *Candida* BSIs in ICU patients can be identified, factors that lead to the acquisition of specific species are still unclear.[26] The emergence of infections caused by *Candida auris*, a novel, pathogenic *Candida* species associated with a high (40%-60%) mortality is concerning. Several outbreaks of *C. auris*, which first appeared in 2009, have been reported in the United Kingdom and Spain. Most infections appear in patients with previous exposure to antifungals and has high potential for interhuman transmission.[50]

Patients' characteristics influence the distribution of *Candida* species: *C. krusei* and *C. tropicalis* in patients with hematologic malignancies, while *C. parapsilosis* is most common in children, neonates, and patients with central lines and receiving parenteral nutrition. Fungemia caused by *C. glabrata* is observed more commonly in adults older than 65 years of age, perhaps due to an increased rate of oral colonization with *C. glabrata* in the elderly, and also associated with antimicrobial use and severity of underlying illness.[15]

Pathophysiology

Candida is acquired via the GI tract, although organisms also can enter the bloodstream via indwelling IV catheters. Immunosuppressed patients, including those with lymphoreticular or hematologic malignancies, diabetes, and immunodeficiency diseases and those receiving immunosuppressive therapy with high-dose corticosteroids, immunosuppressants, antineoplastic agents, or broad-spectrum antimicrobial agents, are at high risk for IFIs (Table 144-8). Major risk factors include the use of CVCs, total PN, receipt of multiple antibiotics, extensive surgery and burns, renal failure and hemodialysis, mechanical ventilation, and prior fungal colonization. Patients who have undergone surgery (particularly surgery of the GI tract) are increasingly susceptible to disseminated candidal infections.[15,26,48]

TABLE 144-8

Risk Factors for Invasive Candidiasis

Colonization
Corrected colonization index (CCI) ≥0.4[a]
Colonization index (CI) ≥0.8[a]
Candida spp. cultured from sites other than blood
Candiduria
Antibiotic use
Number of antibiotics prior to infection (per additional antibiotics)
Use of two or more antibiotics
Use of broad-spectrum antibiotics in previous 10 days
Surgery
Surgery on ICU admission
Gastro-abdominal surgery
Abdominal drainage
Elective surgery
Cardiopulmonary bypass time >120 minutes Hickman catheter
Foreign devices
Central venous catheter
Triple lumen catheter in patients who have undergone surgery
Bladder catheter
Renal failure and dialysis
Prior hemodialysis
Hemofiltration procedures
Increased serum creatinine[b]
New-onset hemodialysis within 3 days of admission to ICU
Acute renal failure
Underlying disease/baseline characteristics
Total parenteral nutrition
Diabetes mellitus Apache II (per point)
Signs of severe sepsis
Diarrhea at any time
Mechanical ventilation ≥10 days
Hospital-acquired bacterial infection
Bacterial peritonitis by ICU day 11
GI disease
ICU length of stay
Transferred from other hospital
Use of corticosteroids
Profound neutropenia (ANC <100/mm^3 [0.100 ×10^9/L])

[a]CI = the ratio of number of nonblood distinct body sites (dbs) heavily colonized with identical strains to the total number of dbs; CCI = the product of the CI and the ratio of the number of dbs showing heavy growth (≥10^5 CFU/mL [10^8 CFU/L]) to the total of dbs growing *Candida* spp.

[b]Serum creatinine >1.2 mg/dL (106 µmol/L) in females, >1.6 mg/dL (141 µmol/L) in males.

Data from Reference 26.

Clinical Presentation of Hematogenous Candidiasis

Dissemination of *C. albicans* can result in infection in single or multiple organs, particularly the kidney, brain, myocardium, skin, eye, liver, spleen, bone, and joints.[48]

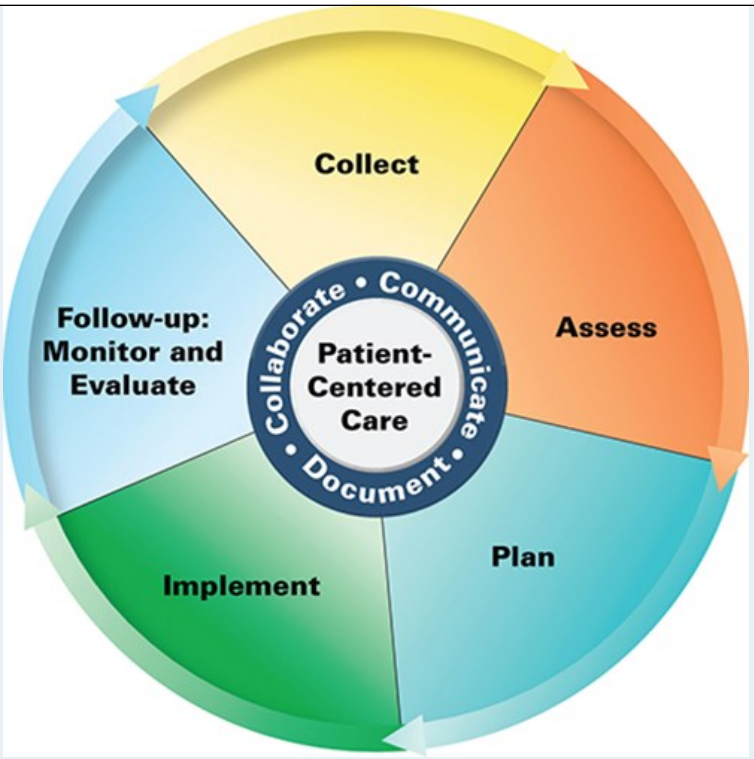
Laboratory Tests

The interpretation of positive surveillance cultures of the skin, mouth, sputum, feces, or urine is hampered by their occurrence as commensal pathogens and in distinguishing colonization from invasive disease. A rapid presumptive identification of *C. albicans* can be made by incubation of *Candida* in serum; formation of a germ tube (the beginning of hyphae, which arise as perpendicular extensions from the yeast cell, with no constriction at their point of origin) within 1 to 2 hours offers a positive identification of *C. albicans*. Unfortunately, *C. dubliniensis* also can produce a germ tube, and a negative germ tube test does not rule out the possibility of *C. albicans*, but further biochemical tests must be performed to differentiate between other non-*albicans* species.

Several rapid diagnostic methods are available at many hospitals, which can result in much more rapid identification of pathogens, including specific species, than with the use of traditional microbiological techniques. Matrix-assisted laser desorption/ionization time-of-flight intact cell mass spectrometry (MALDI-TOF-ICMS), a multiplex polymerase chain reaction (PCR) panel that includes five *Candida* species, and T2 Magnetic Resonance Assays provide rapid detection and identification of pathogenic *Candida* species.[48,51] Also available is the PNA fluorescence in situ hybridization (FISH) method, which uses fluorescein-labeled PNA probes that target *C. albicans* 26S rRNA for the identification of *C. albicans*, and a multiplex polymerase chain reaction (PCR) panel. The test has excellent sensitivity (99%-100%) and specificity (100%) in the direct identification of *C. albicans* from blood cultures.[52]

PATIENT CARE PROCESS

Patient Care Process for Candidemia



Collect

- Patient characteristics (eg, age, sex, pregnant)
- Patient medical history (personal and family)
- Social history (eg, intravenous drug use)
- Current medications including non-prescription aspirin/NSAID use, herbal products, dietary supplements, and prior antifungal therapy
- Prior antifungal therapy (if applicable)
- Objective data
  - Blood pressure (BP), heart rate (HR), respiratory rate (RR), height, weight, O_2-saturation
  - Laboratory findings including white blood cells (WBC) with differential, hemoglobin (Hgb), platelets, serum creatinine (SCr), liver function tests (LFTs), blood cultures and susceptibility data
  - Objective confirmation of candidemia (+ blood cultures)

Assess

- Hemodynamic stability (eg, systolic BP 110 bpm, O_2-sat <90% [0.90], RR)
- Presence of
  - Ability/willingness to pay for antifungal agents
  - Ability/willingness to obtain laboratory monitoring tests
- Emotional status (eg, presence of anxiety, depression)

Plan*

- Empiric drug therapy regimen including specific antifungal agent(s), dose, route, frequency, and duration (see Table 144-9); and plan for step-down antifungal therapy, if appropriate, based on blood culture results (*Candida* species) of susceptibility testing, patient-specific factors (eg, LFTs, SCr, prior antifungal therapy, severity of illness)
- Monitoring parameters including efficacy including signs and symptoms of infection, temperature, BP, HR, WBC, daily blood cultures until negative cultures are obtained, transthoracic or transesophageal echocardiogram (TTE or TEE), ophthalmological examination, and safety (eg, LFTs, SCr, rash)
- Patient education (eg, purpose of treatment, drug-specific information)
- Referrals to other providers when appropriate (eg, ophthalmology)

Implement*

- Provide patient education regarding all elements of treatment plan
- Schedule follow-up (eg, labs, susceptibility data)

Follow-up: Monitor and Evaluate

- Resolution of symptoms (eg, shortness of breath, chest pain, limb swelling, redness, pain)
- Presence of adverse effects (three- to fivefold increase in LFTs, increased SCr, presence of rash)
- Patient adherence to treatment plan using multiple sources of information
- Reevaluate antifungal agent(s) to assess need for specific therapy (pathogen-directed, based on results of blood cultures) including step-down antifungal therapy, once final blood cultures and the results of susceptibility testing are available
- Reevaluate duration of therapy as blood culture and other laboratory data become available after the start of therapy (see text)

****Collaborate with patient, caregivers, and other healthcare professionals.***

Treatment

The list of risk factors for invasive candidiasis in critically ill patients is extensive, and trying to decipher which patients may benefit from antifungal prophylaxis or empirical therapy based on risk factors in an ICU is exceedingly difficult. In addition, the number of risk factors present in ICU patients changes over time, and the majority of ICU patients will have more than one risk factor. Clinically useful, practical predictive algorithms and "scoring systems" to identify high-risk patients early during their ICU admission have not proved successful thus far. To maximize its clinical utility as a decision-making tool, the ideal algorithm would identify high-risk populations (ones with a rate of invasive candidiasis of 10%-15%), providing clinicians with a means of administering prophylaxis to a minimal number of patients, while preventing the maximal number of invasive candidiasis cases.[26]

Although it is common practice in today's standard of care to place indwelling catheters in patients for the administration of medications and parenteral nutrition (TPN), catheter-related infections are a common complication. These foreign bodies (especially triple lumen catheters) double as entry ports for normal skin flora or other nosocomial pathogens, and they provide a readily available site for the binding of pathogens via microbiotic biofilms. Their subsequent role as a source of BSIs is facilitated by frequent use, TPN, and the potential for contamination of catheters by medical staff who are colonized with *Candida* species. Most consensus recommendations urge removal of all existing tunneled CVCs and implantable devices, particularly in patients with fungemia caused by *C. parapsilosis*, which is frequently associated with catheters, as it has been associated with reduced mortality in adults, and a shorter duration of candidemia.[7] Arguments against the removal of all catheters in patients with candidemia include the prominent role of the gut as a source for disseminated candidiasis, the significant cost and potential for complications, and the problems that can be encountered in patients with difficult vascular access. However, in an individual patient it is often difficult to determine the relative contribution of gut

versus catheter as the primary source of fungemia. The evidence for this recommendation is weakest in cancer patients with severe neutropenia and mucositis (eg, acute leukemia, stem cell transplant), in whom candidemia is almost always primarily of gut origin, and removal of CVCs is least likely to have an impact on mortality.[7]

Hematogenous Candidiasis

There is a high rate of mortality in non-neutropenic patients with fungal blood cultures. Delays in the initiation of antifungal therapy may significantly increase mortality.[53,54] Treatment of candidiasis should be guided by knowledge of the infecting species, the clinical status of the patient, and when available, the antifungal susceptibility of the infecting isolate. Therapy should be continued for 2 weeks after documented clearance of blood cultures, with resolution of all signs and symptoms of infection. All patients should undergo dilated fundoscopic examination within the first week of therapy. Susceptibility testing of the infecting isolate is a useful adjunct to species identification during selection of a therapeutic approach, since it can be used to identify isolates that are unlikely to respond to fluconazole or amphotericin B.[7] However, this is not currently available at many institutions.

Non-immunocompromised Patient

Prophylaxis

In ICUs, the use of fluconazole for prophylaxis or empirical therapy is common.[55] However, studies that demonstrated benefit in the prevention of invasive candidal BSIs did so either by using highly selective criteria or by studying patients in an unusually high-risk ICU setting, and the role of antifungal prophylaxis in the surgical ICU remains extremely controversial. For a study to demonstrate efficacy in clinical trials, the baseline rate of invasive candidiasis must be greater than 10%, and that prophylaxis must result in greater than fourfold reduction of disease. Although ICU-specific, greater than 10% rate of invasive candidiasis is generally found only in the setting of high-risk transplant patients (eg, patients undergoing liver transplantation), or in patients with a constellation of risk factors.[26] However, a significant benefit to prophylaxis in such high-risk, non-transplant patients has not been established.[56,57] Prophylactic antifungals may be indicated in patients with recurrent intestinal perforations and/or anastomotic leaks as these patients may be at high risk for invasive candidiasis and the use of empiric fluconazole may significantly decrease the incidence of infection.[58]

"Empirical" Therapy (Also Known as Preemptive Therapy)

The term "preemptive" antifungal therapy is often used to describe early antifungal therapy given to high-risk patients with persistent signs and symptoms and clinical, laboratory, or radiologic surrogate markers of infection but without mycological evidence of infection, or those heavily colonized with *Candida*.[26] Few data are available for assessing the role of antifungals as empirical therapy for *suspected* candidiasis in patients who do not yet exhibit a positive culture. The empiric use of fluconazole in one study, and micafungin in another, did not significantly improve outcomes; thus, preemptive/empiric use is not recommended at this time.[30,59]

Initial Antifungal Therapy in Non-Neutropenic Patients with Documented Candidemia, in Whom the Species Is Not Yet Identified and Results of Antifungal Susceptibility Testing Are Not Known

Azoles (fluconazole or voriconazole) and deoxycholate amphotericin B are similarly effective for the therapy of documented candidemia in non-neutropenic patients; however, fewer adverse effects are observed with azole therapy.[60,61] Echinocandins are at least as effective as amphotericin B, fluconazole, or isavuconazole in (primarily non-neutropenic) adult patients with candidemia.[62-66] Both fluconazole and the echinocandins are associated with fewer drug-related adverse events than amphotericin B preparations. Among the lipid-associated formulations of amphotericin B, liposomal amphotericin B (AmBisome) and ABLC (Abelcet) have been approved for use in proven cases of candidiasis. The lipid-associated formulations are less toxic but as effective as amphotericin B deoxycholate. Although the use of combination therapy (high-dose fluconazole plus amphotericin B) was superior to treatment with fluconazole alone, it was associated with a higher rate of nephrotoxicity, and the routine use of combination therapy in this patient population is not yet recommended.[67]

For empiric therapy in non-neutropenic adults, IDSA guidelines (Table 144-9) recommend use of an echinocandin or fluconazole (intravenous or oral) as initial therapy. Echinocandins are recommended for patients with moderately severe to severe illness, and patients with recent azole exposure. Patients may be transitioned to fluconazole (intravenous or oral) if their *Candida* isolates are known/likely to be susceptible to fluconazole (eg, *C.*

albicans, *C. parapsilosis*) in patients who are clinically stable, and in whom repeat negative blood cultures have been obtained. Fluconazole may be used initially in patients who are less critically ill, with no recent azole exposure, who are not at high risk for *C. glabrata* or with central nervous system or endocardial disease.[7]

TABLE 144-9

Antifungal Therapy of Invasive Candidiasis

Type of Disease and Common Clinical Manifestations	Therapy/Comments
Prophylaxis of Candidemia	
Non-neutropenic patients	Not recommended except for severely ill/high-risk patients in whom fluconazole IV/oral 400 mg daily should be used (see the text)
Neutropenic patients[a]	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. The optimal duration of therapy is unclear but at a minimum should include the period at risk for neutropenia.
Solid-organ transplantation, liver transplantation	*Patients with key risk factors*[b]: Fluconazole 400 mg orally daily is preferred
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 (see the text)
Suspected candidiasis in febrile neutropenic patients	A lipid formulation of amphotericin B, caspofungin, micafungin, voriconazole, isavuconazole, posaconazole, or itraconazole for duration of neutropenia
Initial Antifungal Therapy of Documented Candidemia and Acute Hematogenously Disseminated Candidiasis, Unknown Species	
Patients who are less critically ill and who have had no recent azole exposure	*Remove existing central venous catheters when feasible plus fluconazole IV (loading dose of 800 mg [12 mg/kg], then 400 mg [6 mg/kg] daily) or an echinocandin.* Treatment duration: 2 weeks after the last positive blood culture and resolution of signs and symptoms of infection
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 Transition from an echinocandin to fluconazole IV/oral is recommended for patients who are clinically stable and have isolates (eg, *C. albicans*) likely to be susceptible to fluconazole
Antifungal Therapy of Specific Pathogens	
C. albicans, C. tropicalis, and *C. parapsilosis*	Fluconazole IV/oral 6 mg/kg/day *or* an echinocandin; transition to fluconazole is recommended in patients who are clinically stable and whose isolates are likely to be susceptible to fluconazole (eg, *C. albicans*); voriconazole IV (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*: Amphotericin B lipid complex IV 3-5 mg/kg/day Liposomal amphotericin B IV 3-5 mg/kg/day
C. krusei	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)
Urinary candidiasis	*Asymptomatic disease:* Generally no therapy is required *Symptomatic or high-risk patients*[d]: 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 re-transplantation, re-operation, renal failure requiring hemodialysis, transfusion of ≥40 units of cellular blood products including platelets, packed red blood cells, and auto transfusion; choledochojejunostomy, and Candida colonization in the perioperative period.[68]

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

PO, orally.

Data from Reference 7.

Antifungal Therapy for Specific *Candida* Species

Since *C. glabrata* often demonstrate reduced susceptibility to fluconazole, treatment with echinocandins is recommended as initial therapy (pending the results of susceptibility testing), although there are successful treatment outcomes reported in response to fluconazole therapy of 6 to 12 mg/kg/day, and may be suitable in less critically ill patients.[7,69,70]

Regardless of the species of *Candida*, in the absence of metastatic complications of disease, antifungal therapy should be continued for 2 weeks after the last positive blood culture, and until there is resolution of signs and symptoms of infection. It is important to note when counting days of therapy that the days of treatment "begin" on the first day of documented clearance of *Candida* species from bloodstream, with the use of an effective antifungal agent to which the species is susceptible. As such, blood cultures should be repeated until negative. Existing central venous catheters should be removed when feasible, and all patients should undergo dilated retinal examination (preferably by an ophthalmologist) to rule out *Candida* endopthalmitis.[7]

In non-neutropenic adults, once the species of *Candida* has been identified, echinocandin therapy is recommended for the management of systemic *C. krusei* infections. *C. tropicalis* and *C. parapsilosis* may be treated with fluconazole at 6 mg/kg/day. Candidemia due to *C. parapsilosis* has increased in frequency among pediatric populations and appears to be associated with a lower mortality rate than other species of *Candida*. Since many, but not all isolates of *C. lusitaniae* are resistant to amphotericin B, fluconazole at 6 mg/kg/day is the preferred agent for treatment of this species. In patients with *C. parapsilosis* candidemia,[7] fluconazole is recommended, since MICs of echinocandins tend to be higher for *C. parapsilosis*. However, overall

treatment success of candidemia or invasive candidiasis with echinocandins versus other agents was similar, and there was no difference in 30-day mortality between patients treated with fluconazole or an echinocandin.[71] The in vitro susceptibility of *C. auris* to antifungal agents is variable. However, while most isolates are susceptible to echinocandins, most are resistant to fluconazole, and ~40% of isolates are resistant to more than 2 classes of antifungal agents. An echinocandin is recommended as first-line therapy, with the addition of amphotericin B recommended in case of persistent fungemia or lack of clinical response.[50]

Expert opinion is divided regarding the optimal therapy of infections caused by *C. glabrata*. Guidelines recommend the use of an echinocandin until susceptibility is proven.[7] The severity of illness and choice of antifungal predict response in patients with *C. glabrata* fungemia, and the choice of antifungal (fluconazole or an echinocandin) does not influence mortality.[66,69] When fluconazole is dosed appropriately (Table 144-9), *C. glabrata* fluconazole susceptibility breakpoints are predictive of clinical and microbiological response.[70] Echinocandin therapy is independently associated with treatment success, but not survival, in invasive candidiasis due to *C. glabrata*.[66,69]

Immunocompromised Patients

In immunocompromised patients, the optimal agent, dose, and duration of therapy are unclear, and patients must be monitored carefully with serial blood cultures and careful physical examinations, particularly of the retina. Treatment guidelines in neutropenic patients generally approximate those from non-neutropenic hosts. Patients who experience prolonged neutropenia and persistent candidemia may benefit from administration of a recombinant cytokine (granulocyte colony-stimulating factor) that accelerates recovery from neutropenia.[7]

Prophylaxis

Recognition of the role of the GI tract in invasive *Candida* infections has led to efforts to decrease infections by prophylactic administration of topical or systemically absorbed antifungal agents in immunocompromised patients. The use of systemically absorbable agents such as azole antifungal agents appears to decrease the risk of IFIs.[7,72]

Several antifungal agents, including oral fluconazole (400 mg/day), posaconazole (200 mg three times daily), IV micafungin or caspofungin (50 mg daily) administered from the start of the conditioning regimen until day 75, can reduce the frequency of invasive *Candida* infections and decrease mortality in patients undergoing allogeneic bone marrow transplantation.[7,72]

Similarly, in less risk-selected patients with hematologic malignancies who are undergoing remission-induction chemotherapy, fluconazole, posaconazole, or caspofungin, during induction chemotherapy for the duration of neutropenia, are effective in preventing systemic infection and death caused by *Candida* species.[7,72]

For solid-organ transplant recipients, fluconazole or an echinocandin is recommended as postoperative antifungal prophylaxis for liver, pancreas, and small bowel transplant recipients at high risk of candidiasis.[7,68]

Widespread use of prophylactic fluconazole in all ICU patients is not warranted and may lead to an increase in resistance and adverse events. If utilized, prophylactic fluconazole should target high-risk patients with a presumed risk of invasive candidiasis of 10% to 15%.[7,26]

Empirical Therapy for Febrile Neutropenic Patients

In patients who have not been receiving antifungal prophylaxis, *Candida* spp. are the most likely cause of IFI. In patients receiving fluconazole prophylaxis, fluconazole-resistant *Candida* spp. (eg, *C. glabrata* and *C. krusei*) and invasive mold infections, particularly *Aspergillus* spp., are the most likely causes. A lipid formulation of amphotericin B, caspofungin, micafungin, voriconazole, isavuconazole, posaconazole, or itraconazole are recommended as suitable options for empiric antifungal therapy in neutropenic patients.[72] Guidelines recommend adding empiric antifungal therapy after 4 or more days of fever despite empiric antibiotic therapy in patients who are not receiving prophylaxis with mold-active agents and who are at high risk for mold infections (duration of neutropenia >10 days, allogeneic HSCT recipients, and high-dose corticosteroid treatment).[72]

For persistently febrile patients who have been receiving anti-mold prophylaxis, a different class of antifungal agent with activity against molds should be used for empiric therapy. The choice of the initial antifungal agent may vary based on an institution's experience (ie, epidemiology and

susceptibility patterns) and patient risks for specific mold infections (eg, *Aspergillus* vs infections caused by the Mucorales). In patients with pulmonary nodules or nodular pulmonary infiltrates, invasive mold infection should be strongly suspected and treated. As fluconazole lacks activity against filamentous fungi, its use in patients at high risk for these pathogens should be avoided. In addition, clinicians need to consider that echinocandins are not active against *Cryptococcus* spp., *Trichosporon* spp., and filamentous molds other than *Aspergillus* spp. (eg, *Fusarium* spp.), nor are they active against the endemic fungi (*Histoplasma, Blastomyces,* and *Coccidioides* spp.).[73]

CANDIDURIA

Within the urinary tract, most common lesions are either *Candida* cystitis or hematogenously disseminated renal abscesses. *Candida* cystitis often follows catheterization or therapy with broad-spectrum antimicrobial agents. The diagnosis of *Candida* cystitis can be problematic because of the frequent presence of *Candida* pseudohyphae and yeast cells in urine specimens secondary to urethral colonization. The usefulness of urine colony counts or antibody coating techniques is questionable. The recovery of 10,000 organisms or visualization of both yeast and pseudohyphae from fresh midstream urine or from bladder urine obtained by single catheterization (not indwelling) is suggestive of genitourinary candidiasis. In most patients, the infection is asymptomatic and clears spontaneously without specific antifungal therapy.[7]

Initial therapy of candidal cystitis should focus on removal of urinary catheters whenever possible. Changing the catheter will eliminate candiduria in only 20% of patients, whereas discontinuation will eradicate *Candida* in 40% of patients. Asymptomatic candiduria rarely requires therapy. Therapy should be used in neutropenic patients, very low-birth-weight infants (<1500 g), and those who will undergo urologic manipulation, because of the risk of dissemination.[7]

Oral fluconazole 200 mg/day for 14 days hastens the time to a negative urine culture as compared with placebo treatment, but 2 weeks after the end of therapy, the frequency of a negative urine culture remains the same with both treatments.[74] Treatment should include removal of catheters and stents whenever possible plus 7 to 14 days of therapy. Bladder irrigation with amphotericin B (50 mg in 500 mL sterile water instilled twice daily into the bladder via a three-way catheter) is only transiently effective. Minimal quantities (less than 3%) of amphotericin B are absorbed systemically from the bladder.[7]

ASPERGILLOSIS

Saprophytic molds belonging to the *Aspergillus* spp. can be found around the world, of which, *Aspergillus fumigatus* is the most commonly observed pathogen, followed by *Aspergillus flavus.*

Invasive aspergillosis (IA) is the second most common IFI, with increasing incidence over the last 20 years along with the advances in the treatment of hematological malignancies. The infection most commonly affects immunocompromised patients and patients with acute myeloid leukemia (AML) and those who undergo allogeneic HSCT who develop GvHD are at highest risk. In the highest risk group, IA rates can reach 25%. The frequency of IA and infections caused by other molds have increased over the past 2 decades. Despite heightened awareness of the profiles of patients at risk for *Aspergillus* infections, and despite the advent of liposomal formulations of amphotericin B, IA continues to be associated with extremely high mortality rates. The crude mortality approaches 75% in patients with AIDS and bone marrow transplant patients. Major target sites for primary invasive disease include the lungs and sinuses; frequently, secondary infections involve the central nervous system. The appropriate duration of treatment is based on the extent of the infection, response to therapy, and host factors.[75]

Epidemiology

Aspergillus is a ubiquitous mold that grows well on a variety of substrates, including soil, water, decaying vegetation, moldy hay or straw, and organic debris. Although more than 300 species of *Aspergillus* have been characterized, three species are most commonly pathogenic: *A. fumigatus*, *A. flavus*, and *A. niger*. The varying degrees of pathogenicity of each species depend on their relative geographic prevalence, conidial size and shape, thermotolerance, and production of mycotoxins. For example, transport of *A. fumigatus* conidia into the lungs is facilitated by their smaller diameter in comparison with *A. flavus* and *A. niger.*

The term *aspergillosis* may be broadly defined as a spectrum of diseases attributed to allergy, colonization, or tissue invasion caused by members of the fungal genus *Aspergillus.* A single satisfactory classification system for these disease entities is difficult because different populations of patients

can develop the same type of infection. For example, osteomyelitis can result from local trauma or hematogenous dissemination in an immunocompromised host. Colonization in normal hosts can lead to allergic diseases ranging from asthma to allergic bronchopulmonary aspergillosis (BPA) or, rarely, invasive disease.[75]

Pathophysiology

Aspergillosis is acquired by inhalation of airborne conidia that are small enough (2.5-3 µm) to reach alveoli or the paranasal sinuses. Each conidiophore releases 10^4 conidia that remain suspended for long periods and are viable for months in dry locations. Although some authors advocate monitoring of hospital air for *Aspergillus* conidia, guidelines for interpreting results are not available. The use of high-efficiency particulate air (HEPA) filters in operating rooms and laminar flow rooms and removal of immunocompromised patients from hospital renovation sites can be helpful in preventing infection in this population.

Superficial or locally invasive infections of the ear, skin, or appendages often can be managed with topical antifungal therapy. Skin infections in patients with burn wounds, although uncommon, can progress to deep-tissue invasion despite the use of topical or parenteral antifungal agents. Risk factors for deep infection include extensive thermal injuries, malnutrition, cirrhosis, and previous infection with *Pseudomonas aeruginosa*.

Allergic manifestations of *Aspergillus* range in severity from mild asthma to allergic BPA. BPA, which is almost always caused by *A. fumigatus*, is characterized by severe asthma with wheezing, fever, malaise, weight loss, chest pain, and a cough productive of blood-streaked sputum. Following recurrent episodes of severe asthma, the disease usually progresses to fibrosis and bronchiectasis with granuloma formation. When *Aspergillus* conidia become trapped in the viscous mucus of asthmatic patients, BPA develops. The fungus grows, releasing toxins and antigens. The resulting host sensitization results in a variety of immune reactions. Early in the course of disease, an immunoglobulin E (IgE)-mediated (type I) immune reaction results in bronchospasm, eosinophilia, and immediate skin reactivity. The ensuing fibrosis and pulmonary infiltrates appear to be mediated by circulating or precipitating antibody complexes of IgG antibody, followed by granuloma formation and mononuclear infiltration because of a type IV delayed hypersensitivity reaction. Therapy is aimed at minimizing the quantity of antigenic material released in the tracheobronchial tree. Management of acute asthma attacks minimizes trapping of *Aspergillus* by bronchial secretions, and administration of corticosteroids clears lung infiltrates.[75] Antifungal therapy generally is not indicated in the management of allergic manifestations of aspergillosis, although some patients have demonstrated a decrease in their corticosteroid dose following therapy with itraconazole.[12]

Aspergilloma

Pulmonary aspergillomas are fungus balls arising in preexisting cavities because of tuberculosis, histoplasmosis, lung tumors, or radiation fibrosis, although occasionally no previous pulmonary disease is present. The diagnosis of aspergilloma generally is made on the basis of chest radiographs, on which aspergillomas appear as a solid rounded mass, sometimes mobile, of water density within a spherical or ovoid cavity and separated from the wall of the cavity by an airspace of variable size and shape. Patients generally experience chest pain, dyspnea, and sputum production. Hemoptysis is observed in 50% to 80% of patients, probably because of ulceration of the epithelial lining of the cavity with formation of granulation tissue, and hemoptysis is the cause of death in up to 26% of patients with aspergilloma. A poor prognosis is associated with increasing size or number of aspergillomas, immunosuppression (including corticosteroids), increasing *Aspergillus*-specific titers, underlying sarcoidosis, and HIV infection. Although *Aspergillus* can be cultured in only 50% to 60% of patients, precipitating antibodies are positive in virtually 100% of patients.

Invasive disease occurs rarely, and therapy therefore is controversial. There are no controlled clinical trials with which to guide therapy, and recommendations for treatment have been generated from uncontrolled trials and case reports. Concern regarding the risk of severe hemorrhage has led some clinicians to use aggressive surgical excision of aspergillomas or pulmonary resection in patients with hemoptysis. Complications, including bronchopulmonary fistulas, hemorrhage, empyema, and persistent airspace problems, have led to the recommendation that surgical intervention be reserved for patients with severe (greater than 500 mL per 24 hours) hemoptysis, however. Bronchial artery embolization has been used to occlude the vessel that supplies the bleeding site in patients experiencing hemoptysis. Unfortunately, bronchial artery embolization generally is unsuccessful or only temporarily effective. Collateral circulation eventually develops, supplying blood flow to the affected area, and hemoptysis often recurs; consequently, reembolization is often unsuccessful. Bronchial artery embolization should be used as a temporizing procedure in a patient with life-threatening disease who might respond to more definitive therapy if hemoptysis is stabilized. Mild-to-moderate hemoptysis should be managed conservatively. Patients with spillage during surgery are recommended to receive a minimum of 4 weeks of therapy post-operatively. Hemoptysis generally ceases when the aspergilloma is eradicated.[12,75]

Invasive Aspergillosis

IA remains a disease of very high mortality: for example, in HSCT recipients with a diagnosis of invasive aspergillosis, the 3-month post HSCT mortality rate is 50% for autologous transplant recipients but approaches 75% for allogeneic HSCT recipients.[75]

Although exposure to *Aspergillus* conidia is nearly universal, impaired host defenses are required for the development of invasive disease. Phagocytes (neutrophils, monocytes, and macrophages) rather than antibodies or lymphocytes constitute the primary host defense system against invasive disease with aspergillosis. Macrophages prevent germination of conidia and also eradicate conidia, providing the first line of defense against invasive disease. Administration of corticosteroids appears to impair the killing of conidia by macrophages and to impair mobilization of neutrophils. Neutrophils halt hyphal growth and dissemination and kill mycelia, constituting a second line of defense. Prolonged neutropenia appears to be the most important predisposing factor to the development of IA, accounting for the high frequency of disease in patients with acute leukemia.[75]

Invasive disease with *Aspergillus* can arise de novo or from any of the allergic or colonizing forms of aspergillosis. Predisposing factors to the development of IA include glucocorticoid therapy, particularly following chronic administration or with higher dosages (30-200 mg/day of prednisone), cytotoxic agents, and recent or concurrent therapy with broad-spectrum antimicrobial agents. Patients with chronic hepatitis, alcoholism, diabetes mellitus, chronic granulomatous disease, leukopenia (less than 1,000 cells/mm^3 [1×10^9/L]), leukemia (particularly acute lymphocytic or myelogenous leukemia), lymphoma, and acute rejection of an organ transplant are also at a higher risk of invasive disease. Although rare, IA has been reported in apparently normal hosts.[75] For example, hospitalized patients with severe influenza, or more recently, SARS-CoV-2 infection, may develop superinfection due to *Aspergillus*.[76] Aspergillosis is an uncommon fungal infection in patients with AIDS, usually associated with other risk factors for infection, such as corticosteroid use and neutropenia.[12]

Clinical Presentation

The lung is the most common site of invasive disease. In the immunocompromised host, aspergillosis is characterized by vascular invasion leading to thrombosis, infarction, necrosis of tissue, and dissemination to other tissues and organs in the body. If bone marrow function returns, cavitation of the pulmonary lesion generally occurs, and the spread of infection can be halted. The progressive nature of the disease and its refractoriness to therapy are, in part, caused by the organism's rapid growth and its tendency to invade blood vessels.[75]

Clinical Presentation: Aspergillosis

Signs and Symptoms

Patients with invasive pulmonary aspergillosis (IPA) generally have blunted or non-specific 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. The CNS, liver, spleen, heart, GI tract, pericardium, and other body sites are involved in a substantial minority of cases. In neutropenic patients with *Aspergillus* pneumonia, hyphae invade the walls of bronchi and surrounding parenchyma, resulting in an acute necrotizing, pyogenic pneumonitis. As a result, patients often present with classic signs and symptoms of acute pulmonary embolus: pleuritic chest pain, fever, hemoptysis, and friction rubs.[75]

Diagnosis

The diagnosis of aspergillosis is complicated by the presence of *Aspergillus* as a normal commensal in the human GI tract and respiratory secretions, and establishment of a definitive diagnosis of disease is difficult. The likelihood of IFIs is assessed on a scale of probability (possible, probable, proven) based upon host factors, clinical and microbiological criteria.[29] Demonstration of *Aspergillus* by repeated culture and microscopic examination of tissue provides the most firm diagnosis. A definitive diagnosis of IPA can be made by obtaining a biopsy of lung tissue; however, thrombocytopenia often limits clinicians' ability to perform this procedure. The appearance of *Aspergillus* in tissues varies with increasing host resistance from the normal vegetative hyphae found with necrotic tissue and exudate in the alveoli of immunocompromised hosts to the compact, tangled filaments (*granules*) observed in fungal balls. Identification of *Aspergillus* generally is based on the appearance of 2- to 4-µm-wide septate hyphae that are dichotomously branched at 45° angles. Sporulation is observed rarely in tissue. Although growth on Sabouraud dextrose or brain-heart infusion agar can be used for primary culture, bronchoscopy or bronchoalveolar lavage cultures are positive in only 40% of histopathologically

identified specimens. Blood, CSF, and bone marrow cultures are rarely positive for *Aspergillus*.

The diagnosis is determined with the use of high resolution CT, in which IPA will manifest early on as “halo sign” (an area of low attenuation surrounding a nodular lung lesion, caused by edema or bleeding surrounding an ischemic area). In late IA nodular lesions, diffuse pulmonary infiltrates, consolidation, or ground glass opacities can be observed, and CT scans may demonstrate the crescent sign (an air crescent near the periphery of a lung nodule caused by contraction of infarcted tissue), while chest radiographs can demonstrate wedge-shaped, pleural-based infiltrates or cavities. These signs are not specific to IPA, however, as bacteria and other fungal infections may produce similar findings. CT abnormalities are best documented in neutropenic marrow transplant recipients and commonly precede plain chest radiograph abnormalities.[75]

Laboratory Tests

The diagnosis of aspergillosis, and other invasive mold infections, remains difficult. New laboratory methods that allow for early differentiation of IFIs due to *Aspergillus* species versus zygomycetes and other molds would be helpful in allowing clinicians in the earlier initiation of appropriate antifungal therapy. Although PCR-based testing is being performed in some centers, and appears promising, no FDA-approved method is commercially available.

The galactomannan test is an enzyme-linked immunosorbent assay (ELISA) (Platelia *Aspergillus* EIA test; Bio-Rad Laboratories) that detects galactomannan, an antigen released from *Aspergillus* hyphae upon invasion of host tissue. The clinical utility of this assay has been assessed in the clinical setting by sampling serum, BAL fluid, cerebrospinal fluid (CSF), and pleural fluid; however, the currently approved test is performed on serum. Additionally, while FDA-approved for use in the diagnosis of IA in HSCT recipients and in patients with leukemia; its usefulness in solid-organ transplant and pediatric populations needs to be established. In most patients, circulating antigen can be detected at a mean of 8 days before diagnosis by other means. The test has a sensitivity ranging from 40% to 90% and a specificity of approximately 90%; however, the sensitivity of the assay is decreased in patients receiving mold-active drugs on the day of sampling. False positives can occur, particularly in patients with other IFIs (including histoplasmosis and blastomycosis), receiving antibiotics such as amoxicillin–clavulanate, and in neonates. False negatives can occur during the concomitant use of antifungals, presumably because the level of galactomannan is related to the fungal burden. In addition, it is important to note that the utility of galactomannan testing in the setting of prophylaxis has not been defined.[12,75]

1,3-β-D-Glucan is a component of fungal cell walls that can be detected colorimetrically in clinical samples, including blood and bronchoalveolar lavage specimens, using a chromogenic variant of the limulus amoebocyte lysate assay. However, the current FDA-approved test (Fungitell; Associates of Cape Cod) is performed only on serum, and is nonspecific for *Aspergillus*. The 1,3-β-D-glucan test can be used to detect most fungi, with the exception of *Mucorales*. False positives are problematic with the test, with many processes and products associated with elevated levels, including hemodialysis with cellulose membranes, intravenous immune globulin or serum albumin administration, gastrointestinal surgery, and in other cases for unclear reasons.[77]

Treatment

Invasive Aspergillosis

Therapy for IA is far from optimal at this time in part because of the difficulties in establishing a diagnosis and in part because of a lack of truly effective antifungal agents. Administration of amphotericin B appears to decrease mortality from more than 90% to approximately 45%. These data, however, are difficult to interpret because many patients were diagnosed postmortem, or amphotericin B therapy was not administered until the patient had very advanced disease. Although early diagnosis and administration of antifungal therapy can result in higher response rates, correction of underlying immune deficits (in particular, return of neutrophil counts) is of paramount importance in eradication of infection.[75]

Until the diagnosis of aspergillosis can be determined more rapidly and definitively, empirical therapy must be instituted when invasive disease is suspected. In patients at highest risk for invasive disease (acute leukemia and bone marrow transplant recipients), the most important predisposing factors include prolonged severe neutropenia (less than 100 cell/μL [0.1×10^9/L] for more than 1 week), graft rejection, chronic administration of corticosteroids, and tissue damage from preexisting infection.[75]

Prophylaxis

As noted above in the discussion of prophylaxis for *Candida* infections in immunocompromised hosts, prophylaxis with azoles or echinocandins can

reduce the incidence of aspergillosis in select high-risk populations. The incidence of IFIs following solid organ transplantation varies with the organ being transplanted and the epidemiology at individual centers. *Candida* and *Aspergillus* species are the leading causative agents, with the median time to onset following transplantation depending on the type of transplant. Several organizations have developed guidelines for the prevention of IFIs in patients with malignancies and in those undergoing solid organ or hematopoietic stem cell transplantation.[68,72,78]

Specific Therapy

The outcome of invasive aspergillosis (IA) continues to be associated with significant attributable mortality, especially in patients with hematological malignancies and in HSCT recipients. Older azole antifungal agents (miconazole, ketoconazole, and fluconazole) possess poor in vitro activity against *Aspergillus* species; however, newer triazoles (itraconazole, voriconazole, posaconazole, and isavuconazole) demonstrate improved activity both in vitro and in animal models of infection. Antifungal agents with in vitro activity against *Aspergillus* species include amphotericin B, the echinocandins, and the azoles itraconazole, voriconazole, posaconazole, and isavuconazole. Historically, high dosages (1-1.5 mg/kg/day) of deoxycholate amphotericin B were utilized for the treatment of suspected or proven invasive aspergillosis. Lipid formulations of amphotericin B are overall less nephrotoxic and at least as effective as amphotericin B, and they can be effective when amphotericin B is not.[79] Initial dosing of 10 mg/kg/day and 3 mg/kg/day of liposomal amphotericin B were equally effective, but there was decreased nephrotoxicity with the use of 3 mg/kg/day.[80]

Voriconazole has emerged as the drug of choice of most clinicians for primary therapy of most patients with IA, based on a pivotal study in which a randomized comparison of voriconazole and deoxycholate amphotericin B followed by other licensed antifungal agents for primary therapy for invasive aspergillosis demonstrated superior antifungal efficacy and improved survival at week 12 in the voriconazole arm.[81] Subsequently, isavuconazole has been approved for the primary treatment of aspergillosis, based upon the results of a double-blind, randomized, multinational trial in subjects with proven or probable invasive fungal disease caused by *Aspergillus* spp. or other filamentous fungi. Isavuconazole was well tolerated, with fewer drug-related adverse effects than voriconazole.[82] Posaconazole was shown to be non-inferior to voriconazole for the treatment of aspergillosis in a prospective, double-blind randomized trial.[83] In patients who are unable to tolerate or are not responding to azole therapy, or who are infected with azole-resistant isolates, amphotericin B can be used, with response measured by defervescence and radiographic clearing. To treat microfoci, therapy should be continued after resolution of clinical and radiographic abnormalities until cultures (if they can be obtained) are negative, and reversible underlying predispositions have abated.

Clinical response rather than any arbitrary total dose should guide duration of therapy. The optimal dosage or duration of treatment of invasive disease is unknown and dependent on the extent of disease, the response to therapy, and the patient's underlying disease(s) and immune status. Response to therapy is largely related to the extent of aspergillosis at the time of diagnosis, and host factors, such as resolution of neutropenia and the return of neutrophil function, lessening immunosuppression, and the return of graft function from a bone marrow or organ transplant.[12]

Although caspofungin (and other echinocandins) have in vitro activity against *Aspergillus* species, echinocandins are unable to completely kill or inhibit *Aspergillus* species. Comparative randomized prospective trial data are not available for the echinocandins. Caspofungin is approved by the FDA for use as salvage therapy in patients who are refractory to or intolerant of other therapies such as conventional amphotericin B, lipid formulations of amphotericin B, and/or itraconazole.[12] However, for primary therapy of aspergillosis, response rates are lower with caspofungin than those obtained with voriconazole and amphotericin B.[84]

Given the continued high mortality of aspergillosis, combination therapy has been explored. However, while the advantages of combination therapy include the possibility of more rapid, synergistic killing, disadvantages include the possibility of antagonism, as well as increased cost and the increased risk of drug interactions and adverse effects. Combination therapy with voriconazole plus anidulafungin versus voriconazole alone was explored in a randomized, double-blind, placebo-controlled trial of patients with invasive aspergillosis. Combination therapy demonstrated a trend toward decreased 6-week survival compared to monotherapy, but did not achieve statistical significance (mortality rates 19.3% vs 27.5%, respectively).[85] Thus, there are as yet no firm recommendations regarding the use of combination therapy.[12]

Secondary Prophylaxis

The use of prophylactic antifungal therapy to prevent primary infection or reactivation of aspergillosis during subsequent courses of chemotherapy is recommended.[12] In granulocytopenic patients who recover from an episode of IA, the risk of relapse of aspergillosis during subsequent courses of

chemotherapy is greater than 50%. Voriconazole reduced the incidence of invasive fungal function infection (mostly aspergillosis) to 6.7% when used as secondary prophylaxis in allogeneic stem cell transplant recipients with prior infection.[32]

TREATMENT OPTIONS FOR EMERGING PATHOGENS

The increased frequency of fungal pathogens that were once rare is gaining attention from the medical community. Mucormycosis, fusariosis, lomentosporiosis, and scedosporiosis are the most frequent cause of non-*Aspergillus* mold infections.[16]

Mucorales Infections

Mucormycosis, previously known as zygomycosis, is a term describing infections caused by fungi belonging to the order Mucorales. Permissive environmental conditions, selective antifungal pressure, and increased numbers of immunosuppressed patients have led to increased numbers of infections caused by the Mucorales, which include *Rhizomucor* spp., *Lichtheimia* spp. (formerly *Absidia* spp.), *Rhizopus* spp., *Mucor* spp., and *Cunninghamella* spp. Prompt initiation of antifungal therapy is crucial, as treatment delays are associated with increased mortality.[86]

Of currently available systemic antifungals, only amphotericin B (including the lipid formulations) displays reliable activity against the Mucorales, while posaconazole and isavuconazole display variable activity, with wide MIC ranges.[16,87] Therapy with a liposomal or lipid-complex formulation of amphotericin B at a dosage of greater than or equal to 5 mg/kg/day, in addition to surgical debridement, is advocated by experts.[86,88]

Fusarium, *Scedosporium*, and *Lomentospora*

Unfortunately, the early presentation of *Fusarium, Scedosporium,* and *Lomentospora* infections often mimics that of aspergillosis. On histopathology, *Scedosporium* species resembles *Aspergillus* species with dichotomously branching, septate hyphae and has a tendency for invasion of vascular structures. These pathogens often demonstrate intrinsic to variable resistance to amphotericin B and are associated with high mortality rates. Interpretive CBPs for antifungal MICs and these pathogens are not available, and the optimal choice and duration of therapy is unknown. Global guidelines recommend the following strategies: for fusariosis, voriconazole (with or without a lipid amphotericin B product); for lomentosporosis, voriconazole plus terbinafine; and for scedosporiosis, voriconazole.[16,89]

Antifungal Therapy

Clinicians must have working knowledge of mechanism of action, spectrum of activity, dosing, and adverse effects of antifungals in order to provide appropriate recommendations for therapy. Dosing adjustments are needed for many antifungal agents in the setting of renal or hepatic dysfunction. A summary of the most common adverse effects of systemic antifungal agents are summarized in Fig. 144-3 and described in the text below.

FIGURE 144-3

Adverse effects of systemic antifungal agents.

Data from References 90-92.

Adverse Effect	Polyenes: AmB	Azoles: Flucon	Azoles: Itra	Azoles: Vori	Azoles: Posa	Azoles: Isavu	Echinocandins: Micafungin, Anidulafungin, caspofungin
Nephrotoxicity	✓	✗	✗ (possible with IV)	✗ (possible with IV)	✗	✗	✗
Abdominal discomfort	✗	✓	✓	✓	✓	✓	✗
↑ Hepatic transaminases	✓	✓	✓	✓	✓	✓	✓
Rash, photosensitivity	✗	✓	✓	✓ Can lead to malignancy	✓	✓	✓
Infusion-related reactions/ histamine release	✓	✗	✗	✗	✗	✗	✓
CNS & visual disturbances	✗	✗	✗	✓	✗	✗	✗
Cardiomyopathy (itra), ↑ QT (azoles), ? echinos	✗	✓	✓	✓	✓	↓QT	?

Source: Joseph T. DiPiro, Gary C. Yee, Stuart T. Haines, Thomas D. Nolin, Vicki L. Ellingrod, L. Michael Posey: *DiPiro's Pharmacotherapy: A Pathophysiologic Approach, 12e*

The antifungal armamentarium for the treatment of IFIs includes (a) inhibitors of the fungal cell membrane such as polyenes (eg, amphotericin B) and azole antifungals, (b) inhibitors of DNA (5-flucytosine), and (c) inhibitors of cell wall biosynthesis (echinocandins).

Antifungal therapy generally includes one or more antifungal agents, depending on the severity of infection and the patients' immune status. Rarely are the agents used in combination. Often therapy is initiated with an IV agent such as an echinocandin or amphotericin B, and therapy is changed to an oral (azole) regimen as the patient's clinical status improves and oral therapy is tolerated.

Antifungal stewardship, particularly with integration of real-time decision support for the results of rapid diagnostic testing methods such as MALDI-TOF, may improve diagnosis and quality of care, while decreasing mortality and the cost of antifungal therapy.[93]

Amphotericin B

Amphotericin B remains the therapy of choice for many systemic fungal infections despite a lack of controlled clinical trials documenting the optimal dosage, duration of therapy, or relative efficacy of this agent in comparison with newer azole antifungal agents. During pregnancy, amphotericin B remains the treatment of choice for most fungal infections because azole antifungals are teratogenic.[94] The side effects of amphotericin B generally are categorized as acute (infusion-related) or long term. Amphotericin B commonly causes renal functional impairment, including decreased glomerular filtration rate, hypokalemia, hypomagnesemia, metabolic acidosis due to distal (or type 1) renal tubular acidosis (RTA), and polyuria due to nephrogenic diabetes insipidus. The nephrotoxicity associated with amphotericin B is usually reversible with discontinuation of therapy. However, recurrent renal dysfunction can occur if treatment is reinstituted. The risk of amphotericin B nephrotoxicity is increased by higher daily doses and concurrent therapy with other nephrotoxins, such as an aminoglycoside or cyclosporine. Salt loading (eg, 500-1,000 mL normal saline infusion) prior to dosing ameliorates/delays the onset of nephrotoxicity, and close monitoring and repletion of potassium and magnesium are necessary.[12,95]

Lipid Formulations of Amphotericin B

The use of deoxycholate amphotericin B is frequently associated with the development of induced nephrotoxicity. In an attempt to decrease the incidence of nephrotoxicity, three lipid formulations of amphotericin B have been developed and approved for use in humans: ABLC (Abelcet; Enzon Pharmaceuticals), ABCD (Amphotec; Intermune Pharmaceuticals), and liposomal amphotericin B (AmBisome; Gilead Pharmaceuticals). In these preparations, amphotericin B is incorporated into the phospholipid bilayer membrane rather than in the enclosed aqueous phase.[96]

The various lipid formulations of amphotericin B exhibit markedly different pharmacokinetics; however, whether these differences result in different outcomes in the treatment of specific types of infections (eg, CNS infections) is unclear. Although larger doses of these preparations are required to achieve similar pharmacologic effects as the deoxycholate form of amphotericin B, the toxicity appears to be much lower. Although the FDA-approved dosages of these agents are 5 mg/kg/day (ABLC), 3 to 6 mg/kg/day (ABCD), and 3 to 5 mg/kg/day (liposomal amphotericin B), the agents appear generally equipotent.[96] The optimal dose of these compounds for serious *Candida* infections is unknown; however, dosages of 3 to 5 mg/kg/day

appear reasonable.[7]

Lipid formulations of amphotericin B, especially liposomal amphotericin B and amphotericin B lipid complex, are generally preferred over amphotericin B deoxycholate in clinical practice guidelines given their reduced potential for nephrotoxicity. There is up to a 6.6-fold increase in mortality in patients with amphotericin B–induced nephrotoxicity, and lipid formulations result in a significantly decreased incidence and severity of nephrotoxicity; liposomal amphotericin B may be less nephrotoxic than the ABLC.[96] Liposomal amphotericin B also results in significantly fewer infusion-related reactions than amphotericin B deoxycholate.[96,97]

Flucytosine

Flucytosine (also known as 5-flucytosine) is a fluorinated pyrimidine analog that is highly water-soluble. Patients with creatinine clearances of less than 40 mL/min (0.67 mL/s) should receive careful dosage adjustments. Peak serum concentrations (2 hours after an oral dose) should be monitored in all patients to maintain peak serum concentrations between 20 and 100 mg/L (155 and 775 µmol/L).[98,99]

Flucytosine generally is associated with few side effects in patients with normal renal, GI, and hematologic function, although rash, GI discomfort, diarrhea (5%-10%), and reversible elevations in hepatic enzymes are observed occasionally. In patients with renal dysfunction or concomitant amphotericin B therapy, leukopenia, thrombocytopenia, and (rarely) enterocolitis can occur. Myelotoxicity is well correlated with peak concentrations >100 mg/L (775 µmol/L).[98,99] Flucytosine is rapidly converted to 5-fluorouracil, which is toxic to mammalian cells, once taken up by fungal cells. Patients treated with flucytosine have detectable amounts of 5-fluorouracil in their serum and urine, although the mechanism of flucytosine toxicity is still incompletely understood. Flucytosine may be secreted into the GI tract, deaminated by intestinal bacteria, and reabsorbed as 5-fluorouracil.[98]

Flucytosine is used in combination with amphotericin B or fluconazole in the treatment of cryptococcosis or (less commonly) candidiasis. The rapid development of resistance to flucytosine, however, precludes its use as single-agent therapy. Mechanisms for drug resistance can include loss of deaminase and decreased permeability to the drug.[98]

Echinocandins

The echinocandins (caspofungin, micafungin, and anidulafungin) act as concentration-dependent, non-competitive inhibitors of BG synthase, an essential component of the cell wall of susceptible filamentous fungi that is absent in mammalian cells.

All echinocandins display linear pharmacokinetics following administration of IV dosages, and are degraded primarily by the liver (also in the adrenals and spleen) by hydrolysis and *N*-acetylation. Following initial distribution, echinocandins are taken up by red blood cells (micafungin) and the liver (caspofungin and micafungin) where they undergo slow degradation to mainly inactive metabolites, although two uncommon metabolites of micafungin possess antifungal activity. Degradation products are excreted slowly over many days, primarily through the bile. Among the echinocandins, anidulafungin is unique in being eliminated almost exclusively by slow chemical degradation rather than undergoing hepatic metabolism.

Echinocandins are available only as parenteral formulations, are not dialyzable, and do not require dosage adjustment in patients with renal insufficiency. They have minimal CSF penetration, largely because of their high protein binding and large molecular weights, although the clinical relevance of these findings can be disputed, given that several other antifungal agents (amphotericin B and itraconazole) are effective for the treatment of fungal meningitis despite low CSF concentrations. The echinocandins are well tolerated, although some patients may report histamine release resulting in rash, facial swelling, and itchiness.[100]

Azole Antifungal Agents

Adverse effects of azoles include GI disturbances (primarily nausea, vomiting, epigastric pain, and diarrhea), which appear to be more common in patients receiving ketoconazole and the solution formulation of itraconazole.[12] Although cyclodextrin is not absorbed following oral administration, use of the IV formulations of posaconazole and voriconazole is not recommended by the manufacturers because of concerns for potential nephrotoxicity secondary to accumulation of the cyclodextrin vehicle. This concern is likely not clinically relevant.[101] Fluconazole is well tolerated; intestinal complaints are the most frequently reported, followed by headaches and rash. Unlike ketoconazole, fluconazole does not inhibit testicular

or adrenal steroidogenesis in healthy volunteers or hospitalized patients. Reversible alopecia occurs not infrequently and usually appears after several months of treatment with higher doses of fluconazole.[91] Azoles are potentially teratogenic and should be avoided in pregnant women.[94]

Azole antifungals have been implicated in idiosyncratic drug-induced liver injury with the incidence and pattern of injury varying between specific agents. The exact mechanism of toxicity has not been elucidated and there is varying level of evidence with regards to the effect of dose on the development of the toxicity. It is recommended that baseline liver function tests (LFTs) be obtained for patients being started on therapy with these agents and periodically monitored. In general, hepatotoxicity can occur at any time after initiation of the antifungal with most cases occurring in the first month of therapy. The liver injury is usually reversible with discontinuation of the offending agent. Substitution of the offending azole antifungal with a different azole antifungal can occur without impacting resolution of the toxicity.[91] Isavuconazole is less hepatotoxic than voriconazole.[82]

Azole antifungals are associated with QT prolongation as the result of cardiac hERG-mediated potassium channel blockade. However, azoles alone are not considered significant risk factors for serious drug-induced QT prolongation. Instead, the combination of azoles with other risk factors, such as other QT-prolonging medications, electrolyte abnormalities, and heart disease, is necessary to yield risk for serious QT prolongation. Isavuconazole is unique amongst the azoles in that it shortens the QT interval, and so is an option in cases of azole-induced QT prolongation.[92]

Itraconazole

Itraconazole is triazole antifungal with a broad spectrum of antifungal activity. Despite its marked structural similarity to ketoconazole, itraconazole differs in several important respects. Itraconazole appears to have greater specificity against fungal versus mammalian CYP, resulting in greater potency and a decrease in CYP-mediated side effects. In addition, itraconazole possesses in vitro activity against *Aspergillus* and *Sporothrix* species.

Like ketoconazole, the capsule formulation of itraconazole depends on the availability of low gastric pH for dissolution and absorption. Administration with food appears to enhance significantly the bioavailability of itraconazole capsules. Because itraconazole exhibits pH-dependent dissolution and absorption, absorption of the capsule formulation is impaired in patients receiving antacids or H_2-receptor antagonists and in patients with achlorhydria. Plasma concentrations of itraconazole following a single oral dose (capsules) in HIV-infected patients are approximately 50% lower than concentrations observed in healthy volunteers. The capsule formulation of itraconazole exhibits unpredictable oral bioavailability, particularly in subjects with hypochlorhydria and in patients with enteropathy caused by mucositis or GvHD of the gut. An oral suspension formulation of itraconazole was subsequently developed that uses cyclodextrin as a solubilizing vehicle to increase the solubility of the drug. The oral bioavailability of the solution is unaffected by alterations in gastric pH (such as concomitant omeprazole use) or in patients with enteropathy. The bioavailability of the oral solution is optimized in the fasting state.[102,103] A novel capsule formulation was developed which may result in more rapid and consistent attainment of therapeutic concentrations.[104]

Fluconazole

Fluconazole is a triazole antifungal agent with markedly different pharmacologic features than other marketed azole antifungals. The small molecular weight, low protein binding, and increased water solubility of fluconazole result in rapid, essentially complete absorption of drug following oral administration. Because fluconazole is excreted primarily (greater than 80%) as unchanged drug in the urine, dosage adjustments are necessary in patients with renal dysfunction.[90]

Voriconazole

The hepatic biotransformation of voriconazole is fairly complex and involves CYP2C19, CYP3A4, and CYP2C9, with most metabolism mediated through CYP2C19. Two of the CYPs involved in voriconazole metabolism (CYP2C19 and CYP2C9) exhibit genetic polymorphism; variability in the CYP2C19 genotype accounts for approximately 30% of the overall between subject variability in voriconazole pharmacokinetics. About 3% to 5% of white and African human populations are poor metabolizers, while 15% to 20% of Asian populations are poor metabolizers. Drug levels can be as much as fourfold greater in poor metabolizers than in individuals who are homozygous extensive metabolizers. Coadministration of voriconazole with drugs that are potent CYP450 enzyme inducers can significantly reduce voriconazole levels. Voriconazole drug interactions are dose-dependent, as they exhibit unpredictable non-linear pharmacokinetics; thus, drug interactions are more difficult to predict and manage.[92] Voriconazole is uniquely associated with phototoxicity. In addition, patients receiving long-term voriconazole are risk for development of skin cancer (primarily squamous cell carcinoma) and periostitis.[91,92]

The most common side effect of voriconazole is a reversible disturbance of vision (photopsia), which occurs in approximately 30% of patients but rarely leads to discontinuation of the drug. Symptoms tend to occur during the first week of therapy and decrease or disappear despite continued therapy. Patients experience altered color discrimination, blurred vision, the appearance of bright spots and wavy lines, and photophobia. Patients should be cautioned that driving can be hazardous because of the risk of visual disturbances. The visual effects are associated with changes in electroretinogram tracings, which revert to normal when treatment with the drug is stopped; no permanent damage to the retina has been demonstrated. Less common are visual and/or auditory hallucinations, which are associated with concentrations >5.5 µg/mL (mg/L; 15.7 µmol/L).[92]

Posaconazole

Posaconazole has a broad spectrum of antifungal activity, including *Aspergillus* and *Candida* species and variable activity against the Mucorales. Posaconazole was initially developed as an oral suspension for the prevention of IFIs in immunocompromised patients, including hematologic malignancy patients with prolonged neutropenia from chemotherapy as well as HSCT patients with GvHD.[23,24] However, to ensure adequate absorption, the suspension formulation had to be administered two to three times daily, with a high fat meal or a nutritional supplement. Most patients with GvHD, and many with chemotherapy-associated nausea or vomiting, mucositis or diarrhea, were unable to comply with the requirement for a fatty meal, resulting in decreased plasma concentrations of posaconazole and an increased risk of breakthrough fungal infection. The development of IV and delayed-release tablet formulations of posaconazole has circumvented these absorption issues and allows once daily oral administration of posaconazole following administration of a twice daily loading dose on the first day of therapy.[92]

Isavuconazole

Isavuconazole, available both orally and IV, has a broad spectrum of activity against a number of clinically important yeasts and molds, including *Candida* spp., *Aspergillus* spp., *C. neoformans*, *Trichosporon* spp., and variable activity against the Mucorales. The most commonly reported adverse events, which are mild and limited in nature, include nausea, diarrhea, and elevated liver function tests. The potential advantage of this agent over other currently available broad-spectrum azole antifungals is a clinically useful alternative to voriconazole for the treatment of invasive aspergillosis, due to its lack of genetically determined variability in plasma levels, and more favorable and predictable drug interaction profile.[92]

Drug Interactions with Antifungal Agents

The interaction of azole antifungal agents with other CYP-metabolized drugs is well recognized. All azoles are inhibitors of the CYP3A4 enzyme system, and voriconazole and fluconazole additionally are inhibitors of CYP2C8/9 and CYP2C19. Apart from fluconazole (a substrate of CYP3A4 but mostly eliminated in the urine as unchanged drug) and posaconazole (metabolized by uridine diphosphate glucuronidation), the azoles appear to be metabolized almost entirely via the CYP3A4 subfamily. As expected, numerous clinically significant interactions have been documented with azole antifungals and a variety of other drugs. In most cases, the azole interferes with the metabolism of the other CYP-metabolized drug. Relative to ketoconazole and itraconazole, fluconazole appears to be intermediate in its ability to inhibit human cytochromes P450. The magnitude of fluconazole-induced inhibition of cyclosporine metabolism depends on the dosage of fluconazole. Isavuconazole appears to be a more modest inhibitor of CYP3A4 compared to voriconazole and posaconazole.[92,105]

Predictably, drugs such as rifampin, rifabutin, isoniazid, phenytoin, and carbamazepine, which are known to induce the activity of cytochromes P450, result in increased metabolism of the azole antifungals and can result in therapeutic failures. Increased dosages of azole antifungals can be required in patients receiving these combinations of drugs.[105]

Itraconazole is an inhibitor of intestinal Pgp. Significant increases in digoxin (a Pgp substrate) have been observed in patients receiving both agents concurrently. Interactions with other substrates of Pgp would be expected to occur.[105]

Echinocandins are not inducers of CYP enzymes, nor do they interact with Pgp, and are considered poor substrates of CYP3A4. Nevertheless, drug interactions are noted with caspofungin and cyclosporine and tacrolimus; the mechanism for these interactions is not yet known. Rifampin both inhibits (acutely) and induces (after chronic administration) caspofungin metabolism, and a dosage increase is recommended in patients receiving other enzyme inducers, such as efavirenz, nevirapine, phenytoin, dexamethasone, and carbamazepine. Although micafungin does not significantly affect the clearance (or area under the plasma-concentration vs time curve [AUC]) of tacrolimus, it increases the AUCs of sirolimus and nifedipine and

decreases the clearance of cyclosporine.[100]

Therapeutic Drug Monitoring of Antifungal Agents

There is insufficient data to justify the routine use of therapeutic drug monitoring (TDM) for the prophylaxis or treatment of fungal infections with all antifungal agents. In addition, logistics, cost, and incorporation of TDM have yet to be worked out in modern prophylactic algorithms. However, under certain circumstances, serum or plasma concentration monitoring of select agents is warranted. Given the tremendous interpatient and intrapatient variability in voriconazole metabolism, TDM is warranted in most patients. Also, given the poor oral bioavailability of itraconazole capsules and posaconazole solution, monitoring is recommended, particularly in patients with GvHD of the gut, mucositis, or diarrhea, or poor oral intake or those receiving concomitant therapy with proton-pump inhibitors. Although the use of posaconazole tablets may result in a decreased need for TDM, patients with a higher weight and those experiencing diarrhea are more likely to have lower levels. Additional settings include patients susceptible to flucytosine toxicity, to document adequate oral absorption of poorly bioavailable azoles in cases of suspected treatment failure or concern about compliance or absorption, solubility and finally, when drug interactions that might reduce or accelerate the metabolism of azoles is suspected.[92,99] The need for isavuconazole TDM is undefined, as clinical experience has demonstrated limited pharmacokinetic variability and no clear correlations between concentrations and response or toxicity.[92] Recommendations regarding plasma concentration monitoring of antifungals are summarized in Table 144-10.

TABLE 144-10

Plasma Concentration Monitoring of Antifungal Agents

	Serum Concentration Monitoring Necessary?	Target Concentration Range	Timing of Sample
Echinocandins	No	NA	NA
Amphotericin B (including lipids)	No	NA	NA
Fluconazole	No	NA	NA
Isavuconazole	Unclear; appears to demonstrate limited pharmacokinetic variability and no clear thresholds for efficacy or toxicity have been elucidated	NA	NA
Itraconazole	Yes, to ensure absorption and efficacy	*Efficacy:* Prophylaxis: >0.5 µg/mL (mg/L; 0.7 µmol/L) Treatment: >1 µg/mL (mg/L; 1.4 µmol/L) *Toxicity:* <5 µg/mL (mg/L; 7 µmol/L)	Trough 7 days after initiation of therapy
Voriconazole	Probably yes—in all patients treated for IFI, altered liver function, potential drug-drug interactions, lack of response *Low* concentrations are associated with poor outcome; *high* concentrations are associated with	*Efficacy:* Prophylaxis: trough >0.5-2 µg/mL (mg/L; 1.4-5.7 µmol/L) Treatment: trough >1-2 µg/mL (mg/L; 2.9-5.7 µmol/L) Concentrations >2.0 µg/mL (mg/L; 5.7 µmol/L) are associated with improved	Trough after 5-7 days therapy if no loading dose administered; 48 hours after administration of loading dose in critically ill patient (time to steady state is unpredictable due to nonlinear metabolism)

	adverse effects Variable metabolism due to non-linear PK and genetic variability in CYP2C19 → unpredictable dose-exposure relationship	outcome; 2-5.5 μg/mL (mg/L; 5.7-15.7 μmol/L) is probably the best target *Toxicity:* concentrations >5.5 μg/mL (mg/L; 15.7 μmol/L) are associated with ↑ risk of neurotoxicity	
Posaconazole delayed release tablets	Maybe Outcomes (but not adverse events) correlate with higher plasma concentrations in prophylaxis and possibly treatment	*Efficacy:* Prophylaxis: >0.7 μg/mL (mg/L; 1 μmol/L) Treatment: Not well studied; concentrations >1.25 μg/mL (mg/L; 1.78 μmol/L) *Toxicity:* Correlation with toxicity poorly defined	Random level at SS (>7 days therapy). The long $t_{1/2}$ ensures little fluctuation in peaks and troughs at SS
Flucytosine	Yes—high concentrations are associated with toxicity	*Toxicity:* "Peak" <80-100 μg/mL (mg/L; 620-775 μmol/L) *Efficacy:* Peak >20 μg/mL (mg/L; 155 μmol/L)	2 hours postdose "peak", 3-5 days after initiation of therapy

Data from References 12,92, and 99.

NA, not applicable.

ABBREVIATIONS

AIDS	acquired immunodeficiency syndrome
ABCD	amphotericin B colloid dispersion
ABLC	amphotericin B lipid complex
AUC	area under the plasma-concentration versus time curve
BG	(1,3)-β-D-glucan
BPA	bronchopulmonary aspergillosis
BSI	bloodstream infection
CBP	clinical breakpoint
CT	computed tomography
CVC	central venous catheter
CSF	cerebrospinal fluid

CYP	cytochrome P450
ELISA	enzyme-linked immunosorbent assay
FISH	fluorescence in situ hybridization
GvHD	graft-versus-host disease
HEPA	high-efficiency particulate air
HAART	highly active antiretroviral therapy
HSCT	hematopoietic stem cell transplantation
IA	invasive aspergillosis
ICP	intracranial pressure
ICUs	intensive care units
IDSA	Infectious Diseases Society of America
IPA	invasive pulmonary aspergillosis
IRIS	immune reconstitution inflammatory syndrome
LFT	liver function test
MALDI-TOF-ICMS	matrix-assisted laser desorption ionization time-of-flight mass spectrometry
NSAID	non-steroidal antiinflammatory drug
PDH	progressive disseminated histoplasmosis
PN	parenteral nutrition
PNA	peptide nucleic acid
RR	respiratory rate
SDD	susceptible dose-dependent
TDM	therapeutic plasma drug concentration monitoring
TEE	transesophageal echocardiogram
TTE	transthoracic echocardiogram
WBC	white blood cell

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SELF-ASSESSMENT QUESTIONS

1. In vitro susceptibility testing of antifungal agents:

   A. Is available at most hospital clinical microbiology laboratories.

   B. Reliably predicts clinical outcome, regardless of patient host factors.

   C. Can alert the clinician to the presence of azole-resistant isolates of Candida.

   D. Rely on the use of high temperatures and long incubation times, in order to induce hyphal formation.

   E. Is utilized in practice mostly to inform therapeutic decisions in the treatment of invasive mold infections, like aspergillosis, since clinical breakpoints are established for filamentous fungi.

2. The in vitro spectrum of activity of echinocandins:

   A. Includes typical pathogens encountered in the immunosuppressed patient, including Pseudomonas aeruginosa and methicillin-resistant Staphylococcus aureus.

   B. Includes emerging fungal pathogens such as *Fusarium* and *Cryptococcus neoformans.*

   C. May differ for various *Candida* species, depending on whether the mycelial or the yeast form of the pathogen is utilized in testing.

   D. Includes many pathogenic fungi encountered in the immunosuppressed patient, including *C. albicans* and *Aspergillus* species.

   E. Has demonstrated the rapid emergence of resistant strains of *C. albicans* in patients receiving greater than 2-week therapy.

3. SM is a 34-year-old woman currently being treated with voriconazole for invasive pulmonary aspergillosis caused by *Aspergillus fumigatus.* She develops a skin rash, which you believe due to voriconazole. Which of the following statements is most correct regarding appropriate antifungal therapy for SM?

A. An echinocandin should not be utilized, as its chemical structure is similar to that of azole antifungal agents such as fluconazole.

B. Therapy with an echinocandin (caspofungin or micafungin) is unlikely to cause a rash in this patient, as echinocandins are chemically unrelated to azole antifungal agents.

C. Micafungin should not be utilized as an alternative agent in this patient, as it demonstrates poor in vitro and in vivo activity against *A. fumigatus*.

D. Caspofungin could be utilized as an alternative agent in SM, as it demonstrates excellent in vitro and in vivo activity against Aspergillus fumigatus; however, SM is likely to experience a rash due to cross-sensitivity between azoles and echinocandin antifungals.

E. Micafungin would not be an appropriate alternative agent in this patient, as it demonstrates very poor efficacy in the treatment of pulmonary aspergillosis.

4. Blastomycosis is often mild and self-limited and may not require treatment. However, consideration should be given to treating which of the following infected individuals to prevent extrapulmonary dissemination?

A. All individuals with moderate-to-severe pneumonia

B. HIV-infected individuals

C. Individuals who are immunocompromised

D. Patients who have undergone hematopoietic stem cell transplantation

E. All of the above

5. RH is a 68-year-old male who is 6 months status post allogeneic hematopoietic stem cell transplantation, complicated by graft-versus-host disease. As his most recent chest radiograph indicates that he has invasive pulmonary aspergillosis that appears unresponsive to his current therapy with liposomal amphotericin B, his physician wishes to place RH on combination therapy with voriconazole and anidulafungin. Which of the following statements is most correct regarding RH's therapy?

A. As RH's amphotericin B regimen has resulted in an elevated serum creatinine, his anidulafungin dosage may need to be decreased, as anidulafungin is eliminated primarily via the kidneys.

B. The dosage of the patient's tacrolimus will likely require adjustment, given the CYP3A4 inhibition of voriconazole.

C. Fluconazole would be a more appropriate choice than voriconazole to cover aspergillosis.

D. Prophylaxis with posaconazole would not have been recommended in this patient, and would not have potentially prevented the development of aspergillosis.

E. Combination therapy with voriconazole and anidulafungin is not recommended, as a clinical trial identified higher failure rates with this combination than with voriconazole monotherapy, suggesting a pharmacodynamic interaction.

6. When assessing infections caused by *Candida* species:

A. Candidemia is a rare cause of bloodstream infections in hospitals.

B. Mortality associated with infections due to *C. auris* appears to be quite high.

C. The proportion of infections caused by *C. albicans* has increased, while those caused by non-*albicans* species has decreased.

D. *C. glabrata* resistance to azoles is rare, and does not "cross" to other azoles.

E. Combination therapy is routinely recommended.

7. Visual changes observed in patients during voriconazole therapy:

A. Can cause permanent damage to the retina if therapy is continued for greater than 2 weeks.

B. Generally do not require discontinuation of the drug.

C. Are observed in less than 1% of patients.

D. Do not decrease or disappear despite continued therapy.

E. Are not associated with changes in electroretinogram tracings.

8. Plasma level monitoring of antifungals …

A. Rarely is necessary unless toxicity is observed.

B. Should probably be performed in all patients receiving long-term voriconazole therapy for aspergillosis.

C. Probably is needed for fluconazole, voriconazole, and caspofungin because the efficacy and toxicity of these agents correlate with peak levels.

D. Is only necessary in patients receiving fluconazole therapy for CNS infections.

E. Is not useful for voriconazole since neither efficacy nor toxicity is correlated with plasma concentrations.

9. According to current (2009) Infectious Diseases Society of America guidelines, initial antifungal therapy for Candida bloodstream infections:

A. Is similar for all *Candida* species.

B. Should always be initiated with fluconazole, due to its low cost and excellent safety profile.

C. Should always be initiated with echinocandins, since resistance rates of *Candida* species to fluconazole are high.

D. Should take into consideration whether the patient is unstable or severely immunocompromised, has a history of recent exposure to fluconazole or other azoles, or if non-*albicans* species are suspected.

E. Should be initiated as recommended in all patients, prior to obtaining positive blood cultures, if they are critically ill and not responding to antibacterial agents

10. All of the following statements regarding fungal disease are correct except:

A. Histoplasma capsulatum exists as mycelial forms at room temperature and yeast forms at body temperature.

B. All patients with early coccidioidal infections should be treated aggressively to prevent disseminated disease.

C. Blastomycosis often involves skin, bones, joints, and genitourinary tract.

D. Histoplasmosis may result in mediastinal fibrosis.

E. Pregnant women are at high risk for developing disseminated coccidioidomycosis.

11. All of the following are true regarding infections caused by *Candida* species except:

A. Infections are associated with a low rate of mortality when appropriate antifungal therapy is promptly initiated as soon as a patient becomes febrile.

B. While *C. albicans* remains the most common species causing infection, other species, including *C. glabrata* and *C. parapsilosis*, have become more common.

C. The role of antifungal prophylaxis in the surgical ICU remains extremely controversial.

D. Prophylactic antifungals are indicated in patients with recurrent intestinal perforations and/or anastomotic leak.

E. Alternatives to fluconazole should be considered when patients have a history of recent exposure to fluconazole or other azoles, and when non-*albicans* species are isolated.

12. In the treatment of coccidioidal meningitis:

A. Fluconazole 400 mg daily is the drug of choice.

B. Lifelong suppressive therapy must be followed.

C. Ketoconazole should not be recommended routinely due to its poor CNS penetration.

D. May require intrathecal amphotericin B therapy in patients who do not respond to fluconazole or itraconazole.

E. All of the above.

13. In patients with AIDS who have successfully completed primary therapy, lifelong maintenance therapy to prevent relapse of cryptococcal disease:

A. Is recommended for all patients after successful completion of primary induction therapy, with fluconazole 800 mg orally daily.

B. Is necessary and recommended for most patients, utilizing a low dosage of fluconazole (200 mg orally daily)

C. Is recommended for patients who are NOT on HAART therapy with a sustained CD4 cell count greater than 100 cells/mL (0.1×10^6/L) and undetectable viral load.

D. Ketoconazole is an effective and cost effective therapy.

E. Amphotericin B 1 mg/kg IV weekly is more effective and better tolerated than oral fluconazole 200 mg/day.

14. Prophylaxis of candidemia:

A. Is recommended in all non-neutropenic patients who are admitted to the ICU.

B. Is recommended in neutropenic patients for 1 week prior to and 6 months after they become neutropenic.

C. May be indicated in patients with recurrent intestinal perforations and/or anastomotic leaks.

D. Should never be utilized since the risk of antifungal resistance is increasing rapidly and our antifungal armamentarium is limited.

E. Is unnecessary, since prompt initiation of antifungal therapy in patients with clinical, laboratory, or radiologic surrogate markers of infection results in high rates of clinical success.

15. Risk factors for invasive candidiasis include all of the following except:

A. Long ICU stay.

B. Prior infection with *P. aeruginosa.*

C. The use of total parenteral nutrition (TPN).

D. The presence of acute renal failure.

E. The presence of central venous catheter.

SELF-ASSESSMENT QUESTION-ANSWERS

1. **C.** Antifungal susceptibility testing is not performed at most hospital clinical laboratories. Clinical breakpoints have only been established for selected antifungal agents and Candida. However, clinical failure may still occur despite in vitro susceptibility, depending on host and drug characteristics. See "Mycology" (Clinical Versus Microbial Resistance and Susceptibility Testing of Antifungal Agents) section.

2. **D.** Echinocandins are antifungal agents with a spectrum limited to Candida and Aspergillus. However, these are the most common pathogens encountered in clinical practice, especially in the immunosuppressed. See Tables 144-1 and 144-2 and "Mycology" (Epidemiology and Pathogenesis) section.

3. **B.** Echinocandins are a distinct class of agents from the azole antifungals, structurally, mechanistically, and in terms of common toxicities. While they are not preferred options for the treatment of invasive aspergillosis, they may be considered in patients refractory to or intolerant of other therapies. See "Aspergillosis" (Specific Therapy and Antifungal Therapy) sections.

4. **E.** All individuals with moderate-to-severe pneumonia, disseminated infection, or those who are immunocompromised require antifungal therapy. See "Blastomycosis" (Treatment) section.

5. **B.** Antifungal prophylaxis with posaconazole has been shown to significantly reduce the risk of aspergillosis in high-risk patients such as RH. While combination therapy with voriconazole and anidulafungin is controversial, it has demonstrated a trend towards improved survival. Anidulafungin is not predominantly renally eliminated and thus does not require renal dose adjustment, but voriconazole is a significant inhibitor of several CYP enzyme systems. See "Aspergillosis" (Specific Therapy and Antifungal Therapy) section.

6. **B.** *C. auris* is an emerging pathogen and has been associated with poor outcomes. The proportion of infections caused by non-albicans species has increased, most notably *C. glabrata*, which is complicated by its cross-resistance to the azole class of antifungals. See "Candida Infections" (Epidemiology) section.

7. **B.** Photopsia is a unique side effect to voriconazole, is common, and often decreases in severity or disappears with continued therapy. No permanent damage to the retina has been demonstrated. See "Antifungal Therapy" (Voriconazole) section.

8. **B.** Therapeutic drug monitoring (TDM) is rarely performed or indicated in patients receiving fluconazole, echinocandins, or amphotericin B products. TDM is warranted in most patients receiving voriconazole due to significant pharmacokinetic variability and correlations of clinical success and toxicity to levels. See "Therapeutic Drug Monitoring of Antifungal Agents" section.

9. **D.** Echinocandins are generally preferred as initial antifungal therapy for candidemia, but fluconazole may be appropriate in patients who are not severely ill, have no recent azole exposure, and who are unlikely to have a fluconazole-resistant isolate. See "Candida Infections" (Treatment) section.

10. **B.** Approximately 60% of patients infected with Coccidioides have an asymptomatic, self-limited infection. Patients with disease located outside the lung should generally receive therapy. Regarding isolated pulmonary disease, patients with a large inoculum, severe infection, or concurrent risk factors probably should be treated. See "Coccidioidomycosis" (Primary Respiratory Infection) section.

11. **A.** Unfortunately, mortality due to invasive candidiasis remains high, despite available antifungal therapies. This may be a reflection of the underlying comorbidity of patients who are at risk for developing candidiasis, such as critically ill surgical patients and those with significant immunocompromise. See "Candida Iinfections" (Epidemiology) section.

12. **E.** Fluconazole is the drug of choice for the treatment of coccidioidal meningitis. However, since fluconazole therapy only leads to remission, suppressive therapy must be continued for life. Patients with refractory infection may require intrathecal amphotericin B. See "Coccidioidomycosis" (Meningeal Disease) section.

13. **C.** Relapse is common in AIDS patients with cryptococcal meningitis, although certain patients appear to be at lower risk. Such patients include those who have successfully completed therapy and have a sustained increase in their CD4 cell counts to greater than 100-200 cells and an undetectable HIV viral load. See "Cryptococcosis" (Suppressive (Maintenance) Therapy for Cryptococcal Meningitis in HIV-Infected Patient) section.

14. **C.** Prophylaxis of candidemia, especially in non-neutropenic patients, is controversial. Given the high mortality of invasive candidiasis, studies have attempted to delineate whether prophylaxis in certain patient populations could improve outcomes. Unfortunately, clinical trials in these settings

have generally not been successful, although one small study did identify a benefit in patients with recurrent intestinal perforations and/or anastomotic leaks. See "Candida Infections" (Nonimmunocompromised Patient, Prophylaxis) section.

15. **B.** Major risk factors for invasive candidiasis include the use of central venous catheters, total parenteral nutrition, multifocal Candida colonization, and extensive surgery. While receipt of multiple antibiotics is also a risk factor for candidiasis, prior bacterial infection has not been identified as a strong risk factor for subsequent development of invasive candidiasis. See Table 144-8.