DIAGNOSIS

The definitive diagnosis of any fungal infection requires histopathologic identification of the fungus invading tissue and accompanying evidence of an inflammatory response. The identification of an inflammatory response has been especially important with regard to *Aspergillus* infection. *Aspergillus* is ubiquitous and can float in the air onto biopsy material. Therefore, in rare but important instances, this fungus is an ex vivo contaminant during processing of a specimen for microscopy, with a consequent incorrect diagnosis. The stains most commonly used to identify fungi are periodic acid–Schiff and Gomori methenamine silver. *Candida*, unlike other fungi, is visible on gram-stained tissue smears. Hematoxylin and eosin stain is not sufficient to identify *Candida* in tissue specimens. When positive, an india ink preparation of cerebrospinal fluid (CSF) is diagnostic for cryptococcosis. Most laboratories now use calcofluor white staining coupled with fluorescent microscopy to identify fungi in fluid specimens.

Extensive investigations of the diagnosis of deep organ fungal infections have yielded a variety of tests with different degrees of specificity and sensitivity. The most reliable tests are the detection of antibody to *Coccidioides immitis* in serum and CSF; of *Histoplasma capsulatum* antigen in urine, serum, and CSF; and of cryptococcal polysaccharide antigen in serum and CSF. These tests have a general sensitivity and specificity of 90%; however, because of variability among laboratories, testing on multiple occasions is advisable. The test for galactomannan has been used extensively in Europe and is now approved in the United States for diagnosis of aspergillosis. Sources of concern regarding galactomannan are the incidence of false-negative results and the need for multiple serial tests to reduce this incidence. The β-glucan test for *Candida* is also under evaluation but, like the galactomannan test, still requires additional validation; this test has a negative predictive value of ~90%. Both of these tests are being used with increasing frequency, especially for guiding the timing of initiation and duration of therapy. The galactomannan test is being evaluated in both serum and bronchoalveolar lavage fluid. Numerous polymerase chain reaction assays to detect antigens are in the developmental stages, as are nucleic acid hybridization techniques; currently, these tests are not widely available.

Of the fungal organisms, *Candida* is by far the most frequently recovered from blood. Although *Candida* species can be detected with any of the automated blood culture systems widely used at present, the lysis-centrifugation technique increases the sensitivity of blood cultures for *Candida* and for less common organisms (e.g., *H. capsulatum*). Lysis-centrifugation should be used when disseminated fungal infection is suspected.

Except in the cases of coccidioidomycosis, cryptococcosis, and histoplasmosis, there are no fully validated and widely used tests for serodiagnosis of disseminated fungal infection. Skin tests for the endemic mycoses are no longer available.

TREATMENT FUNGAL INFECTIONS

This discussion is intended as a brief overview of general strategies for the use of antifungal agents in the treatment of fungal infections. Regimens, schedules, and strategies are detailed in the chapters on specific mycoses that follow in this section. The doses cited here are standard doses for adults with invasive infection.

Since fungal organisms are eukaryotic cells that contain most of the same organelles (with many of the same physiologic functions) as human cells, the identification of drugs that selectively kill or inhibit fungi but are not toxic to human cells has been highly problematic. Far fewer antifungal than antibacterial agents have been introduced into clinical medicine.

AMPHOTERICIN B

The introduction of amphotericin B (AmB) in the late 1950s revolutionized the treatment of fungal infections in deep organs. Before AmB became available, cryptococcal meningitis and other disseminated fungal infections were nearly always fatal. For nearly a decade after AmB was introduced, it was the only effective agent for the treatment of life-threatening fungal infections. AmB remains the broadest-spectrum antifungal agent but carries several disadvantages, including significant nephrotoxicity, lack of an oral preparation, and unpleasant side effects (fever, chills, and nausea) during treatment. To circumvent nephrotoxicity and infusion side effects, lipid formulations of AmB were developed and have virtually replaced the original colloidal deoxycholate formulation in clinical use (although the older formulation is still available). The lipid formulations include liposomal AmB (L-AmB; 3–5 mg/kg per day) and AmB lipid complex (ABLC; 5 mg/kg per day). A third preparation, AmB colloidal dispersion (ABCD; 3–4 mg/kg per day), is rarely used because of the high incidence of side effects associated with infusion.

The lipid formulations of AmB have the disadvantage of being considerably more expensive than the deoxycholate formulation. Experience is still accumulating on the comparative efficacy, toxicity, and advantages of the different formulations for specific clinical fungal infections, including central nervous system (CNS) infection. Whether there is a clinically significant difference in these drugs with respect to CNS penetration or nephrotoxicity remains controversial. Despite these issues and despite the expense, the lipid formulations are now much more commonly used than AmB deoxycholate in developed countries. In developing countries, AmB deoxycholate is still preferred because of the expense of the lipid formulations.

AZOLES

This class of antifungal drugs offers important advantages over AmB: the azoles cause little or no nephrotoxicity and are available in oral formulations. Early azoles included ketoconazole and miconazole, which have been replaced by newer agents for the treatment of deep organ fungal infections. The azoles' mechanism of action is inhibition of ergosterol synthesis in the fungal cell wall. Unlike AmB, these drugs are considered fungistatic, not fungicidal.

Fluconazole Since its introduction, fluconazole has played an extremely important role in the treatment of a wide variety of serious fungal infections. Its major advantages are the availability of both oral and IV formulations, a long half-life, satisfactory penetration of most body fluids (including ocular fluid and CSF), and minimal toxicity (especially relative to that of AmB). Its disadvantages include (usually reversible) hepatotoxicity and—at high doses—alopecia, muscle weakness, and dry mouth with a metallic taste. Fluconazole is not effective for the treatment of aspergillosis, mucormycosis, or *Scedosporium apiospermum* infections. It is less effective than the newer azoles against *Candida glabrata* and *Candida krusei.*

Fluconazole has become the agent of choice for the treatment of coccidioidal meningitis, although relapses have followed therapy with this drug. In addition, fluconazole is useful as both consolidation and maintenance therapy for cryptococcal meningitis. This agent has been shown to be as efficacious as AmB in the treatment of candidemia. The effectiveness of fluconazole in candidemia and the drug's relatively minimal toxicity, in conjunction with the inadequacy of diagnostic tests for widespread hematogenously disseminated candidiasis, have led to a change in the paradigm for candidemia management. The standard of care is now to treat all candidemic patients with an antifungal agent and to change all their intravascular lines, if feasible, rather than merely removing a singular suspect intravascular line and then observing the patient. The usual fluconazole regimen for treatment of candidemia is 400 mg/d given until 2 weeks after the last positive blood culture.

Fluconazole is considered effective as fungal prophylaxis in bone marrow transplant recipients and high-risk liver transplant patients. Its general use for prophylaxis in patients with leukemia, in AIDS patients with low CD4+ T cell counts, and in patients on surgical intensive care units remains controversial. Because of concerns about the possibility of infection due to resistant *Candida* species and of infection with *Aspergillus* species, many clinicians are initiating therapy with an echinocandin, which is then replaced by fluconazole once a susceptible *Candida* species is recovered and concern about *Aspergillus* is diminished.