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therapy with deferasirox (plus LAmB) documented excess mortality among patients treated with deferasirox. Of note, the study popula tion 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 melli tus without malignancy (the setting in which its preclinical efficacy was optimal) remains uncertain.

Posaconazole and isavuconazole are the only FDA-approved azoles with reliable in vitro activity against the Mucorales. However, there are limited data regarding the efficacy of posaconazole mono therapy for mucormycosis, and in contrast to polyene-echinocandin therapy, no data support the use of combination posaconazolepolyene regimens. Although the minimal inhibitory concentra tions (MICs) of isavuconazole against the Mucorales are four- to eightfold higher than those of posaconazole, blood levels may be higher with standard isavuconazole dosing than with posaconazole. Isavuconazole is FDA-approved for the treatment of mucormycosis based on a small, historically controlled study. Given this limited dataset, many experts continue to think that lipid polyenes are first-line options and that isavuconazole, like posaconazole, is best reserved for oral transitional therapy in patients whose condition has substantially improved on polyene-based therapy, or for salvage therapy in patients who are intolerant of polyene-based regimens or whose infection is refractory to these regimens. No studies in mice or humans have ever shown benefit of add ing posaconazole to another antifungal agent for combination therapy of mucormycosis. In contrast, in mice, a combination of isavuconazole plus polyene regimens did prolong survival time and lowered tissue fungal burden compared to monotherapy. However, this combination has not been studied compared to monotherapy in people. Some experts use triple therapy with a polyene, echino candin, and either posaconazole or isavuconazole for patients who have extensive disease or whose disease has progressed on prior therapy. Empirical, dual lipid polyene–azole therapy is a rational choice in a patient with likely invasive mold infections when septate molds and mucormycosis are both in the differential diagnosis and the etiologic agent has not yet been confirmed. Alternatively, initial therapy with isavuconazole monotherapy may be reasonable for a brief period of time in a stable patient if mucormycosis is felt to be possible but less likely than a septated mold infection. PART 5 Infectious Diseases 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 from uncontrolled case series have described the use of hyperbaric oxygen in centers with the

appropriate technical expertise and facilities; its efficacy remains undefined. As mentioned previously, one study in mice with DKA found that administration of sodium bicarbonate improved survival from mucormycosis; however, because insulin was not adminis tered to the mice, it is unclear whether the therapeutic effect is clinically relevant. In general, antifungal therapy for mucormycosis should be con tinued until resolution of clinical signs and symptoms of infec tion and resolution of underlying immunosuppression. However, after a week or two of daily therapy in a patient who is clinically improving, it is reasonable to consider switching to thrice-weekly lipid polyene doses—with ultimate weaning down to twice-weekly doses—for maintenance therapy. For patients with mucormyco sis who are receiving immunosuppressive medications, second ary antifungal prophylaxis is typically continued for as long as the immunosuppressive regimen is administered. Transitioning to azoles for chronic suppression is a reasonable alternative to continuing polyene therapy in this setting, with re-initiation of polyenes during periods of deep neutropenia. One common source of error in the long-term management of mucormycosis is follow-up radiology. Analysis of data from the DEFEAT Mucor study indicated that early radiographic progres sion (within the first 2 weeks) did not predict long-term mortality.

Changing the therapeutic plan based on early radiographic changes can result in therapeutic errors. For example, it is common for CNS Mucorales to cavitate in the brain parenchyma over time. This does not necessarily reflect therapeutic failure, but rather may reflect increased immune reactivity to the fungus, particularly in patients recovering from neutropenia or with removal of immune suppres sion. Thus, it may not be advisable to obtain serial radiographic studies in the short-term, and if such studies are obtained, caution should be used in reacting to their results. Greater emphasis should be placed on clinical response, particularly within the first 2–4 weeks after initiation of therapy. ■ ■PROGNOSIS Over the past two decades, the prognosis of mucormycosis has sub stantially improved with aggressive antifungal therapy. Even CNS infection is often successfully treated. As mentioned, the key driver of outcome may be control of the patient’s predisposing condition. ■ ■FURTHER READING Alqarihi A et al: Mucormycosis in 2023: An update on pathogenesis and management. Front Cell Infect Microbiol 13:1254919, 2023. Baldin C, Ibrahim AS: Molecular mechanisms of mucormycosis: The bitter and the sweet. PLoS Pathog 13:e1006408, 2017. Cornely O et al: Global guideline for the diagnosis and management of mucormycosis: An initiative of the ECMM in cooperation with ESCMID/EFISG. Lancet Infect Dis 19:e405, 2019. Danion F et al: What is new in pulmonary mucormycosis? J Fungi (Basel) 9:307, 2023. Pettrikos G et al: Epidemiology of mucormycosis in Europe. Clin Microbiol Infect 20:67, 2014. Joseph Pechacek, Carol A. Kauffman,

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Superficial Fungal

Infections Fungal infections of the skin and skin structures are caused by molds and yeasts that do not invade deeper tissues but rather cause disease merely by inhabiting the superficial layers of skin, hair follicles, and nails. These agents cause the most common human fungal infections but only rarely cause serious infections. ■ ■MALASSEZIA INFECTIONS Etiologic Agents, Epidemiology, and Pathogenesis Malassezia species, primarily M. furfur and M. pachydermatis, are lipophilic yeasts that generally cause only minor skin infections but, on occasion, can cause invasive infection. Malassezia species are part of the indigenous human microbiota found in the stratum

corneum of the back, chest, scalp, and face—areas rich in sebaceous glands. The organisms do not invade below the stratum corneum and generally elicit little inflam mation. Cutaneous interleukin (IL)-17 signaling controls Malassezia species in the skin, but excessive, Malassezia-induced IL-17 responses have been associated with exacerbating atopic inflammation. Clinical Manifestations Malassezia species cause tinea versicolor (also called pityriasis versicolor), folliculitis, and seborrheic dermati tis. Tinea versicolor presents as flat round scaly patches of hypo- or hyperpigmented skin on the neck, chest, or upper arms. The lesions are usually asymptomatic but can be pruritic. They can be mistaken

for vitiligo, but the latter is not scaly. Folliculitis occurs on the back and chest and mimics bacterial folliculitis. Seborrheic dermatitis manifests as erythematous pruritic scaly lesions in the eyebrows, moustache, nasolabial folds, and scalp (dandruff). Seborrheic dermatitis can be severe in patients with AIDS. Fungemia and disseminated infection occur rarely with Malassezia species, and they almost always occur in premature neonates receiving parenteral lipid nutrition preparations. Diagnosis Malassezia infections are diagnosed clinically in most cases. If scrapings are collected on a microscope slide on which a drop of potassium hydroxide has been placed, a mixture of budding, bottleshaped yeasts and short septate hyphae is seen. To culture Malassezia from patients with suspected disseminated infection, sterile olive oil must be added to the medium. Treatment and Prognosis Topical creams and lotions, includ ing selenium sulfide shampoo, ketoconazole shampoo or cream, and terbinafine cream, are effective in treating Malassezia infections and are usually given for 2 weeks. Mild topical steroid creams are some times used to treat seborrheic dermatitis. For extensive disease, oral itraconazole or fluconazole (200 mg/day) can be used for 5–7 days. The rare cases of fungemia caused by Malassezia species are treated with amphotericin B (AmB) or an azole, such as voriconazole, prompt removal of central catheters, and discontinuation of parenteral lipid infusions. Malassezia skin infections are benign and self-limited, although recurrences are common. The outcome of systemic infec tion depends on the host’s underlying conditions, but most infected neonates do well. ■ ■MUCOCUTANEOUS CANDIDA INFECTIONS Candidiasis is discussed in Chap. 222, and this section briefly describes mucocutaneous manifestations of candidiasis. Etiologic Agents, Epidemiology, and Pathogenesis The most common species responsible for mucocutaneous candidiasis—e.g., oral thrush, esophageal candidiasis, vulvovaginal candidiasis (VVC)—is Candida albicans. Candida species are commensal organisms residing primarily in the oral mucosa, gastrointestinal tract, and genitourinary tract with the skin being colonized in certain settings, such as after antibiotic use in the intensive care unit or by certain species such as C. parapsilosis or C. auris. C. auris is an emerging multidrug-resistant spe cies with a propensity for long-term colonization of the human skin, health care environments, and medical devices and for causing noso comial outbreaks. C. auris grows avidly in human sweat and colonizes deep skin layers including hair follicles. IL-17–producing lymphoid cells at mucocutaneous barrier sites such as TH17 cells, γδ T cells, and innate lymphoid cells mediate control against Candida. Risk factors for oral thrush include inherited and pharmacologic defects of IL-17 signaling, AIDS, and conditions with excessive mucosal interferon γ responses such as autoimmune polyendocrine syndrome type 1. Antibiotic use, diabetes, and pregnancy are major risk factors for VVC. Skin candidiasis is uncommon and most often seen in inborn errors of immunity that cause chronic mucocutaneous candidiasis, primarily STAT1 gain-of-function. Diagnosis Diagnosis of oral thrush is generally clinical with white mucosal plaques that are removed with gentle scraping. Culture reveals the responsible Candida species. Biopsy of affected tissue may be needed to differentiate thrush from mimics such as leukoplakia. Biopsy of affected oral or esophageal tissue shows yeasts,

pseudohyphae, and hyphae invading into the epithelium; observing only yeast forms super ficial to epithelial tissue usually represents solely colonization. VVC is diagnosed with culture and microscopy of vaginal secretions collected via swabs. Skin and nail candidiasis is diagnosed by skin biopsy or nail clippings with culture and microscopy. Treatment and Prognosis Mild oral thrush may be treated with topical agents such as nystatin suspension or clotrimazole troches, but moderate and severe disease or esophageal involvement should be treated with systemic, primarily azole therapy. VVC may be treated with topical or oral azoles. Newer options for VVC include the

triterpenoid antifungal ibrexafungerp, which inhibits β-glucan, and oteseconazole, a long-acting tetrazole that cannot be used in patients of reproductive potential owing to potential fetal ocular toxicity.

■ ■DERMATOPHYTE INFECTIONS Etiologic Agents, Epidemiology, and Pathogenesis The molds that cause skin infections in humans include the genera Tricho phyton, Microsporum, and Epidermophyton. These organisms, which are not components of the normal skin microbiota, can live within the keratinized structures of the skin—hence the term dermatophytes. Dermatophytes occur worldwide, and infections with these organisms are extremely common with an estimated ~1 billion people affected globally. Some organisms cause disease only in humans and can be transmitted by person-to-person contact and by fomites, such as hairbrushes or wet floors, that have been contaminated by infected individuals. Several species cause infections in cats and dogs and can readily be transmitted from these animals to humans, and others are spread from contact with soil. The characteristic ring shape of cutane ous lesions is the result of the organisms' outward growth in a cen trifugal pattern in the stratum corneum. Fungal nail invasion usually occurs through the lateral or superficial nail plates and then spreads throughout the nail; when hair shafts are invaded, the organisms can be found either within the shaft or surrounding it. Symptoms are caused by the inflammatory reaction elicited by fungal antigens and not by tissue invasion. Dermatophyte infections are restricted by IL-17 responses and occur more often in males; progesterone can inhibit dermatophyte growth. CHAPTER 225 Clinical Manifestations Dermatophyte infection of the skin is often called ringworm. This term is confusing because worms are not involved. Tinea, the Latin word for worm, describes the serpentine nature of the skin lesions. Tinea is a less confusing term and can be used with the name of the body part affected—e.g., tinea capitis (head), tinea pedis (feet), tinea corporis (body), tinea cruris (crotch), and tinea unguium (nails, more often termed onychomycosis). Superficial Fungal Infections Tinea capitis occurs most commonly in 3- to 7-year-old children. Children with tinea capitis usually present with well-demarcated scaly patches in which hair shafts are broken off right above the skin; alope cia can result. Tinea corporis manifests as well-demarcated, annular, pruritic, scaly lesions that undergo central clearing. Usually, one or sev eral small lesions are present; however, in some patients, tinea corporis can involve much of the trunk. The rash should be differentiated from contact dermatitis, eczema, and psoriasis. Tinea cruris is seen almost exclusively in men. The perineal rash is erythematous and pustular, has a discrete scaly border, is without satellite lesions, and is usually pru ritic. The rash must be differentiated from intertriginous candidiasis, erythrasma, and psoriasis. Tinea pedis also is also more common among men. It usually starts in the web spaces of the toes; peeling, maceration, and pruritus are followed by development of a scaly pruritic rash along the lateral and plantar surfaces of the feet. Hyperkeratosis of the soles of the feet often ensues. Tinea pedis has been implicated in lower-extremity cellulitis, as strepto cocci and staphylococci can gain entrance to the tissues through fissures between the toes. Onychomycosis affects toenails more

often than fin gernails and is most common among persons who have tinea pedis. The nail becomes thickened and discolored and may crumble; onycholysis almost always occurs. Onychomycosis is more common in older adults and in persons with vascular disease, diabetes mellitus, and nail trauma. Fungal infection must be differentiated from psoriasis, which can mimic onychomycosis but usually has associated skin lesions. Diagnosis Many dermatophyte infections are diagnosed by their clinical appearance. If the diagnosis is in doubt, scrapings should be taken from the edge of a lesion with a scalpel blade, transferred to a slide to which a drop of potassium hydroxide is added, and examined under a microscope for the presence of hyphae. Cultures are indicated if an outbreak is suspected or the patient does not respond to therapy. Treatment and Prognosis Dermatophyte infections usually respond to topical therapy with azoles or terbinafine. Lotions or sprays

TABLE 225-1 Suggested Oral Treatment for Extensive Tinea Infections and Onychomycosis ANTIFUNGAL AGENT SUGGESTED DOSAGE COMMENTS Extensive Tinea Infection Terbinafine 250 mg/day for

1–2 weeks Adverse reactions minimal with short treatment period Itraconazolea 200 mg/day for

1–2 weeks Adverse reactions minimal with short treatment period except for drug interactions Onychomycosis Terbinafine 250 mg/day for

3 months Slightly superior to itraconazole; monitor for hepatotoxicity Itraconazolea 200 mg/day for

3 months or 200 twice daily for

1 week each month for 3 months Drug interactions frequent; monitor for hepatotoxicity; rarely causes hypokalemia, hypertension, edema; use with caution in patients with congestive heart failure Other triazoles such as posaconazole may be considered as alternative therapy aItraconazole capsules require food and gastric acid for absorption, whereas itraconazole solution is taken on an empty stomach. The newer SUBA-itraconazole formulation exhibits improved oral bioavailability and reduced interpatient variability. are easier than creams to apply to large or hairy areas. Particularly for tinea cruris, the affected area should be kept as dry as possible. When patients have extensive skin lesions, oral itraconazole or terbinafine can hasten resolution (Table 225-1). Terbinafine interacts with fewer drugs than itraconazole and is generally the first-line systemic agent. PART 5 Infectious Diseases Onychomycosis generally does not respond to topical therapy, although efinaconazole topical solution applied to the affected nail for as long as a year has been beneficial in several trials. Itraconazole and terbinafine both accumulate in the nail plate and can treat onychomy cosis (Table 225-1). The major decision to be made regarding therapy is whether the extent of nail involvement justifies the use of systemic antifungal agents that may have adverse effects, may interact with other drugs, and are costly. Relapses of tinea cruris and tinea pedis are com mon and should be treated as early as possible with topical creams to avoid development of more extensive disease. Relapses of onychomy cosis follow treatment in 25–30% of cases. ■ ■SPOROTRICHOSIS Etiologic Agent, Epidemiology, and Pathogenesis Sporothrix schenckii complex comprises six closely related organisms; S. schenckii and S. brasiliensis are the species that cause most human infections.

S. globosa has grown in importance in Asia. Sporothrix species are rela tively intolerant to heat and are found worldwide in sphagnum moss, decaying vegetation, and soil. Sporotrichosis most commonly affects persons who participate in outdoor activities such as landscaping, gar dening, and tree farming. Infected animals—such as dogs, armadillos, and most commonly cats—can transmit S. schenckii to humans. A large ongoing outbreak of sporotrichosis in Brazil caused by S. brasiliensis has been traced to cats, which are highly susceptible to this infection. Sporotrichosis is primarily a localized infection of skin and subcutane ous tissues that follows traumatic conidial inoculation. 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 following fungal inhalation. Dissemination occurs almost entirely in markedly immunocompromised patients, especially those with AIDS. Clinical Manifestations and Differential Diagnosis 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. 225-1). Some patients develop a fixed cutaneous lesion that can be verrucous

FIGURE 225-1 Several nodular lesions in a lymphangitic spread pattern that developed on the patient’s arm after traumatic inoculation. Cultures from the biopsied lesion (circle) yielded growth of Sporothrix schenckii. or ulcerative and that remains localized without lymphatic exten sion. The differential diagnosis of lymphocutaneous sporotrichosis includes nocardiosis (especially by Nocardia brasiliensis), tularemia, nontuberculous mycobacterial infection (especially by Mycobacterium marinum), and leishmaniasis. Osteoarticular sporotrichosis is usually monoarticular and can present as chronic synovitis or septic arthritis. Pulmonary sporotrichosis presents with cavitary or occasionally mul tifocal noncavitary pneumonia and must be differentiated from tuber culosis and other fungal pneumonias. Numerous ulcerated skin lesions, with or without spread to visceral organs (including the central ner vous system [CNS]), are characteristic of disseminated sporotrichosis. Diagnosis S. schenckii usually grows readily as a mold on Sab ouraud’s agar when material from a cutaneous lesion biopsy is incu bated at room temperature. Histopathologic examination of biopsy material shows a mixed granulomatous and pyogenic reaction, and tiny oval or cigar-shaped yeasts sometimes can be seen with special stains. Treatment and Prognosis Guidelines for the management of the various forms of sporotrichosis have been published by the Infectious Diseases Society of America (Table 225-2). Itraconazole is the drug of choice for cutaneous and lymphocutaneous sporotrichosis. Fluco nazole is less effective, voriconazole is ineffective, and posaconazole has been used successfully in a small number of patients. Saturated solution of potassium iodide (SSKI) continues to be used for lympho cutaneous infection because of its low cost; however, SSKI is poorly TABLE 225-2 Suggested Treatment for Sporotrichosis FIRST-LINE THERAPY ALTERNATIVES/COMMENTS DISEASE Cutaneous, lymphocutaneous Itraconazole, 200 mg/ day until 2–4 weeks after lesions resolve SSKI, increasing dosesa Terbinafine, 500 mg twice daily Pulmonary, osteoarticular Itraconazole,

200 mg twice daily for 12 months Lipid AmBb for severe pulmonary disease until stable; then itraconazole Disseminated, central nervous system Lipid AmBb for

4–6 weeks Itraconazole, 200 mg twice daily after AmB for 12 months Patients with AIDS: itraconazole maintenance, 200 mg/day until CD4+ T cell count is >200/μL

for ≥12 months aThe starting dosage is 5–10 drops three times daily in water or juice. The dosage is increased weekly by 10 drops per dose, as tolerated, up to 40–50 drops three times daily. 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; SSKI, saturated solution of potassium iodide.

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