then be changed to itraconazole (Table 243-1). Patients who have mild symptoms can be treated from the start with itraconazole. For patients with AIDS, suppressive therapy with itraconazole is recommended until immune reconstitution (related to successful therapy for HIV infection with antiretroviral drugs) is evident. Disseminated penicilliosis is usually fatal if not treated. With treatment, the mortality rate is ~10%.

PHAEOHYPHOMYCOSES

In these common soil organisms (also called *dematiaceous* fungi), melanin causes the hyphae and/or conidia to be darkly pigmented. The term *phaeohyphomycosis* is used to describe any infection with a pigmented mold. This definition encompasses two specific syndromes—eumycetoma and chromoblastomycosis—as well as all other types of infections caused by these organisms. It is important to note that eumycetomas can be caused by hyaline molds as well as brown-black molds and that only about half of all mycetomas are due to fungi. Actinomycetes cause the remainder (Chap. 199). Most of the involved fungi cause localized subcutaneous infections after direct inoculation, but disseminated infection and serious focal visceral infections also occur, especially in immunocompromised patients.

Etiologic Agents A large number of pigmented molds can cause human infection. All are found in the soil or on plants, and some cause economically important plant diseases. The most common cause of eumycetoma is *Madurella* species. *Fonsecaea* and *Cladophialophora* species are responsible for most cases of chromoblastomycosis. Disseminated infection and focal visceral infections are caused by a variety of dematiaceous fungi; *Alternaria*, *Exophiala*, *Curvularia*, and *Wangiella* species are among the more common molds reported to cause human infection. Recently, *Exserohilum* species have caused a large outbreak of severe, sometimes fatal CNS and osteoarticular infections following the injection of methylprednisolone contaminated with this fungus.

Epidemiology and Pathogenesis Eumycetoma and chromoblastomycosis are acquired by inoculation through the skin. These two syndromes are seen almost entirely in tropical and subtropical areas and occur mostly in rural laborers who are frequently exposed to the organisms. Other infections with dematiaceous molds are acquired by inhalation, by traumatic inoculation into the eye or through the skin, or by injection of contaminated medication. Melanin is a virulence factor for all the pigmented molds. Several organisms, specifically *Cladophialophora bantiana* and *Rhinocladiella mackenziei*, are neurotropic and likely to cause CNS infection. In an immunocompromised patient or when a pigmented mold is injected directly into a deep structure, these organisms become opportunists, invading blood vessels and mimicking better-known opportunistic infections, such as aspergillosis.

Clinical Manifestations Eumycetoma is a chronic subcutaneous and cutaneous infection that usually occurs on the lower extremities and that is characterized by swelling, development of sinus tracts, and the appearance of grains that are actually colonies of fungi discharged from the sinus tract. As the infection progresses, adjacent fascia and bony structures become involved. The disease is indolent and disfiguring, progressing slowly over years. Complications include fractures of infected bone and bacterial superinfection.

Chromoblastomycosis is an indolent subcutaneous infection characterized by nodular, verrucous, or plaque-like painless lesions that occur predominantly on the lower extremities and grow slowly over months to years. There is hardly ever extension to adjacent structures, as is seen with eumycetoma. Long-term consequences include bacterial superinfection, chronic lymphedema, and (rarely) the development of squamous cell carcinoma.

Dematiaceous molds are the most common cause of allergic fungal sinusitis and a less common cause of invasive fungal sinusitis. Keratitis occurs with traumatic corneal inoculation. Even in many immunocompromised patients, inoculation through the skin generally produces localized cyst-like, nodular lesions at the entry site. However, other immunocompromised patients develop pneumonia, brain abscess, or disseminated infection. Epidural injection of *Exserohilum*-contaminated steroids has led to meningitis, basilar stroke, epidural abscess or phlegmon, vertebral osteomyelitis, and arachnoiditis.

Diagnosis The specific diagnosis of infection with a pigmented mold is established by growth of the organism in culture. However, in eumycetoma, a tentative clinical diagnosis can be made when a patient presents with a lesion characterized by swelling, sinus tracts, and grains. Histopathologic examination and culture are necessary to confirm that the etiologic agent is a mold and not an actinomycete. In chromoblastomycosis, the diagnosis rests on the histologic demonstration of sclerotic bodies (dark brown, thick-walled, septate fungal forms that resemble large yeasts) in the tissues; culture establishes which pigmented mold is causing the infection. For other infections, growth of the organism is essential to differentiate infection with a hyaline mold (e.g., *Aspergillus* or *Fusarium*) from that due to a pigmented mold. No serologic assays for pigmented molds are available. Polymerase chain reaction (PCR) assays are increasingly used in the diagnosis of infection due to pigmented molds but are available only through fungal reference laboratories.

Treatment and Prognosis Treatment of eumycetoma and chromoblastomycosis involves both surgical extirpation of the lesion and use of antifungal agents. Surgical removal of the lesions of both eumycetoma and chromoblastomycosis is most effective if performed before extensive spread has occurred. In chromoblastomycosis, cryosurgery and laser therapy have been used with variable success. The antifungal agents of choice are itraconazole, voriconazole, and posaconazole. The most experience has accrued with itraconazole; less experience has been gained with the newer azoles, which are active in vitro and have been reported to be effective in a few patients. Flucytosine and terbinafine also have been used to treat chromoblastomycosis. Chromoblastomycosis and eumycetoma are chronic indolent infections that are difficult to cure but are not life-threatening.

Disseminated and focal visceral infections are treated with the appropriate antifungal agent; the choice of agent is based on the location and extent of the infection, in vitro testing, and clinical experience with the specific infecting organism. AmB is not effective against many of these organisms but has been used successfully against others. The most experience has accrued with itraconazole in the treatment of localized infections. Voriconazole is increasingly used when infections are disseminated or involve the CNS because this drug reaches adequate concentrations within the CNS and because both IV and well-absorbed oral formulations are available. The role of posaconazole has not been established but will likely expand. Disseminated and focal visceral infections, especially those involving the CNS, are associated with high mortality rates.

OPPORTUNISTIC FUNGAL INFECTIONS

Two genera of hyaline (nonpigmented) molds, *Fusarium* and *Scedosporium*, and one yeast-like genus, *Trichosporon*, have become prominent pathogens among immunocompromised patients. Infections caused by *Fusarium* and *Scedosporium* species overlap with invasive aspergillosis in their clinical manifestations, and, when seen in tissues, these organisms appear similar to *Aspergillus*. In the immunocompetent host, these fungi cause localized infections of skin, skin structures, and subcutaneous tissues, but their role as causes of infection in immunocompromised patients will be emphasized in this section.

FUSARIOSIS

Etiologic Agent, Epidemiology, and Pathogenesis *Fusarium* species, which are found worldwide in soil and on plants, have emerged as major opportunists in markedly immunocompromised patients. Most human infections follow inhalation of conidia, but ingestion and direct inoculation also can lead to disease. An outbreak of severe *Fusarium* keratitis among soft contact lens wearers was traced back to a particular brand of contact lens solution and