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tolerated because of adverse reactions, including metallic taste, salivary gland swelling, rash, and fever. High-dose terbinafine may be effective for lymphocutaneous infection. Treatment for lymphocutaneous sporotrichosis is continued for 2–4 weeks after all lesions have resolved, usually for a total of 3–6 months. The success rate for treatment of lymphocutaneous sporotrichosis is 90–100%. Pulmonary and osteoarticular forms of sporotrichosis are treated with itraconazole for at least 1 year. Severe pulmonary infection and disseminated sporotrichosis, including that involving the CNS, should be treated initially with amphotericin B (AmB), with a switch to itraconazole after improvement has been noted. Lifelong suppressive therapy with itraconazole is often required for patients with AIDS. These forms of sporotrichosis respond poorly to antifungal therapy. ■

■ **EUMYCETOMA AND CHROMOBLASTOMYCOSIS** Etiologic Agents, Epidemiology, and Pathogenesis Dematiaceous or brown-black fungi, the common soil organisms that cause phaeohyphomycoses, contain melanin, which causes the hyphae and conidia to be darkly pigmented. The term phaeohyphomycosis is used to describe any infection with a pigmented mold. This definition encompasses two cutaneous syndromes discussed herein—eumycetoma and chromoblastomycosis—and all other types of invasive infections caused by these organisms, which are discussed in Chap. 226. It is important to note that eumycetomas can be caused by hyaline molds and by brown-black molds and that only ~50% of all mycetomas are due to fungi. Actinomycetes cause the remainder (Chap. 180). The most common cause of eumycetoma is *Madurella* species. *Fonsecaea*, *Phialophora*, and *Cladophialophora* species are responsible for most cases of chromoblastomycosis and exhibit a pathogenic muriform phase. These infections are most often seen in resource-limited rural settings and affect mostly adult men. Inoculation is via minor, often unnoticed, trauma with soil or plant material contamination. Although exposure to these pathogens is common, the development of clinical disease is infrequent. Eumycetoma is found predominantly in tropical and subtropical areas with most cases reported from Sudan, Mexico, and India. Neutrophils mediate early inflammation around the hyphae-containing grains, and macrophages form granulomas at the site of infection. Chromoblastomycosis is also prevalent in tropical and subtropical regions, with most cases reported from Latin America, Madagascar, and

China. A broader geographic distribution is seen with certain species such as *Cladophialophora carrionii*, which thrives in semiarid climates and is a chief cause of chromoblastomycosis in Australia. Following traumatic inoculation, transformation of the fungus into thickwalled, multiseptated, muriform cells ensues. These cells can evade phagocytosis, resulting in chronic disease development. Clinical Manifestations and Differential Diagnosis

Eumycetoma—commonly called Madura foot—is a chronic cutaneous and subcutaneous infection that usually occurs on the lower extremities and manifests with swelling, sinus tract development, and appearance of grains that are actually fungal colonies discharged from the sinus tract. As the infection progresses, adjacent fascia and bony structures may 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. **Diagnosis** A tentative clinical diagnosis of mycetoma 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 actinomyces. In chromoblastomycosis, the diagnosis rests on the histologic

demonstration of muriform cells or “sclerotic bodies” in tissues; culture establishes the causative pigmented mold. In culture-negative cases, PCR-based detection of the 28S ribosomal subunit or the rRNA internal transcribed spacer (ITS) may assist with identification.

Treatment and Prognosis Treatment of eumycetoma and chromoblastomycosis involves both surgical excision of lesions and antifungal therapy. Surgical removal of lesions is most effective if performed before extensive spread has occurred and is strongly recommended as a mainstay of treatment for both syndromes. In chromoblastomycosis, cryosurgery, heat therapy, and laser therapy have been used with variable success. Optimal antifungal therapy may vary depending on the causative fungal agent. Eumycetoma has been treated with itraconazole, voriconazole, posaconazole, and less commonly terbinafine with variable success rates. Long-term antifungal therapy is required, and cost or tolerability of these agents may limit their use. Itraconazole, terbinafine, and flucytosine have been used to treat chromoblastomycosis, again with variable success and with cost or tolerability limiting long-term treatment. Muriform cells may respond to antifungal therapy differently from hyphal forms, so caution is needed in interpreting in vitro susceptibility results. Species identification may be useful in determining optimal therapy, as different dematiaceous molds can differ in their susceptibilities to azoles, AmB, and flucytosine. ■

■ **FURTHER READING** Bonifaz A, Tirado-Sanchez A: Cutaneous disseminated and extra cutaneous sporotrichosis: Current status of a complex disease. *J Fungi* 3:6, 2017. Hay R: Dermatophytosis (ringworm) and other superficial mycoses, in **CHAPTER 226** Mandell, Douglas, and Bennett’s *Principles and Practice of Infectious Diseases*, 10th ed. Blaser MJ et al (eds). Philadelphia, Elsevier, 2025. Hospenthal D: Uncommon fungi and related species, in Mandell, Douglas, and Bennett’s *Principles and Practice of Infectious Diseases*, 10th ed. Blaser MJ et al (eds). Philadelphia, Elsevier, 2025. **Uncommon Disseminated Fungal Infections** Joseph Pechacek, Carol A. Kauffman,

Uncommon Disseminated

Fungal Infections ENDEMIC MYCOSES (DIMORPHIC FUNGI) Dimorphic fungi—so named for their ability to convert between mold and yeast forms (or spherules or adiaspores in the case of *Coccidioides* and *Emmonsia crescens*, respectively) in a temperature-dependent manner—are found in discrete environmental niches as molds that produce conidia, which are the infectious form. In infected tissues and at temperatures of $>35^{\circ}\text{C}$, they are found in the yeast form. The most common invasive endemic mycoses in the United States—

histoplasmosis, coccidioidomycosis, and blastomycosis—are discussed in Chaps. 218–220, respectively, and sporotrichosis is discussed in Chap. 225. ■ ■ **PARACOCCIDIOIDOMYCOSIS**
Etiologic Agent, Epidemiology, and Pathogenesis The species constituting the *Paracoccidioides brasiliensis* complex and the less frequently reported *Paracoccidioides lutzii* are thermally dimorphic fungi found in humid areas of Central and South America. The highest incidence of *Paracoccidioides* infections is seen in Brazil, Colombia, Venezuela, and Ecuador although infections have been identified as far north as Mexico. Most cases are found in an ecological niche

characterized by high rainfall and humidity and the presence of tropical or subtropical forests. A striking male-to-female ratio ranges from 14:1 to as high as 70:1 in various reports; this observation is largely accounted for by chronic disease, as the acute form of the infection lacks this stark male predominance. Most patients are middle-aged or elderly men from rural areas. *Paracoccidioidomycosis* develops after the inhalation of aerosolized conidia encountered in the environment into the lungs. In this early stage, neutrophils and macrophages play an important role in controlling the infection and preventing dissemination. Granulomas may be found in the lung and at sites of extrapulmonary dissemination in infected patients. Disease rarely develops at the time of the initial infection but appears years later, presumably after reactivation of a latent infection. Inborn errors of immunity affecting the interleukin (IL)-12/interferon (IFN)- γ signaling axis predispose to severe, disseminated *paracoccidioidomycosis*.

Clinical Manifestations The majority of patients exposed to *Paracoccidioides* develop asymptomatic pulmonary disease, which is contained and does not become clinically apparent. When clinical disease develops, two major syndromes are associated with *paracoccidioidomycosis*: the acute or juvenile form and the chronic or adult form. The acute form is uncommon, develops typically in persons <30 years old, and manifests primarily as disseminated infection of the reticuloendothelial system. The interval from initial fungal exposure to developing the acute form of *paracoccidioidomycosis* varies from as early as 45 days to as late as several months. Immunocompromised individuals also can develop this type of rapidly progressive disease. Peripheral eosinophilia is often seen in this form of the disease. The chronic form of *paracoccidioidomycosis* accounts for $\sim 90\%$ of cases and predominantly affects older men. The primary

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TABLE 226-1 Suggested Treatment for Uncommon Disseminated Fungal Infections
DISEASE FIRST-LINE THERAPY ALTERNATIVES/COMMENTS *Paracoccidioidomycosis* Chronic (adult form) Itraconazole, 100–200 mg/day for

6–12 months Voriconazole, 200 mg twice daily for 6–12 months Posaconazole, 300 mg/day for 6–12 months TMP-SMX, 160/800 mg twice daily for 12–36 months Acute (juvenile form) Lipid AmBb until improvement Itraconazole, 200 mg twice daily after AmB for 12 months Voriconazole or posaconazole at doses noted above may be used Talaromycosis Mild or moderate Itraconazole, 200 mg twice daily for

12 weeks Voriconazole, 200 mg twice daily Posaconazole 300 mg/day Severe Lipid AmBb until improvement Itraconazole, 200 mg twice daily after AmB for 12 weeks Voriconazole or posaconazole may be considered as an alternative Maintenance therapy (AIDS) Itraconazole, 200 mg/day until CD4+

T cell count is >100/μL for ≥6 months Emergomycosis (Emmonsiosis) Mild or moderate Itraconazole 200 mg twice daily for

12 weeks Voriconazole, 200 mg twice daily Posaconazole 300 mg/day Severe Lipid AmBb until improvement Itraconazole, 200 mg twice daily after AmB for 12 weeks Voriconazole or posaconazole may be considered as an alternative Phaeohyphomycosis Voriconazole, 200 mg twice daily Itraconazole, 200 mg twice daily Posaconazole, 300 mg/day Lipid AmB may be effective against some mold species Fusariosis Voriconazole, 200–300 mg twice daily Lipid AmB, 5 mg/kg/day Posaconazole, 300 mg/day Lipid AmB plus voriconazole or posaconazole is used by some physicians for initial therapy. Investigational olorofim or fosmanogepix may be considered if available. Voriconazole, 200–300 mg twice daily Posaconazole, 300 mg/day Not susceptible to AmB. *Lomentospora prolificans* is resistant to almost all commercially available antifungal drugs. Investigational olorofim or fosmanogepix may be considered if available. Scedosporiosis and lomentosporiosis Trichosporonosis Voriconazole, 200–300 mg twice daily Posaconazole, 300 mg/day aDosing should be adjusted for appropriate drug trough levels. bThe dose of lipid AmB is 3–5 mg/kg daily; the higher dose should be used when the central nervous system is involved. Abbreviations: AmB, amphotericin B; TMP-SMX, trimethoprim-sulfamethoxazole.

manifestations are progressive pulmonary disease, primarily in the lower lobes, with fibrosis and ulcerative and nodular mucocutaneous lesions that occur primarily in mucous membranes of the upper respiratory tract and that must be differentiated from leishmaniasis (Chap. 233) and squamous cell carcinoma (Chap. 82). Metastatic foci of paracoccidioidomycosis may also occur via hematogenous or lymphatic spread, most often involving the central nervous system (CNS), skin, or adrenal glands, which can lead to the development of adrenal insufficiency. Diagnosis The diagnosis is established by growth of the mold form of *Paracoccidioides* in culture at room temperature. A presumptive diagnosis can be made by detection of the distinctive thick-walled yeast in tissue biopsy specimens, which appears as a central yeast with multiple daughter cells attached circumferentially via narrow-necked buds and is classically described as a mariner's wheel. Serologic testing also can aid in diagnosis, although it should be noted that certain available tests may not detect *P. lutzii*. Treatment and Prognosis Itraconazole is the treatment of choice for paracoccidioidomycosis (Table 226-1) owing to its longer-standing experience in this disease, although voriconazole and posaconazole also are active in vitro and have been effective in small patient cohorts. Sulfonamides have been used for years and are the least costly agents; however, the response is slower and the relapse rate higher. Seriously ill patients, such as those with respiratory failure, should be initially treated with amphotericin B (AmB) with subsequent azole

therapy following clinical improvement. Patients with paracoccidioidomycosis have an excellent response to therapy, regardless of the causative species, but pulmonary fibrosis can be progressive in those with chronic disease.

■ ■ **TALAROMYCOSIS** Etiologic Agent, Epidemiology, and Pathogenesis *Talaromyces marneffei* (formerly *Penicillium marneffei*) is a thermally dimorphic fungus that is endemic in the soil in certain areas of Vietnam, Thailand, and other southeastern Asian countries. The epidemiology of talaromycosis (formerly penicilliosis) is linked to bamboo rats that are infected with the fungus but rarely manifest disease. The disease occurs most often among persons living in rural areas in which the rats are found, but there is no evidence for transmission of the infection directly from rats to humans. Accidental laboratory inoculation has also been reported. Infection is rare in immunocompetent hosts, and most cases are reported in persons who have advanced AIDS. Other immune deficiencies associated with a higher risk of developing talaromycosis include corticosteroid use, solid organ transplantation, idiopathic CD4 lymphocytopenia, inborn errors of immunity affecting the IL-12/IFN- γ signaling axis, and neutralizing autoantibodies against IFN- γ . Infection is presumed to result from the inhalation of conidia from the environment though a definitive environmental reservoir that has yet to be identified. The organism converts to the yeast phase in the lungs and then spreads hematogenously throughout the reticuloendothelial system. IFN- γ -primed monocytes/macrophages and neutrophils both play a role in control of *Talaromyces* via fungal phagocytosis and killing. Clinical Manifestations The clinical manifestations of talaromycosis mimic those of disseminated histoplasmosis and include fever, fatigue, weight loss, dyspnea, lymphadenopathy, hepatosplenomegaly, and mucocutaneous lesions, which appear as papules that often umbilicate and resemble molluscum contagiosum (Chap. 201). Patients with mild talaromycosis may present with isolated skin lesions. Diagnosis Talaromycosis is diagnosed by culture of *T. marneffei* from blood or from biopsy samples of skin, bone marrow, or lymph node. The organism usually grows within 1 week as a mold producing a distinctive red pigment that diffuses into the agar. Histopathologic examination of tissues, blood smears, or material from skin lesions shows oval or elliptical yeast-like organisms that reproduce via bipolar fission (i.e., appearing as two elliptical yeasts separated by a central septation) and can quickly establish a presumptive diagnosis. Intramacrophage yeast-like organisms can also be seen on tissue or lymph node sections or bone marrow aspirates. *T. marneffei*-specific antigen and polymerase chain reaction (PCR)-based assays are under investigation. Treatment and Prognosis Disseminated talaromycosis is usually fatal if not treated. With treatment, the mortality rate is ~10%. For mild or moderate infection, itraconazole is the drug of choice. Voriconazole also can be used, and posaconazole has good in vitro activity and has been successfully used in few case reports. Severe infection should be treated with AmB until clinical improvement occurs; then therapy can be changed to an effective triazole (Table 226-1). For patients with AIDS, suppressive therapy with itraconazole is recommended until the CD4⁺ T cell count has been >100 cells/ μ L for at least 6 months. Primary prophylaxis may be considered in certain patients with AIDS in endemic areas who are unable to receive effective antiretroviral therapy. ■ ■ **EMERGOMYCOSIS (DISSEMINATED EMMONSIOSIS)** Etiologic Agents, Epidemiology, and Pathogenesis As the name implies, *Emergomyces* (several members of which are formerly of the genus *Emmonsia*) is a genus of emerging thermally dimorphic fungi consisting of seven species, six of which have been shown to cause human disease. Among them, *E. pasteurianus* is the most geographically widespread species, and *E. africanus* has been the most studied given its relatively high incidence of infection in South Africa. Infection by *Emergomyces* species have now been reported in Europe, Asia

(primarily in China and India), Africa (Uganda and South Africa), and North America (United States and Canada). Although *Emergomyces* has yet to be cultured from the environment and no animal

reservoir has been identified thus far, infection is thought to begin, as with other dimorphic fungi, through inhalation of conidia released by the mold form of the pathogen in the environment. The organism then undergoes temperature-dependent transformation into the invasive yeast form within the lungs and disseminates hematogenously to cause systemic disease in immunocompromised patients. Clinically apparent disease appears largely restricted to patients with impaired cellular immunity, including those with AIDS, hematologic malignancy, or solid organ transplantation, and recipients of immunosuppressive therapy such as corticosteroids.

Clinical Manifestations Pulmonary disease can manifest with parenchymal lesions and/or endobronchial lesions. Although isolated lung involvement has been described, the vast majority of patients with pulmonary disease have concomitant cutaneous involvement, which most frequently manifests with disseminated ulcers, papules, or nodules. Dissemination to the liver, bone marrow, and lymph nodes may also occur, whereas dissemination to the CNS is rare. **Diagnosis** Diagnosis is made by culturing *Emergomyces* species from blood or tissue or by showing tissue invasion upon histologic examination. *Emergomyces* may grow from aerobic blood culture bottles within 7 days; the use of fungal isolator culture bottles may improve sensitivity. The yeast form appears on histopathology as intracellular and extracellular round or ovoid yeasts with narrow-based budding that may be misidentified as *Histoplasma capsulatum*; therefore, definitive identification is made on mold phase in culture. It is worth noting that the commercially available *Histoplasma* antigen test has a high degree of cross-reactivity with *Emergomyces* species. **CHAPTER 226 Treatment and Prognosis** Given the lack of clinical trials to guide optimal treatment of emergomycosis, treatment recommendations are currently based on expert opinion and largely mirror treatment recommendations for disseminated histoplasmosis. Immunosuppressed patients with emergomycosis should initiate treatment with AmB until clinical improvement occurs followed by therapy with a mold-active azole. Itraconazole is the azole most often used, although in vitro susceptibility testing results of voriconazole and posaconazole have been favorable. In case reports, itraconazole monotherapy has been used successfully for mild disease. Prolonged secondary prophylaxis may be considered in patients without a reversible cause of immunodeficiency. **Uncommon**

Disseminated Fungal Infections ■ ■ ADIASPIROMYCOSIS Adiaspiromycosis is a rare infection caused predominantly by the mold *Emmonsia crescens*, which is found in soil. Occupational dust exposure is a major risk factor. Human infections have been broadly reported including from the Americas, Europe, and Asia. The lungs are by far the most frequently affected organ, although cases of ocular and appendiceal disease have been described. The disease is defined by the presence of adiaspores in affected tissue, which results in a marked inflammatory response. After exposure to conidia via inhalation, ingestion, or mucosal contact with dust, the host mounts an immune response leading to the development of noncaseating granulomas. Once within host tissue and driven by thermal pressure, the conidia enlarge to thick-walled adiaspores measuring up to 500 µm in diameter that are incapable of budding or replication. Clinical sequelae, including respiratory failure, are caused by the host's granulomatous inflammatory response in infected tissue. As *E. crescens* has not been cultured from human tissue with adiaspiromycosis, diagnosis depends upon histopathologic identification of adiaspores with surrounding granulomas, often with the assistance of molecular methods. The disease is often self-limiting. However, in severe disease, corticosteroids, with or without antifungal therapy, have been used successfully in several

reports. **MOLD INFECTIONS** Molds produce conidia or spores, which cause infection via inhalation or traumatic skin inoculation. In infected tissues, filamentous structures termed hyphae form. The most common invasive mold infections—aspergillosis and mucormycosis—are discussed

in Chaps. 223 and 224, respectively. Dematiaceous or brown-black molds cause phaeohyphomycoses that can be either localized or disseminated infections, the latter mostly in immunocompromised patients. Three genera of hyaline (nonpigmented) molds, *Fusarium*, *Scedosporium*, and *Lomentospora*, have become prominent pathogens among immunocompromised patients. Infections with these fungi mimic aspergillosis in their clinical manifestations and their histopathologic appearance in tissues.

■ ■ **PHAEOHYPHOMYCOSES** Dematiaceous or brown-black fungi cause phaeohyphomycoses. The term phaeohyphomycosis is used to describe any infection with a melanin-producing fungus with filamentous growth. Melanin is a virulence factor for all pigmented molds. Most dematiaceous fungi cause localized subcutaneous infections after direct inoculation. Disseminated infections and serious focal visceral infections can occur in immunocompetent individuals but are much more often seen in immunocompromised patients. Two specific cutaneous phaeohyphomycoses—*eumycetoma* and *chromoblastomycosis*—are discussed in Chap. 225.

Etiologic Agents, Epidemiology, and Pathogenesis A large number of genera and species of pigmented molds can cause human infection. Most are found in the soil or on plants, and some cause economically important plant diseases. *Alternaria*, *Exophiala*, *Curvularia*, *Cladophialophora*, *Bipolaris*, and *Wangiella* species are among the more common pigmented molds reported to cause human infection. Infections with dematiaceous molds are acquired by traumatic inoculation into the eye or through the skin, by inhalation, or by injection of contaminated medication. In 2012, *Exserohilum* species caused a large outbreak in the United States of severe—and in some patients fatal—infections of the CNS following the injection of methyl prednisolone contaminated with this fungus. Subcutaneous infections follow traumatic inoculation and are frequently caused by *Curvularia*, *Exophiala*, and *Phialophora*, among other genera. Several organisms, specifically *Cladophialophora bantiana* and *Rhinocladiella mackenziei*, are neurotropic and likely to cause CNS infection. When a patient is immunocompromised or when a pigmented mold is injected directly into a deep structure, these organisms become opportunistic pathogens, invading blood vessels and mimicking better-known opportunistic infections, such as aspergillosis.

PART 5 Infectious Diseases Disseminated phaeohyphomycosis may occur in patients with solid organ or hematopoietic stem cell transplantation or after corticosteroid use. It has also been described in patients with autosomal recessive deficiency in *CARD9*, an intracellular adaptor protein that relays fungus-sensing signals from multiple cell-surface C-type lectin receptors (CLRs). A recent report indicated that ~70% of putatively immunocompetent patients who developed disseminated and brain phaeohyphomycosis carried deleterious variants in *CLEC7A*, the gene that encodes for the *CARD9*-coupled CLR Dectin-1, which recognizes fungal cell wall β -glucan. Dectin-1 and *CARD9* protect against this infection by mediating the production of proinflammatory cytokines in response to fungal infection, promoting macrophage fungal killing.

Clinical Manifestations 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 only localized nodular lesions at the entry site. Other immunocompromised patients develop pneumonia, brain abscess, or disseminated infection. Patients with brain abscess often have no other signs of

dissemination at the time of diagnosis and typically present with an indolent course. Certain species, such as *Cladophialophora bantiana*, exhibit a propensity for intraventricular spread within the CNS. In the *Exserohilum* outbreak mentioned above, epidural injections of fungus-contaminated gluco corticoids led to meningitis, basilar stroke, epidural abscess and phleg mon, vertebral osteomyelitis, and arachnoiditis. **Diagnosis** The specific diagnosis of infection with a pigmented mold is established by growth of the organism in culture. Histologically,

FIGURE 226-1 Histologic stains revealing pigmented mold from brain biopsy of a man with multifocal brain lesions. Cultures grew *Cladophialophora bantiana*. Images show tissue stained with hematoxylin and eosin (left panel) showing goldenbrown pigmented hyphae (arrow) within multinucleated giant cells and associated neutrophilic infiltrate and Fontana-Masson stain (right panel) highlighting the melanin found in the cell wall of this organism. Scale bars, 20 μ m. (Images taken by Dr. Stefania Pittaluga, NCI.) observation of melanized hyphal forms appearing golden-brown on biopsy specimens stained with hematoxylin and eosin supports the diagnosis of phaeohyphomycosis. Specialized melanin stains, such as the Fontana-Masson stain, highlight melanized fungal structures in infected tissues and provide important diagnostic support (Fig. 226-1). PCR assays are increasingly used in the diagnosis of infection due to dematiaceous molds but are available only through fungal reference laboratories. **Treatment and Prognosis** Surgical debridement is vital for the treatment of phaeohyphomycosis in addition to antifungal treatment, which may need to be prolonged, especially in patients with CNS involvement. The choice of antifungal agent to treat disseminated and focal visceral infections with brown-black molds is based on the loca tion and extent of the infection, in vitro test results, and clinical experi ence with the specific infecting organism. AmB is not effective against many of these organisms but has been used successfully against some species (Table 226-1). Itraconazole, voriconazole, or posaconazole can be used in the treatment of localized infections. Voriconazole has been the preferred azole when infections involve the CNS because it reaches adequate concentrations at that anatomic site; recent reports support posaconazole as an alternative azole. For certain pigmented molds, such as *C. bantiana*, flucytosine may have a role in addition to AmB or an azole. Disseminated and focal visceral infections, especially those involving the CNS, are associated with high mortality rates. ■

■ **FUSARIOSIS** Etiologic Agent, Epidemiology, and Pathogenesis *Fusarium* species, which are found worldwide in soil and on plants, have emerged as major opportunistic pathogens in markedly immunocompromised patients. Strains of the *F. solani* complex are most commonly respon sible for human infections, followed by *F. oxysporum*, *F. proliferatum*, and other species. *Fusarium* are molds with distinctive banana-shaped macroconidia. While *Fusarium* keratitis and onychomycosis can occur in immunocompetent patients, disseminated disease develops in immunodeficient patients. An outbreak of severe *Fusarium* keratitis among soft contact lens wearers was traced back to a particular brand of contact lens solution and individual contact lens cases that had been contaminated with this mold. In 2022 and 2023, two separate outbreaks of *F. solani* meningitis were reported in previously healthy young women who had received epidural anesthesia for plastic surgery proce dures at two private clinics in Mexico. The case-fatality rate was ~50%. Disseminated infection is reported most often in patients who have a hematologic malignancy, are neutropenic, have received hemato poietic stem cell or solid organ transplantation or corticosteroids, or have severe burn wounds. Neutrophils are the most critical cells for protection against fusariosis; hence the correlation with profound and prolonged neutropenia and susceptibility to disseminated infec tion. Neutrophil-derived reactive oxygen species are partly respon sible for effective host defense against *Fusarium*. Patients with chronic granulomatous

disease (CGD), who carry deleterious mutations in the NADPH oxidase complex that impair the phagocyte oxidative burst,

are at risk for fusariosis, albeit with far lower frequency compared with aspergillosis. Several studies have shown that the prognosis of fusariosis in neutropenic patients is significantly improved in those who recovered their neutrophil counts relative to those who remained persistently neutropenic. Exposure to *Fusarium* can be through inhalation of conidia or direct inoculation via trauma, but disseminated disease can also occur secondary to pre-existing local disease, such as sinusitis or onychomycosis. For example, the presence of *Fusarium* onychomycosis preceding allogeneic hematopoietic stem cell transplantation has been associated with a higher risk of developing disseminated fusariosis post-transplantation. Clinical Manifestations In immunocompetent persons, *Fusarium* species cause localized infections of various organs. These organisms are a common cause of fungal keratitis, which can extend into the anterior chamber of the eye, cause loss of vision, and require corneal transplantation. Onychomycosis due to *Fusarium* species, while a potential source of discomfort in immunocompetent patients, is a source of subsequent hematogenous dissemination and should be aggressively sought and treated in neutropenic patients. In profoundly immunocompromised patients, fusariosis is angioinvasive, and clinical manifestations mimic those of aspergillosis. Pulmonary infection is characterized by multiple nodular lesions that are best identified on CT scan. Fusariosis typically presents with persistent fever in neutropenic patients despite the administration of broad-spectrum antibiotics. Disseminated fusariosis differs from disseminated aspergillosis in that skin lesions are extremely common with fusariosis and may develop shortly after or even concurrently with the development of fever; the lesions are nodular or necrotic, are usually painful, and may appear over time in different locations (Fig. 226-2). Diagnosis The diagnostic approach usually includes both documentation of the growth of *Fusarium* species from involved tissue and demonstration of invasion by histopathologic techniques that show acute angle septate hyphae in tissues. The organism is difficult to differentiate from *Aspergillus* species in tissues; therefore, identification with culture is imperative. An extremely helpful diagnostic clue is growth in blood cultures, which are positive in as many as 50% of patients with disseminated fusariosis. A positive blood culture may lead to rapid identification; subsequent rapid growth on agar reveals the characteristic banana-shaped macroconidia of *Fusarium*. Further identification of the species and antimicrobial susceptibility testing, generally in a reference laboratory, may aid in choosing the most appropriate therapy. Treatment and Prognosis *Fusarium* species are resistant to many antifungal agents. A lipid formulation of AmB, voriconazole, or posaconazole is recommended. Many physicians use both a lipid FIGURE 226-2 Painful necrotic foot lesion that developed over a week in a woman with acute leukemia who had been neutropenic for 2 months. *Fusarium* species grew from a punch biopsy. (Courtesy of Dr. Nessrine Ktaich.)

formulation of AmB and either voriconazole or posaconazole because susceptibility information is not standardized and is not always predictive of clinical response, bearing in mind that the prognosis is largely dictated by the degree of immune restoration. *F. solani* complex is frequently resistant to all azoles, while other species may have lower minimum inhibitory concentrations (MICs) to voriconazole and posaconazole. AmB is the most active antifungal drug against *Fusarium*; however, the MICs are relatively high for these organisms compared with other molds (Table 226-1). Mortality rates for disseminated fusariosis can be as high as 85%, with survival dependent on reversal of neutropenia. With the improved antifungal therapy now available, mortality rates

have fallen to ~50%. However, if neutropenia persists, the mortality rate approaches 100%.

Two newer investigational antifungal agents show promise for the treatment of fusariosis. Fosmanogepix, which inhibits fungal Gwt1 and glycosylphosphatidylinositol-mannoprotein synthesis and anchoring, exhibits in vitro activity against *F. solani*, including against strains that are resistant to all available antifungals; it has been reported to successfully treat a few patients with meningeal and disseminated fusariosis. Olorofim, which inhibits fungal dihydroorotate dehydrogenase and pyrimidine synthesis, has shown favorable, but strain-specific, activity against *F. solani* complex in vitro. ■ ■ SCEDOSPORIOSIS AND LOMENTOSPORIOSIS Etiologic Agent, Epidemiology, and Pathogenesis *Scedo sporium apiospermum* complex, which is composed of several related species, is reported more often as a cause of human infection than *Lomentospora prolificans*, formerly *Scedosporium prolificans*, but both are major emerging opportunistic pathogens in immunocompromised hosts and can cause pneumonia, disseminated infection, and brain abscess. Organisms of the *S. apiospermum* complex are found worldwide in temperate climates in tidal flats, swamps, ponds, manure, and soil. *L. prolificans* is also found in soil but is more geographically restricted with a greater representation of reported infections from Australia and Spain. Infection occurs predominantly through inhalation of conidia, but direct traumatic inoculation through the skin or the eye can also occur. *S. apiospermum* infections of the lungs and CNS have been described in putatively immunocompetent patients following near-drowning accidents, likely owing to the associated heavy burden of fungal exposure from contaminated water. CHAPTER 226 Uncommon Disseminated Fungal Infections Clinical Manifestations Among immunocompetent persons, *Scedosporium* and *Lomentospora* species are a prominent cause of eumycetoma (Chap. 225). Keratitis resulting from accidental corneal inoculation is a sight-threatening infection. Traumatic inoculation during accidents may also lead to deep-seated infections, such as osteoarticular infections including septic arthritis, in immunocompetent patients. In patients who have hematologic malignancies, especially those with acute leukemia and prolonged neutropenia, recipients of solid organ or hematopoietic stem cell transplants, CGD patients, and patients receiving corticosteroids, these organisms are angioinvasive and can cause pneumonia and extrapulmonary dissemination, with a propensity for CNS spread. Pulmonary infection mimics that of aspergillosis both clinically and in appearance on CT scan: nodules, cavities, and lobar infiltrates are common radiographic findings. Contiguous spread from the lung to adjacent anatomic sites, such as the vertebrae, has rarely been described. Disseminated infection often involves the heart, brain, and many other organs. Skin lesions are not as common or as painful as those in patients with fusariosis. Diagnosis Diagnosis depends on the growth of *Scedosporium* or *Lomentospora* species from infected tissue and the histologic demonstration of acute-angle septate hyphae invading tissues. Culture evidence is essential because these molds are difficult to morphologically differentiate from *Aspergillus* in tissues. Demonstration of tissue invasion is essential because these ubiquitous environmental molds can be mere contaminants or colonizers in the respiratory tract, especially in persons with bronchiectasis. As with *Fusarium*, *L. prolificans* can grow in blood cultures, but *S. apiospermum* usually does not.