The optimal dosages for antifungal treatment of mucormycosis are not known. Starting dosages of 1 mg/kg per day for AmB deoxycholate and 5 mg/kg per day for LAmB and ABLC are commonly given to adults and children. Dose escalation of LAmB to 7.5 or 10 mg/kg per day for CNS mucormycosis may be considered in light of the limited penetration of polyenes into the brain. Because of auto-induction of metabolism, which results in paradoxically lower drug levels, there is no advantage to escalating the LAmB dose above 10 mg/kg per day, and doses of 5 mg/kg per day are probably adequate for non-CNS infections. ABLC dose escalation above 5 mg/kg per day is not advisable given the lack of relevant data and the drug's potential toxicity.

Echinocandin–lipid polyene combinations improved survival rates among mice with disseminated mucormycosis (including CNS disease) and were associated with significantly better outcomes than polyene monotherapy in a small retrospective clinical study involving patients with rhino-orbital-cerebral mucormycosis. Although combination therapy may be considered on the basis of these limited data sets, definitive clinical trials are needed to establish whether it offers any real advantage over monotherapy for mucormycosis. Echinocandins should be administered at standard, FDA-approved doses, since dose escalation has resulted in paradoxical loss of efficacy in preclinical models.

In contrast to deferoxamine, the iron chelator deferasirox is fungicidal against clinical isolates of the Mucorales. In mice with DKA and disseminated mucormycosis, combination deferasirox-LAmB therapy resulted in synergistic improvement of survival rates and reduced the fungal burden in brain. Unfortunately, a randomized, double-blind, phase 2 safety clinical trial of adjunctive therapy with deferasirox (plus LAmB) documented excess mortality in the patients treated with deferasirox. It is noteworthy that the study population included primarily patients with active malignancy, and few patients in the study had diabetes mellitus as their only risk factor. Deferasirox is therefore contraindicated as therapy in patients with active malignancy, but its role in patients who have diabetes mellitus without malignancy (the setting in which its preclinical efficacy was optimal) remains uncertain.

Posaconazole is the only FDA-approved azole with in vitro activity against the Mucorales. However, pharmacokinetic/pharmacodynamic data raise concerns about the reliability with which adequate in vivo levels of orally administered posaconazole are attained. Furthermore, posaconazole is inferior in efficacy to AmB for the treatment of murine mucormycosis and is not superior to placebo for treatment of murine infection with *R. oryzae*. Moreover, posaconazole-polyene combination therapy is not superior to polyene monotherapy for mucormycosis in mice, and no comparative data are available for combination therapy in humans.

The roles of recombinant cytokines and neutrophil transfusions in the primary treatment of mucormycosis are not clear, although it is intuitive that earlier recovery of neutrophil counts should improve survival rates. Limited data indicate that hyperbaric oxygen may be useful in centers with the appropriate technical expertise and facilities.

In general, antifungal therapy for mucormycosis should be continued until resolution of clinical signs and symptoms of infection and resolution of underlying immunosuppression. For patients with mucormycosis who are receiving immunosuppressive medications, secondary antifungal prophylaxis is typically continued for as long as the immunosuppressive regimen is administered.

The role of radiographic follow-up in determining prognosis and therapeutic duration is being studied. Analysis of data from the phase 2 DEFEAT Mucor study indicated that early radiographic progression (within the first 2 weeks) did not predict long-term mortality risk, nor did early radiographic stability/regression predict long-term survival. Therefore, caution should be used in reacting to short-term, serial radiographic results, and greater emphasis should be placed on clinical response, particularly within the first 2–4 weeks after initiation of therapy.

243 Superficial Mycoses and Less Common Systemic Mycoses

Carol A. Kauffman

ENDEMIC MYCOSES (DIMORPHIC FUNGI)

Dimorphic fungi exist in discrete environmental niches as molds that produce conidia, which are their infectious form. In tissues and at temperatures of >35°C, the mold converts to the yeast form. **Other endemic mycoses—histoplasmosis, coccidioidomycosis, and blastomycosis—are discussed in Chaps. 236, 237, and 238, respectively.**

SPOROTRICHOSIS

Etiologic Agent *Sporothrix schenckii* is a thermally dimorphic fungus that is found worldwide in sphagnum moss, decaying vegetation, and soil.

Epidemiology and Pathogenesis Sporotrichosis most commonly infects persons who participate in outdoor activities such as landscaping, gardening, and tree farming. Infected animals can transmit *S. schenckii* to humans. An outbreak of sporotrichosis in Rio de Janeiro that began in 1998 and that has involved >2000 people has been traced to cats, which are highly susceptible to this infection. Sporotrichosis is primarily a localized infection of skin and subcutaneous tissues that follows traumatic inoculation of conidia. Osteoarticular sporotrichosis is uncommon, occurring most often in middle-aged men who abuse alcohol, and pulmonary sporotrichosis occurs almost exclusively in persons with chronic obstructive pulmonary disease who have inhaled the organism from the environment. Dissemination occurs rarely, almost always in markedly immunocompromised patients, especially those with AIDS.

Clinical Manifestations Days or weeks after inoculation, a papule develops at the site and then usually ulcerates but is not very painful. Similar lesions develop sequentially along the lymphatic channels proximal to the original lesion (Fig. 243-1). Some patients develop a fixed cutaneous lesion that can be verrucous or ulcerative and that remains localized without lymphatic extension. The differential diagnosis of lymphocutaneous sporotrichosis includes nocardiosis, tularemia, nontuberculous mycobacterial infection (especially that due to *Mycobacterium marinum*), and leishmaniasis. Osteoarticular sporotrichosis can present as chronic synovitis or septic arthritis. Pulmonary sporotrichosis must be differentiated from tuberculosis and from other fungal pneumonias.

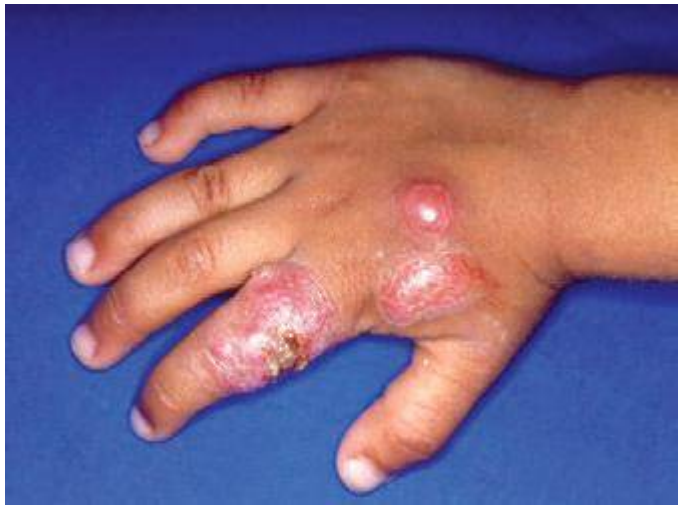

FIGURE 243-1 **Several nodular lesions** that developed after a young boy pricked his index finger with a thorn. A culture yielded *S. schenckii*. *(Courtesy of Dr. Angela Restrepo.)*