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265 Coccidioidomycosis (*Coccidioides* Species)

John N. Galgiani

SHORT VIEW SUMMARY

Definition

- The dimorphic fungi *Coccidioides immitis* and *Coccidioides posadasii* cause a systemic fungal infection, coccidioidomycosis, also known as *San Joaquin Valley fever* or *Valley fever.*

Epidemiology

- Coccidioidomycosis is endemic to arid regions of the Western Hemisphere.
- Approximately 150,3192 new US infections occur annually, of which 50,000 produce significant illness; of those reported to the Centers for Disease Control and Prevention, 66% are from Arizona and 31% from California.
- Infections most frequently occur during dry seasons, and the incubation period until first symptoms ranges from 1 to 3 weeks.
- The most common illness is a community-acquired pneumonia, lasting weeks to months whether treated with antifungal agents or not. Progressive pneumonia or hematogenous dissemination to other organs is a serious complication that requires treatment.
- Patients with diabetes are more likely to suffer pulmonary complications.
- The risk of dissemination is much more frequent in patients with impaired cellular immunity.

Microbiology

- *Coccidioides* has been found in desert soil and associated with animal burrows but is sparsely distributed, even within the most highly endemic regions.
- Throughout the 20th century, coccidioidomycosis was recognized as caused by a single fungal species, *C. immitis.* This population contains two genetically and geographically distinct clades, now recognized as separate species: *C. immitis* predominantly found in California and *C. posadasii* in all other endemic regions.
- On most laboratory media, growth by apical mycelial elongation is visible within a week.
- Alternate hyphal cells autolyze, leaving behind single 3- to 5-μm cells (arthroconidia) that can become airborne and are capable of being inhaled deep into airways.
- In mammalian tissue, an arthroconidium remodels into a spherical cell that enlarges isotropically to form large mature spherules with scores of endospores developing within.
- Endospores, when released during spherule rupture, can develop into a new spherule within host tissue or revert to mycelial growth if removed from the infection.
- A sexual phase has not been observed, but population genetics suggest that one exists. Sequence analysis indicates that *Coccidioides* is an ascomycete.

Diagnosis

- Isolation of *Coccidioides* in culture from a clinical specimen is diagnostic of infection.
- Recognizing endospore-containing spherules in wet mounts or histologic sections is also definitive.
- Diagnosis in most patients is made presumptively by detecting anticoccidioidal antibodies in serum or cerebrospinal fluid.
- Complement-fixing anticoccidioidal antibodies are quantitated by serial dilution titration. More extensive infections are frequently associated with higher titers, and clinical improvement is associated with decreasing titers.
- Immunodiffusion techniques are routinely used to provide a qualitative mimic of the complement-fixing antibody test and also to detect other *Coccidioides*-specific antibodies, often immunoglobulin M (IgM), which occur earlier.
- Proprietary enzyme immunoassay kits that measure anticoccidioidal IgM and IgG antibodies are in wide use. They are more sensitive in detecting early coccidioidal infections but may not be as specific.
- A test for coccidioidal antigen is commercially available and is most frequently positive in patients with extensive infection.
- A skin test that measures dermal hypersensitivity in patients with prior coccidioidal infection is again commercially available.

Therapy

- Healthy patients with uncomplicated coccidioidal pneumonia usually improve with general supportive management whether or not antifungal drugs are used. If antifungal treatment is initiated for such patients, it usually consists of fluconazole given orally at a dose of 400 mg/day for periods ranging from 3 to 6 months.
- Patients with severe early pneumonia sufficient to require intensive care hospitalization are often treated with intravenous amphotericin B initially until the respiratory status stabilizes or improves.
- When infection results in symptomatic chronic fibrocavitary pneumonia or extrapulmonary dissemination, antifungal therapy involves oral fluconazole (400 mg daily or higher) or itraconazole (200 mg twice or three times daily). Treatment would normally be continued for at least 1 year. In such patients, it is not infrequent for treatment to continue for several years because relapse off treatment is common.
- In some patients, surgery in addition to antifungal drugs is essential to control infection.
- Treatment of coccidioidal meningitis is most frequently managed with oral fluconazole in doses of 400 mg or more daily. This treatment is lifelong for all patients. Patients who develop hydrocephalus usually require the placement of an internal ventricular shunt.

Prevention

- A preventive vaccine does not exist. A vaccine candidate is under development for dogs but not yet for humans.

Although the systemic fungal infection now known as coccidioidomycosis has been recognized for more than a century,[1] its endemic domains continue to be expanded.[2,3] A medical intern is credited with first identifying in 1892 a patient who had widespread disease.[4] Organisms seen microscopically were mistakenly thought to be parasites, and only several years later was the true mycotic etiology determined and the agent given the name *Coccidioides immitis.*[5] For 3 decades, coccidioidomycosis was thought to be a rare and nearly always fatal infection. In 1929, an accidental laboratory exposure of a medical student at Stanford University resulted in only a transient respiratory infection. His unexpected survival stimulated a reassessment of the natural history of coccidioidal infections, which soon led to the recognition that a common respiratory condition in the San Joaquin Valley of California (Valley fever) was the more usual result of infection.[6] This conclusion

was corroborated with the development by Smith and colleagues of a specific skin test[7] and serologic assays[8] for coccidioidomycosis. With these tools, the clinical spectrum became well described by the mid-1950s; an excellent monograph published by Fiese[9] remains a valuable contemporary reference on the disease.

The growing impact of coccidioidomycosis on public health can be attributed to changes in demography and in contemporary medicine.[10] First, the populations at risk of exposure are greatly expanded. Regions in which *Coccidioides* spp. are endemic, which previously were sparsely populated, now encompass major metropolitan centers such as Phoenix, Arizona. Many of those relocating to the Southwest are retirees, and case rates in older persons are higher than in young adults.[11–13] With this population growth has come greatly increased tourism and commerce-related movement of people into and out of endemic areas. As a result, increased numbers of people are acquiring coccidioidal infections both within and beyond endemic regions.[14,15] Second, a major segment of the population has emerged with compromised cellular immunity because of either underlying diseases or immunosuppressive therapies to control other diseases.[16–24] These patients are unusually susceptible to serious coccidioidal infections, and as a result, the severity of coccidioidal infections as a public health problem has increased. Third, advances in prevention and treatment of fungal infections offer new opportunities for management. These trends have made coccidioidomycosis more relevant to physicians everywhere.[25] Finally, the emergence of *Coccidioides* spp. as potential agents of bioterrorism was identified by the Centers for Disease Control and Prevention (CDC) in 1997.[26,27] Although *Coccidioides* spp. have since been removed from the CDC list of select agents, awareness of their potential remains in light of continued technical advances in genetic transformation.[28]

MYCOLOGY

Coccidioides spp. are dimorphic fungi that exist either as mycelia or as unique structures known as spherules.[29] Both forms of growth are asexual, and it is not possible to classify *Coccidioides* spp. in relation to other fungi by classic taxonomy. By molecular analysis, however, *Coccidioides* spp. appear related most to other ascomycetes, most closely to the medically important organisms *Blastomyces dermatitidis* and *Histoplasma capsulatum*.[30] Although a sexual phase has not been found, population genetics studies suggest that one does exist.[31,32] Two genetically distinct populations have been identified among the etiologic agents of coccidioidomycosis. The occurrence of two populations was correlated with separate endemic regions where patients resided. This finding prompted classification of the previously known single species, *C. immitis,* into two species: *C. immitis* and *Coccidioides posadasii*. Most of the *C. immitis* isolates have been obtained from California, whereas *C. posadasii* isolates have been obtained from patients in other states and from countries other than the United States.[33,34] DNA sequence analysis of *C. posadasii* strains enabled investigators to deduce the approximate geographic origin of some infections.[34,35] The two species have shown few phenotypic differences; the clinical manifestations resulting from infection with either species appear the same, and in vitro susceptibility to antifungals is similar.[36,37] Molecular identification methods for differentiation of *C. immitis* from *C. posadasii* have been described[38] but are not yet routinely employed. Thus references in the literature to *C. immitis* may actually be referring to either species. Isolates for which the species has not been determined are best designated as simply *Coccidioides* spp., which is the convention followed in this chapter.

Mycelial (Saprobic) Growth

On routine microbiologic nutrient agar media and presumably in the soil, *Coccidioides* spp. grow as mycelia by apical extension, and true septa form along their course. Maturation within 1 week of growth results in alternating mycelial cells undergoing a process of autolysis and thinning of the cell walls. The remaining intact cells become barrel-shaped arthroconidia approximately 5 µm in length, develop a hydrophobic outer layer, and are capable of remaining viable for years. Because the attachments of arthroconidia to adjacent cell remnants are fragile, they are prone to separation by physical disruption or mild air turbulence. As a result, arthroconidia readily become airborne in a form capable of deposition in the lungs if inhaled.

Spherule (Parasitic) Growth

In the lungs, arthroconidia remodel into spherical cells, shedding their hydrophobic outer wall.[39,40] During this phase, nuclear division and cell multiplication occur, and septa extend from the internal surface of the wall to transect the growing spherule into scores of subcompartments, each containing viable daughter cells or endospores. In tissue, spherules can become 75 µm in diameter (Fig. 265.1). Spherules grown in vitro demonstrate nuclear division throughout maturation, although their size is smaller and the number of endospores is fewer.[41] As a spherule matures, its outer wall thins and eventually ruptures. Early in the course of experimental infections, this rupture occurs in approximately 4 days,[42] and with the release of endospores, the number of viable fungal units is amplified by approximately 100-fold, each of which may continue to propagate in tissue or revert to mycelial growth if removed from the site of an infection.

EPIDEMIOLOGY

Geographic Range

Coccidioides spp. are endemic to the soils of certain regions of only the Western Hemisphere, nearly all of which are within the north and south 40-degree latitudes. Well-described transport of arthroconidia, either in soil on fomites[43–45] or as the result of unusually severe dust storms,[46] has produced infections in persons without endemic exposure, but this generally has not led to the establishment of new areas of endemicity. Regions of the United States in which *Coccidioides* spp. are endemic are shown in Fig. 265.2. Noncontiguous foci of endemicity also exist, such as those studied at Dinosaur National Monument, Utah[47] and in eastern Washington.[2] These regions generally have the characteristics of the "lower Sonoran life zone," which include an arid climate, yearly rainfall of 5 to 20 inches, hot summers, winters with little freezing weather, and alkaline soil. Other areas where *Coccidioides* spp. have been identified include Mexico (adjacent to the US border; western portions of the states of Sonora, Nayarit, Jalisco, and Michoacan; central regions, including the states of Coahuila, Durango, and San Luis Potosi); Central America (Guatemala, Honduras, Nicaragua); and South America (Argentina, Paraguay, Venezuela, Colombia, Brazil).[10] An archeological investigation has provided evidence that *Coccidioides* spp. infected bison 8500 years ago in what is now Nebraska, far beyond the current endemic regions.[48] This raises the possibility that climatic change could potentially affect the geographic distribution of *Coccidioides* spp.[49]

Within the endemic regions, the likelihood of finding *Coccidioides* spp. in soil samples varies considerably among different locations[32,50,51] and different seasons. The fungus is recovered most easily toward the end of winter rains.[52] This is opposite to the seasonal relationship for acquisition of new infections, which in California and Arizona occur most frequently during the summer months, after the soil has become dry. In Arizona, there is a second peak of new clinical infections from October until the winter rains, which corresponds to a similar dry period after the late summer rains in that region.[53]

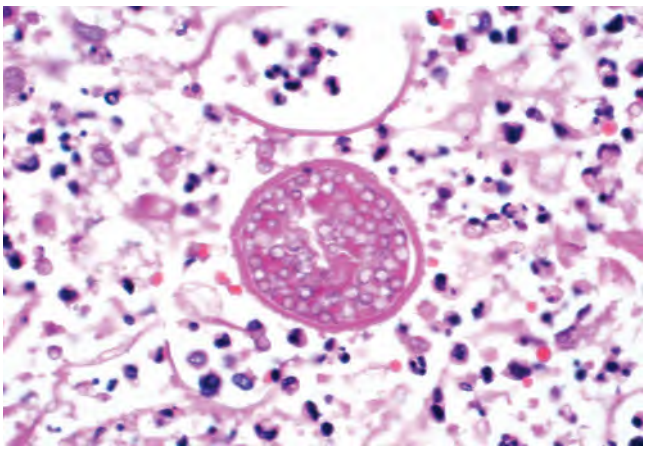

FIG. 265.1 Photomicrograph of a spherule in a tissue. Hematoxylin and eosin staining. *(Courtesy Richard Sobonya, MD, University of Arizona.)*

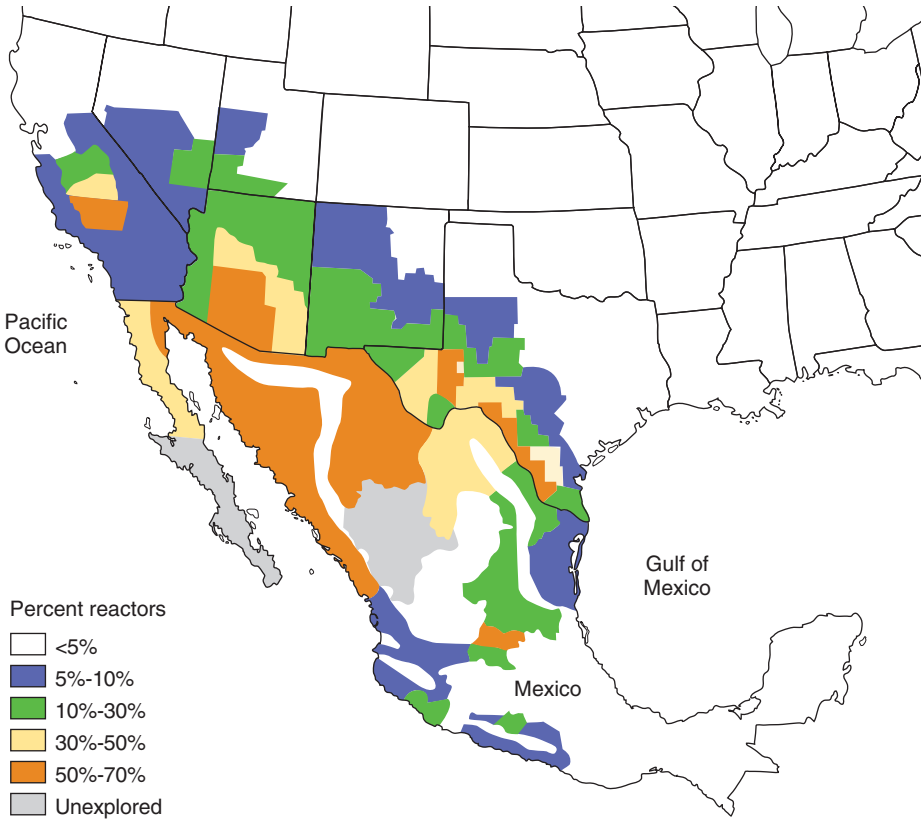

FIG. 265.2 Dermal hypersensitivity mapping of the endemic intensity of coccidioidomycosis. (*From Nguyen C, Barker BM, Hoover S, et al. Recent advances in our understanding of the environmental, epidemiological, immunological, and clinical dimensions of coccidioidomycosis.* Clin Microbiol Rev. *2013;26:505–525.*)

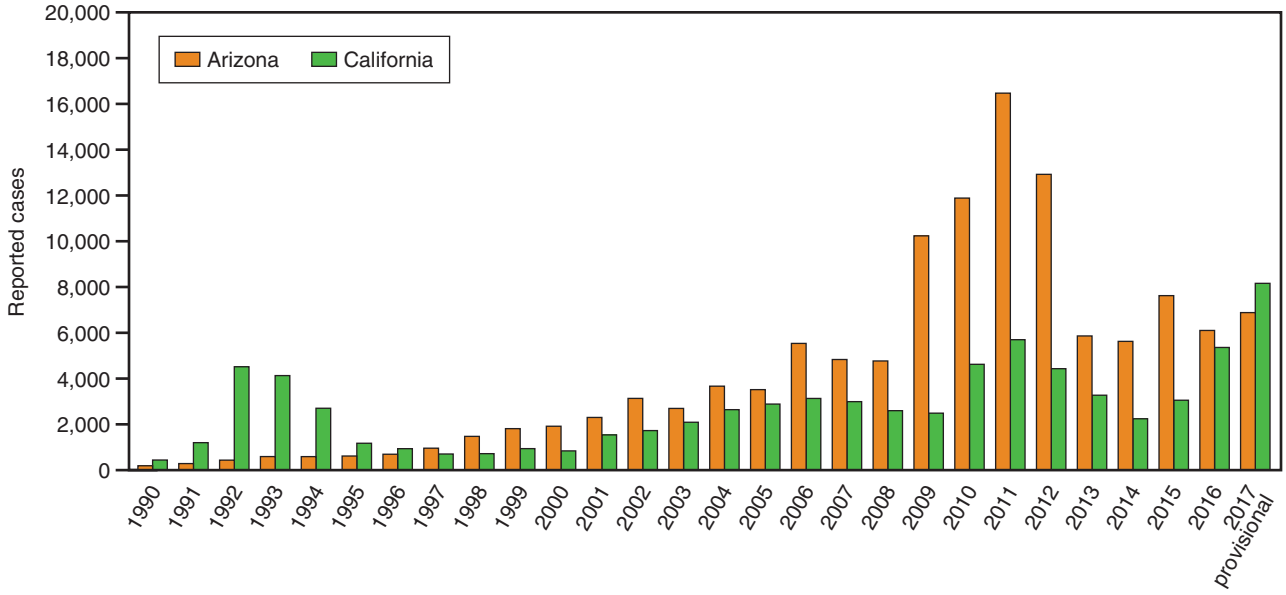

FIG. 265.3 New cases of coccidioidomycosis reported to the Arizona and California Departments of Public Health. *(Data source: Centers for Disease Control and Prevention.)*

Rates of Coccidioidal Infection

Prevalence surveys in the 1950s of skin test reactivity to coccidioidal antigens in school-age children of California's Central Valley suggested that the annual risk of infection was approximately 15%.[54] Smith and colleagues[55] showed that in 25% to 50% of military personnel in the San Joaquin Valley, skin test results converted to positive during a single year. More contemporary estimates from the same areas in California and from Tucson, Arizona, indicate that the risk has declined to approximately 3% per year.[54,56] Because of these lower rates and because of the large influx of new residents to the endemic regions from non-endemic locales (in the 2010 census, estimated to total >7 million persons for southern Arizona and south central California), the proportion of persons within the endemic region with prior infection is approximately 30%. Based upon these estimates, the expected number of infections is on the order of 150,000 annually, resulting in approximately 50,000 persons sick enough to seek medical attention.

The numbers of infections reported to state departments of public health differ significantly from year to year (Fig. 265.3). Some variation

has been associated with total winter rainfall; more cases occur in the summers after wetter winters.[53] On occasion, epidemics also have been associated with disruption of infected soil by human intent, such as with excavation; after natural events, such as severe dust storms or earthquakes; or during military maneuvers.[57–59] Some fluctuations in rates of infections are not explained, however. Such is the case for an exceptionally large epidemic in California's Central Valley in the period from 1992 to 1995, in which the incidence of infection at times was more than 10 times that normally reported, and in 2010 to 2011, in which the total number of reported cases was the highest since coccidioidomycosis was made a reportable disease.[11,60] An analysis of death certificates indicated that approximately 160 persons die each year from coccidioidomycosis,[61] although these statistics may be an underestimate.[62]

PATHOGENESIS AND CONTROL

Nearly all infections are the result of inhaling arthroconidia. Cutaneous inoculations have been reported, producing lymphatic extension to regional lymph nodes and resolving without treatment. These occurrences are exceedingly rare, however.[63]

A single arthroconidium may be sufficient to produce a naturally acquired respiratory infection. This is the case for experimental infections in mice,[64] and air sampling within coccidioidal endemic regions suggests that the ambient density of arthroconidia in the air is low.[65,66] The size of the arthroconidium would allow its deposition within the terminal bronchiole but probably not as deeply as the alveolar space. With spherule rupture, inflammation ensues,[67,68] forming a local pulmonary lesion. Extracts of *Coccidioides* spp. have been shown to react with complement, releasing mediators of chemotaxis for neutrophils.[69] In some infections, *Coccidioides* spp. leave the lungs to establish disseminated lesions in other parts of the body. In this sequence of events, fungal elements must move from the distal bronchiole into the lung parenchyma, gain entry into the vascular space, and leave the vascular space to create extrapulmonary sites of infection. It is possible that endospores within macrophages travel through lymphatic vessels to the bloodstream, as has been described for dissemination of tuberculosis and histoplasmosis. This possibility is also compatible with the common finding of infected hilar, peritracheal, supraclavicular, and cervical lymph nodes in patients with extrapulmonary coccidioidal infections.[67]

Histopathology

Microscopic examination of tissue infected with *Coccidioides* spp. shows elements of acute and chronic inflammation. Acute inflammation, including neutrophils and eosinophils, is associated with active infections and rupturing spherules.[67,68] Granulomatous lesions that include lymphocytes, histiocytes, and multinucleated giant cells are associated with chronic or arrested infections and with mature unruptured spherules.[70] In patients with widespread infections, it is common to find both inflammatory responses represented concurrently at different anatomic sites.

Host Defenses

Control of coccidioidomycosis depends on T lymphocytes. This conclusion is supported by studies of experimentally produced infections in mice[71–75] and by the increased severity of naturally acquired infections in T-cell–deficient patients.[21,23,76–79] Peripheral mononuclear blood cells from patients with active disseminated coccidioidomycosis have virtually no interferon-γ response to coccidioidal antigens.[80] This is in contrast to the brisk stimulation of similar leukocyte preparations from patients in whom coccidioidal infections are competently controlled and who have delayed-type dermal hypersensitivity to coccidioidal skin-testing antigens.[81] These findings are consistent with an absent type 1 helper T cell (Th1) response described in some experimental animals[82,83] and human infectious diseases, in which cellular immunity plays a role. In humans, however, despite the observed depression of interferon-γ levels, interleukin-4 and interleukin-10 levels were not reciprocally elevated,[81] which would be indicative of a type 2 helper T cell (Th2) response. Recently, specific mutations in Th1 pathway genes have been associated with disseminated infection.[84–86]

In addition to T-cell–mediated control of infection, innate cellular responses may contribute to host defense.[87,88] Inhibition of growth of *Coccidioides* spp. can be shown in vitro by human neutrophils and mononuclear cells from persons with or without prior coccidioidal infection as judged by skin test reactivity to coccidioidal antigens.[89] Although neutrophils do not seem to be fungicidal against *Coccidioides* spp., mononuclear cells or natural killer cells have been shown to reduce fungal viability.[90,91] These innate cellular inhibitory effects are most evident against arthroconidia or endospores and are lost as spherules increase in size and mature.[92] These in vitro observations can be extrapolated to indicate that innate defenses may serve primarily to slow fungal proliferation after infection, transforming what otherwise might be a more fulminant infection to a more subacute or chronic process.

Coccidioidal infections engender a variety of humoral responses to several different antigens in patients, and, as discussed subsequently, several are diagnostically useful. *Coccidioides*-infected B-cell–deficient mice are not as protected by vaccination as are normal mice.[93] However, a specific defensive role for immunoglobulins has thus far not been defined.

CLINICAL MANIFESTATIONS

At least one-half to two-thirds of all infections caused by *Coccidioides* spp. are either inapparent or sufficiently mild not to prompt medical evaluation.[55] Of those that do become medically significant, a large majority result in a respiratory illness that is indistinguishable without specific testing from community-acquired pneumonia caused by other entities.[94–96] In two observational studies in southern Arizona, coccidioidomycosis was estimated to be responsible for approximately one-quarter to one-third of all cases of community-acquired pneumonia in that endemic area.[95,96] Nonetheless, misunderstandings of the manifestations of coccidioidomycosis or the perceived unimportance of diagnosis of early infections have led to significant delays in diagnosis[96a,96b] and gross disparities between the numbers of expected and reported coccidioidal infections.[97–99] For example, the number of coccidioidal infections reported to Arizona's Department of Health Services (see Fig. 265.3) represent only a fraction of the expected 30,000 new illnesses. Underdiagnosis may be even more likely for patients with coccidioidomycosis evaluated outside the endemic region.[57,100] Most coccidioidal infections, whether detected or not, follow a self-limited course; only a few produce residual sequelae or chronic progressive infections. Although complications of untreated coccidioidal infections are typically manifested within weeks, months, or rarely up to 2 years after the original infection, the severity of the initial respiratory infection is not correlated with the likelihood of complications. In this context, the identification of even mild primary infections takes on added significance and clinical relevance.

Early Respiratory Infection

The first symptoms of the primary infection usually appear 7 to 21 days after exposure. Most infections seem to develop as a result of exposure to one or a small numbers of arthroconidia. However, when exposure is unusually intense, symptoms are more likely to appear early.[101] In an epidemic of coccidioidomycosis that occurred in the San Joaquin Valley of California between 1991 and 1994,[102] the findings in 536 patients with new infections included cough (73%), chest pain (44%), shortness of breath (32%), fever (76%), and fatigue (39%). These findings are typical of earlier reports. Although the infection is often subacute in development, patients occasionally report abrupt onset of symptoms, especially that of pleurisy. Weight loss is also a common sign, and headache has been noted in 21% of patients in the absence of meningeal infection.[103] Skin manifestations develop as part of the primary illness. Most frequent and easily missed is a nonpruritic fine papular rash that occurs early and transiently during the illness. More striking are erythema nodosum and erythema multiforme, which occur predominantly in women. Migratory arthralgias are also common complaints, and the triad of fever, erythema nodosum, and arthralgias (especially symmetrically of the knees and ankles) has been termed *desert rheumatism*. Routine laboratory findings, including serum procalcitonin levels,[104] are usually normal except for slightly increased peripheral blood leukocytosis and an increase in the erythrocyte sedimentation rate. Peripheral blood eosinophilia may be present, occasionally accounting for two-thirds of the circulating leukocytes. Chest radiograph results

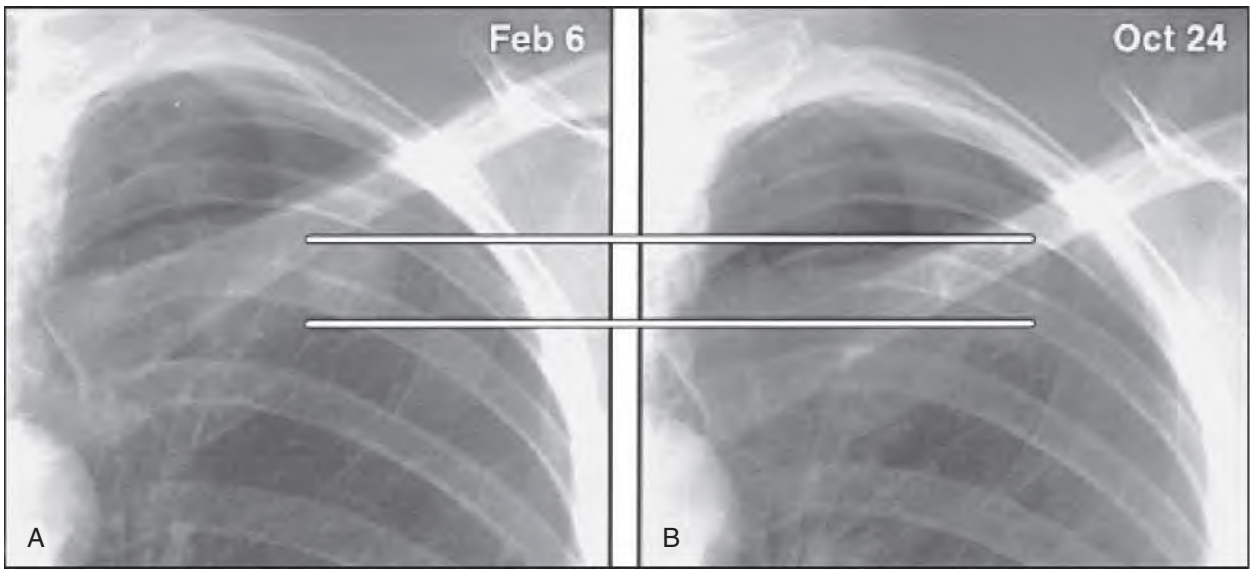

FIG. 265.4 Cavitation of a coccidioidal nodule. (A) A 1.8-cm nodule can be seen. (B) Eight months later, this lesion has become a thin-walled cavity.

are abnormal in more than half of patients. This partially accounts for different estimates in two Arizona studies of coccidioidomycosis as a cause of community-acquired pneumonia. A case definition that required an abnormal chest radiograph in one study[96] was lower than one that did not.[95] Common radiographic findings include unilateral infiltrates, hilar adenopathy, and peripneumonic pleural effusions. Persistent hilar or peritracheal adenopathy may be associated with extrathoracic spread of infection.[105] Lung cavities are present initially in approximately 8% of infections recognized in adults but are less frequent in children.[106]

Uncommonly, coccidioidal pneumonia manifests as a diffuse process leading to respiratory failure, either because of high-inoculum exposure[107,108] or because of fungi in the bloodstream that seed the lung in many sites.[22,109] The manifestation is often fulminant, mimicking that of septic shock or a bacterial infection, and despite treatment, the rate of mortality is high. Approximately one-third of human immunodeficiency virus (HIV)–infected patients with clinically acquired immunodeficiency syndrome (AIDS) exhibit this radiographic appearance. Although fungemia associated with diffuse pulmonary infiltrates may occur in immunologically intact patients,[110] it is nearly always attributable to a recognizable cellular immunodeficiency state.[111] In HIV-infected patients with fungemia, the $CD4^+$ counts are typically less than 100 cells/mm^3 and the viral load is high.[112]

Although some of the presenting signs, symptoms, and routine laboratory studies are statistically more likely to occur with coccidioidal infections than with respiratory illness of other causes, the overlap of clinical syndromes is substantial.[94–96] For most patients, specific testing is necessary to secure a definitive diagnosis of coccidioidomycosis.

Most coccidioidal respiratory infections resolve without complications but often take several weeks to many months to do so. When resolution of the self-limited illness is protracted, the symptom of fatigue is frequently the last to resolve. This fatigue syndrome, disproportionate to other evidence of infection syndrome, may strikingly interfere with normal daily activities or the ability to return to work, and it can be a source of considerable distress. A recent small study of such subjects demonstrated a striking oxygen utilization deficit,[113] but further studies will be needed to determine how extensively this mechanism accounts for this very common complaint. A few patients with infections develop various pulmonary sequelae, and even fewer patients manifest disseminated infection outside the lungs. Despite their relative infrequency, these complications pose significant difficulties in diagnosis and management (discussed later).

Pulmonary Nodules and Cavities

Approximately 4% of pulmonary infections result in a nodule, ranging up to 5 cm in diameter. A nodule typically causes no symptoms but may be indistinguishable from a neoplasm without histologic examination.[114–116] On occasion, nodules liquefy and drain into a bronchus to form a cavity (Fig. 265.4).

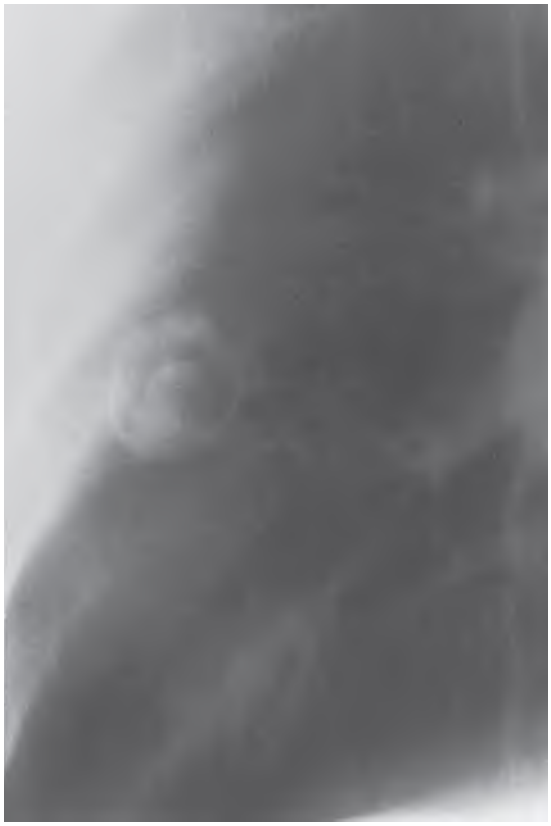

FIG. 265.5 Fungus ball in the right lung of a coccidioidal cavity. Bronchoscopy specimens yielded *Coccidioides* spp. in culture. *(From Winn RE, Johnson R, Galgiani JN, et al. Cavitary coccidioidomycosis with fungus ball formation.* Chest. *1994;105:412–416.)*

Pulmonary cavities may be present initially or in the later stages of the primary infection. They are usually peripheral and solitary, and with time, most develop a distinctive thin wall.[106] Cavities may not cause any symptoms, and half close within 2 years. Others are associated with local symptoms of pleuritic pain, cough, or hemoptysis. A fungus ball may develop within cavities, either from mycelia of *Coccidioides* spp.[117,118] or with other species of fungi (Fig. 265.5). Another infrequent but well-recognized complication is rupture of a peripheral coccidioidal

cavity into the pleural space and its manifestation as a pneumothorax. Ruptures commonly occur in athletic young men and are not associated with underlying immunodeficiency. Because the fungal walls of *Coccidioides* spp. are inflammatory, ruptured coccidioidal cavities often produce fluid in the pleural space, and the presence of an air-fluid level within the pleural space is a clue that the process is not a spontaneous pneumothorax or a ruptured pulmonary bleb (Fig. 265.6). If the cavity is diagnosed early, surgical resection of the cavity and closure of the pulmonary leak is the preferred treatment.[119,120] Less commonly, pleural disease can occur without rupture of a cavity. In a study of pleural coccidioidomycosis, 10 of 36 (28%) patients had pleural-predominant disease without cavity or cavity rupture.[121]

Chronic Fibrocavitary Pneumonia

In contrast to thin-walled coccidioidal cavities, a chronic fibrotic pneumonic process that develops in some patients is characterized by pulmonary infiltrates and pulmonary cavitation (Figs. 265.7 and 265.8).[122] This form of infection is not common among patients with T-cell deficiencies but seems to be associated with diabetes or preexisting pulmonary fibrosis related to smoking or other causes.[123] Involvement of more than one lobe is more common, and these lesions may cause systemic symptoms, such as night sweats and weight loss, and local symptoms. Recently, two patients with a mutation of *STAT1* have been described with a chronic consumptive coccidioidal pneumonia, which is strikingly devoid of cavitation in contrast to what occurs more commonly.[86]

FIG. 265.6 Chest computed tomography scan of ruptured coccidioidal cavity with pneumothorax. White star points to air in the pleural space.

Extrapulmonary Dissemination

Coccidioides spp. spread beyond the lungs in approximately 0.5% of all infections in the general population. Several factors dramatically increase the risk of dissemination, however: immunodeficiency conditions, such as the later stages of HIV infection[112] and Hodgkin lymphoma[23]; and therapies that suppress immune function, such as therapy to prevent solid-organ rejection,[124] high-dose corticosteroid therapy (equivalent to long-term prednisone doses >20 mg/day),[78] and therapeutic inhibitors of tumor necrosis factor.[18,125] In two-thirds of renal-transplant recipients who developed coccidioidal infection, the infection progressed to dissemination.[76] With transplantation, the risk is heightened mostly by either newly acquired disease or reactivation of prior infection. Transmission by the engrafted organ has also been reported.[126–128] Dissemination is more likely to develop in men than in women.[129–131] Dissemination is also more likely, however, if infection is diagnosed during pregnancy, especially during the third trimester or in the immediate postpartum period.[132] The risk of dissemination also appears to be increased among persons of African or Filipino ancestry, although the exact magnitude of the risk is controversial.[129,133,134] Extrapulmonary dissemination is not associated often with pulmonary complications. Many patients with disseminated coccidioidal infection have entirely normal chest radiographs.

The most common site of dissemination is the skin. The range of lesions includes superficial maculopapular lesions, keratotic and verrucose ulcers, and subcutaneous fluctuant abscesses. There is a predilection for lesions at the nasolabial fold (Fig. 265.9). Although most extrapulmonary dissemination is the result of hematogenous spread, supraclavicular and cervical lymphadenopathy is also a frequent manifestation and probably represents lymphatic drainage from the primary pulmonary infection. A rare manifestation is peritoneal coccidioidomycosis, which clinically resembles tuberculous peritonitis.[135]

Joints and bones are common sites of dissemination. Joint infections differ from the self-limited joint complaints of desert rheumatism in that infections are typically asymmetrically distributed and are associated with a prominent synovitis and effusion. Although any joint can become infected, the knee is involved most frequently; other common locations include the joints of the hands and wrists, feet and ankles, vertebrae, and pelvis.[136–140] Infection may be limited to the synovium or may erode to involve the underlying bone. Alternatively, bones may be involved first with secondary extension into the joint.[141,142] Although long bones

FIG. 265.7 Pulmonary cavity in the right upper lobe with surrounding fibrosis.

FIG. 265.8 Computed tomography scan of the fibrocavitary process shown in Fig. 265.7.

FIG. 265.9 Ulcerative lesion of disseminated coccidioidal infection. *(From Galgiani JN. Coccidioidomycosis.* West J Med. *1993;159:153–171.)*

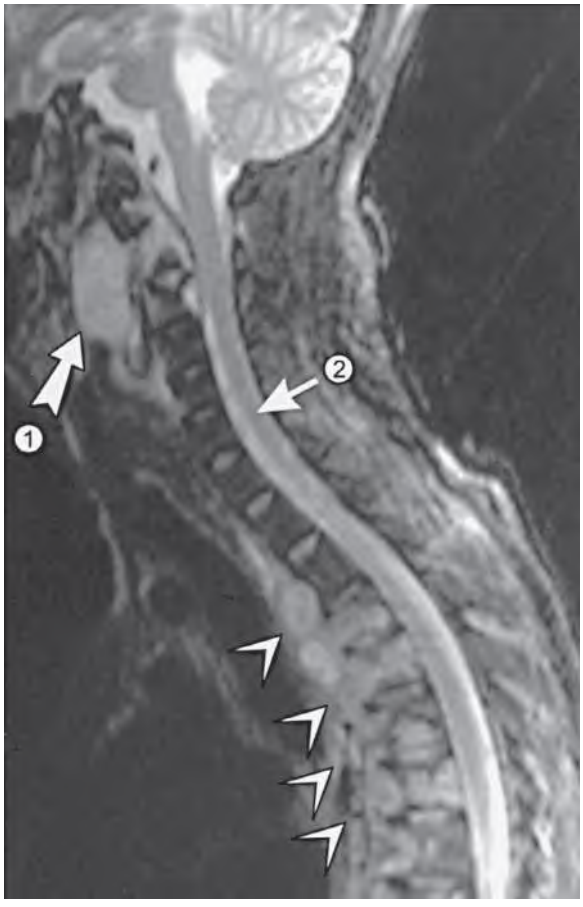

FIG. 265.10 Sagittal magnetic resonance imaging shows an anterior paraspinous abscess extending from the base of the skull to the midthoracic vertebrae. Arrow 1 points to an abscess that originated in a cervical vertebra and dissected anteriorly. Arrow 2 identifies a normal spinal cord. The arrowheads indicate abscesses anterior to the thoracic vertebrae. Multiple surgical procedures were necessary to control this infection.

may be affected, vertebral infection is much more common. Involvement of multiple vertebrae is typical.[143] These may coalesce to produce anterior or posterior paraspinous soft tissue abscesses or an epidural abscess (Fig. 265.10). Magnetic resonance imaging (MRI) is often helpful in defining the exact location of these lesions.[144]

Coccidioidal meningitis is the most serious form of disseminated infection. Untreated, it is nearly always fatal within 2 years of diagnosis.[145,146] Like most other complications of coccidioidomycosis, meningitis usually develops relatively soon after the initial infection. In one study of 22 patients who developed meningitis after a large dust storm, central nervous system symptoms developed on average after 5.4 weeks of illness.[147] Similarly, a review of cases from the Department of Veterans Affairs and military records showed that, of 25 patients who developed meningitis, 20 did so within 6 months of their first symptoms of infection.[146] Common presenting symptoms are headache, vomiting, and altered mental status.[148–150] In addition to cerebrospinal fluid (CSF) findings of an elevated white blood cell count, elevated protein levels, and a depressed glucose level, CSF eosinophils are occasionally prominent.[151] The main areas of involvement are the basilar meninges. Hydrocephalus is a common complication, especially early in children.[152] Attention has been drawn to vasculitis and focal intracerebral coccidioidal abscesses as less frequent complications.[153–155]

DIAGNOSIS

The manifestations of most early coccidioidal infections overlap substantially with those of other respiratory infections.[94–96] Specific laboratory testing is usually necessary to establish a diagnosis of coccidioidomycosis. In regions where *Coccidioides* spp. are endemic, this testing is commonplace. In most of the rest of the United States, the possibility of coccidioidomycosis is unlikely to be considered unless a geographic exposure is elicited in the patient's history. Because the incubation period is usually 1 to 3 weeks, endemic exposure within this period should raise the possibility of coccidioidomycosis to account for a respiratory condition of new onset. Exposure need not be extensive. Infections have occurred in patients whose only exposure occurred while changing airplanes at the Phoenix airport or during a single drive across California's Central Valley.

Complications of the initial infection, such as chronic pneumonia or extrathoracic dissemination, may take longer to become apparent but nearly always emerge within 2 years after exposure. One exception to this rule is the detection of a pulmonary nodule or a solitary pulmonary cavity, which may persist without symptoms for many years after the original infection. Another special case is the setting of waning immunity, such as after the development of AIDS or with immunosuppressive therapy associated with solid-organ transplantation. In such circumstances, exposure to *Coccidioides* spp. in the distant past may be sufficient to account for the current clinical illness.[156]

When the possibility of coccidioidomycosis has been raised, diagnosis is usually established in two ways: (1) identifying spherules in, or recovering *Coccidioides* spp. from, a clinical specimen; or (2) detecting specific anticoccidioidal antibodies in serum, CSF, or other body fluid.

Direct Examination and Culture

Isolating *Coccidioides* organisms from a patient is definitive evidence of a coccidioidal infection, and this diagnostic approach is used most frequently for patients with complicated pulmonary or disseminated syndromes. Sputum or other clinical specimens can be collected at no risk to personnel because the infection is not transmitted from the primary specimen. Direct microscopic examination of secretions can be performed immediately or after the addition of potassium hydroxide. Calcofluor staining of the cell wall in a wet mount may also help to distinguish spherules from leukocytes. *Coccidioides* spp. cannot be detected on Gram stains. Spherules also can be detected by cytology stains (e.g., in bronchoscopy specimens)[157]; hematoxylin and eosin stains; and other specialized procedures, such as silver or periodic acid–Schiff staining. Hematoxylin and eosin staining of spherules produces a distinctive autofluorescence that may help to identify a few organisms in tissues.[158] Using species-specific probes, researchers found that in situ hybridization was not as sensitive as silver staining but was more specific.[159] Although culture results are more sensitive, identification of spherules by direct examination is more rapid and may speed diagnosis. Direct detection of *Coccidioides* in sputum by polymerase chain reaction has been reported and may become clinically available soon.[38,160–162]

Coccidioides spp. grow well on most mycologic or bacteriologic media after 5 or 7 days of incubation. Aerobic conditions are required. When

growth occurs, it is typically as a white (nonpigmented) mold. There are many exceptions to this general appearance, however, and the morphologic appearance is not reliable in determining whether the fungus is *Coccidioides* spp.[163] When growth is evident on culture medium, care should be taken not to open the culture container except in an appropriate biocontainment cabinet. Cultures at this stage are highly infectious, and infections have occurred in laboratory personnel when cultures have not been handled properly.[164]

The mycelial form of growth is not specific for *Coccidioides* spp., and further testing is required for species identification. The most common way for microbiologists to test this is to detect a specific ribosomal RNA sequence using a commercially available DNA probe (Accuprobe, Hologic, San Diego).[165] At present, molecular methods to differentiate between *C. immitis* and *C. posadasii* are available only at a limited number of reference laboratories. Genus identification can also be done by detection of an exoantigen in an extract of fungal growth.[166,167] Until December of 2012, fungal isolates identified as *Coccidioides* spp. were subject to strict federal security regulations developed for all select agents of bioterrorism. However, *Coccidioides* spp. have been delisted, and CDC oversight is no longer in effect.

Serologic Testing

Serologic testing is the most frequent means of diagnosing primary coccidioidal infections because the patients may not be able to produce a sputum specimen, and fungal cultures often are not practical in an ambulatory setting. It may also be indispensable in establishing the cause of chronic meningitis because cultures of CSF are commonly negative in coccidioidal meningitis. Of the variety of tests available, most are highly specific for an active infection.[168,169] Minimally reactive test results are often diagnostically important and should not be dismissed as insignificant. A negative serologic test result never excludes the presence of a coccidioidal infection, however. Performing one or more repeated serologic tests over the course of 2 months increases the sensitivity of serologic diagnosis, especially for recently acquired infections.

Tube Precipitin Antibodies

Tube precipitin antibodies stimulated by a coccidioidal infection were originally detected by the presence of a precipitin button that formed at the bottom of a test tube after overnight incubation of the patient's serum mixed with coccidioidal antigen.[7] Because immunoglobulin M (IgM) is most avid at forming immune precipitins, and because these reactions were detected early after the onset of infection, this test is sometimes referred to as the *IgM test.* The antigen responsible for this reaction is a polysaccharide from the fungal cell wall. At some time within the first 3 weeks of symptoms, tube precipitin antibodies are detected in 90% of patients; this prevalence declines to less than 5% more than 7 months after the onset of a self-limited illness.

Complement-Fixing Antibodies

When the patient's serum is mixed with coccidioidal antigen, an immune complex forms that consumes complement.[170] This event is detected by the subsequent addition of sensitized red blood cells, which normally lyse in the presence of complement but remain intact if the complement is depleted. Because immunoglobulin G (IgG) is the immunoglobulin class usually involved in these immune complexes, this test is sometimes referred to as the *IgG test.* Although this test originally was developed through the use of various complex extracts of *Coccidioides* spp., it is now known that the antigen involved in this reaction is a chitinase.[171–173] Subsequent work demonstrated that a recombinant truncation of amino acids 20 to 310 eliminated serologic cross-reactivity with antibodies stimulated during histoplasmosis,[174] and that all of the coccidioidal antibody reactivity was located from amino acids 111 to 310.[175] In early coccidioidal infections, complement-fixing antibodies are detected later and for longer periods than are tube precipitin antibodies.[8] Complement-fixing antibodies can be detected in other body fluids, and their detection in CSF is an especially important aid to the diagnosis of coccidioidal meningitis. Complement-fixing antibody concentration is expressed as a titer, such as 1:4 or 1:64, indicating the greatest dilution of serum at which complement consumption is still detected. Traditionally, a titer of 1:16 or greater has been associated frequently with extrathoracic dissemination. Because of technical factors, however, end point results for the same serum samples may vary considerably on testing by different laboratories. More useful are serial determinations of complement-fixing antibody concentrations performed by the same laboratory. In general, higher titers reflect more extensive coccidioidal infection, increasing complement-fixing antibody concentrations are associated with worsening disease, and decreasing titers are useful in monitoring response to therapy. These are general relationships that are occasionally not borne out by the course of individual patients.[175a]

Immunodiffusion Tests

Antibodies that were detected by the original tube precipitin or complement-fixing tests can be detected by alternative procedures known as the *immunodiffusion tube precipitin* and *immunodiffusion complement-fixing* tests. Although these tests are conducted similarly, different antigens are used to measure different types of antibodies. As with the original tests, the immunodiffusion tube precipitin test result is reported by some laboratories as the IgM test result, and the immunodiffusion complement-fixing result is reported as the IgG test result. Both tests have been found to be at least as sensitive as their original counterparts.[176,177] The quantitative immunodiffusion procedure closely correlates with the quantitative complement-fixing antibody test.[178] Immunodiffusion tests are more amenable to being manufactured and distributed in commercially prepared kits, which allow them to be performed in laboratories not fully dedicated to a mycology specialty.

Enzyme-Linked Immunoassays

Enzyme immunoassays for coccidioidal antibodies are available commercially (Meridian Bioscience, Inc., Cincinnati, OH; IMMY, Norman OK; Mira Vista Diagnostics, Indianapolis, IN). The test kits allow the specific detection of IgM or IgG antibodies; however, these results are not interchangeable with the complement fixation or immunodiffusion test results. Positive results with this commercial kit are highly sensitive for coccidioidal infection. On occasion, false-positive results are noted, especially with the IgM enzyme immunoassay.[179–181] At present, enzyme immunoassay results should ordinarily be confirmed with immunodiffusion tube precipitin, immunodiffusion complement-fixing, or complement-fixing test results. When the more established tests fail to corroborate the enzyme immunoassay, a coccidioidal infection may in fact exist, but the diagnosis is less firmly established.[182–184]

Latex Tests

Latex tests for coccidioidal antibodies are also available commercially. They are attractive to clinical laboratories because they are easy to use, and results are obtained rapidly. There are significant numbers of false-positive reactions, however, and the latex test is not as reliable as the other tests described in this section.[168]

Skin Testing

Dermal delayed-type hypersensitivity to coccidioidal antigens is highly specific for coccidioidal infection.[185] In clinical practice, especially within endemic regions for coccidioidomycosis, perhaps the best use of coccidioidal skin testing in patients when they are not ill is to determine if they are immune from future disease as a result of past infection. Because skin test results remain positive after infection in most people for life, however, a result may not be related to the current illness. In addition, some of the most serious infections may be associated with selective anergy, and the skin test may not reveal reactivity. As useful as skin test results are for epidemiologic studies, the tests have important limitations as screening procedures for recent infection. For patients in whom coccidioidomycosis has been diagnosed by other means, skin testing may have prognostic significance.[186] Coccidioidal skin testing reagents ceased being available commercially in the 1990s. However, a reformulation of the spherule-derived skin test antigen was reintroduced in 2015 as Spherusol (Nielsen BioSciences, Inc., San Diego, CA), and is approved to test for immune responsiveness in patients previously diagnosed with coccidioidomycosis.[187–189]

Coccidioidal Antigen Detection

Antigenemia may occur with either early or chronic coccidioidal infections and could be the basis of a diagnostic test.[190–193] A commercial

test is available (MiraVista Diagnostics, Indianapolis, IN) for detecting coccidioidal antigens.[194] This test, applied to CSF specimens, may be particularly useful for diagnosing meningitis.[195,196]

MANAGEMENT

General Approaches

The three components of managing coccidioidal infections are (1) assessment of the need for intervention, (2) selection of antifungal agents for patients who would benefit from treatment, and (3) choice of surgical procedures for débridement and reconstruction of destructive lesions. A revised practice guideline has been published[25] and is available online from the Infectious Diseases Society of America (IDSA; www.idsociety.org). A training manual for nonspecialists is also available (vfce.arizona.edu).

In patients with newly diagnosed coccidioidal infections, it is crucial to assess the extent of disease at present and the factors that increase the risk of future complications. The current extent of disease can usually be assessed with a careful review of systems, physical examination, and chest radiographs. When new focal complaints of discomfort or swelling are identified, these should be evaluated further with appropriate imaging or, if necessary, biopsy. Pain referable to bones might be assessed with a radionuclide bone scan or an MRI.[197,198] Recently, positron emission tomography/computed tomography scans have been used to also detect extrapulmonary disease activity, although to what extent the metabolic activity represents areas of tissue destruction is uncertain.[199,200] An effusion that develops in a joint could be aspirated for cell count and culture, a progressively severe headache may necessitate MRI and especially lumbar puncture to evaluate the possibility of meningitis, and a nonhealing skin lesion may necessitate biopsy.

In the general population, pulmonary or extrapulmonary complications are uncommon. There is a special risk of disseminated infection, however, with conditions that prominently suppress T-cell immunity as detailed earlier. Patients with active infection and these risk factors nearly always should be treated with antifungal therapy even if there is no evidence of extrapulmonary spread. Patients with diabetes mellitus are not prone to extrapulmonary dissemination. They are more likely to develop pulmonary cavitation or chronic pneumonia, however, and may be more likely to require treatment.[123]

Therapy

Available antifungal agents include amphotericin B and the azole antifungal agents. Their pharmacology is described in detail in Chapters 40A to 40D. In coccidioidomycosis, selecting between amphotericin B and azole antifungals is based primarily on the degree of respiratory compromise in pulmonary infections or the rate of progression of disseminated infections. Amphotericin B is perceived to have a more rapid onset of action; therefore despite its well-known toxic effects, it is the preferred initial therapy for patients who have developed serious respiratory compromise or who are deteriorating rapidly. There is no evidence that a lipid formulation of amphotericin B improves on the efficacy of colloidal (conventional) amphotericin B, but liposomal or lipid complex amphotericin B is often used because of less toxicity. Azole antifungals are often selected for patients with chronic processes because possible differences in rate of response to azole antifungals would be outweighed by their ease of administration and lack of toxicity. Ketoconazole was the only orally available azole antifungal approved by the US Food and Drug Administration for the treatment of coccidioidomycosis but is no longer the preferred drug for this disease because of hepatotoxicity. Several clinical trials have indicated that fluconazole and itraconazole are efficacious.[201–207] No studies have demonstrated general superiority of one azole antifungal over another. In a comparison of fluconazole (400 mg once a day) and itraconazole (200 mg twice daily), the primary analysis showed that the two drugs were within 20% of each other in producing responses.[204] In a secondary analysis of skeletal lesions, response was obtained in twice as many subjects treated with itraconazole as those treated with fluconazole. The newer azoles, voriconazole and posaconazole, have also been used to treat coccidioidomycosis. In one study, 17 of 20 patients treated with 400 mg/day of posaconazole suspension improved.[208] However, of 9 patients in whom treatment was discontinued, 3 suffered relapse. In another study of 15 patients in whom previous treatments had failed, 11 treated with 800 mg/day of posaconazole improved.[209] In a report of 3 patients with coccidioidal meningitis, 2 improved with posaconazole.[210] For voriconazole, there is less published literature, but case reports suggest that it may also be effective.[211–214] There is also very little published experience with isavuconazole.[214a]

Because the manifestations, locations, and severity of progressive forms of coccidioidomycosis vary among patients, the need for surgery is determined by the nature of specific lesions on a case-by-case basis. In some patients, especially in whom skeletal involvement is extensive, débridement and drainage of infected sites may be essential to achieving control of the infection. Even if therapy is effective in arresting fungal proliferation, fungal debris already present may continue to produce tissue destruction until it is surgically removed. Patients with persistent fever and malaise may benefit from drainage of large collections of pus. Also, surgery may be needed to stabilize bones that are structurally unsound or when the spinal cord is at risk of compression. Advances in imaging with computed tomography or MRI have aided greatly in the evaluation of specific lesions.[215] Repeated use of these modalities often helps to identify lesions that are progressing despite the current management strategy and patients who may benefit from additional surgical intervention or other changes in management.

Early Uncomplicated Infections

For patients with neither risk factors for nor evidence of extrapulmonary spread, treatment is of unproven benefit. To date, no placebo-controlled trials concerning this self-limited form of infection have determined whether treatment hastens the resolution of symptoms or prevents the risk of complications. Experts familiar with coccidioidomycosis have widely varying recommendations for management of specific patients in this category. Although some physicians recommend treatment for all patients, others recommend treating only patients with more severe manifestations. Even with selective therapy, its benefit is uncertain.[216,217] A nonrandomized, uncontrolled, single-site study found no statistical difference in symptom resolution in patients with primary mild-to-moderate pulmonary infection treated or not treated with antifungals.[218] In that study, 20 of 36 patients received therapy, 18 of whom received fluconazole at 400 mg daily for a median of 8.5 weeks. Evidence that is often considered to indicate more severe infection includes loss of more than 10% of body weight, intense night sweats for more than 3 weeks, infiltrates involving more than half of one lung or portions of both lungs, prominent or persistent hilar or peritracheal adenopathy, anticoccidioidal complement-fixing antibody titer greater than 1:16, failure to develop dermal hypersensitivity to coccidioidal antigens, inability to work, or symptoms that persist for more than 2 months.[25] Because persons of African or Filipino descent seem to have some increased risk of dissemination, this factor sometimes also weighs in the decision for treatment. If treatment is recommended, commonly prescribed therapies include currently available oral azole antifungal agents, usually fluconazole, for courses ranging from 3 to 6 months.

Although extrapulmonary dissemination usually occurs in the first several months of untreated coccidioidal infections, it is now clear that early treatment of the pulmonary syndrome does not prevent but may delay dissemination in some patients. In fact, late dissemination may not be recognized until years after initial azole treatment is stopped.[216,218] Also, it has been noted that persons treated for early pneumonia are less likely to develop a complement-fixing antibody response.[219] These considerations should be taken into account when deciding whether to treat the early otherwise uncomplicated coccidioidal pneumonia with antifungals.

Diffuse Pneumonia

Diffuse bilateral infiltrates represent either hematogenous infection of the lungs or multiple foci of infection resulting from exposure to a high inoculum of arthroconidia. In either case, even early infections are regarded as serious and warranting therapy. Initial therapy in such cases is usually with amphotericin B, at least for the first several weeks and until the illness seems to be improving. Concomitant use of a brief course of corticosteroids in this situation is controversial but advocated by some authorities.[220] After this time, therapy is often switched to an antifungal azole agent for at least 1 year. Fungemia resulting in diffuse pulmonary infiltrates is often the consequence of severe immunodeficiency, and in such patients, treatment may need to be continued indefinitely to prevent relapse.

Pulmonary Cavity

Cavitation as a sequela of coccidioidal pneumonia is often asymptomatic and may not necessitate treatment. With the passage of time, some cavities disappear. Cavities that do not close spontaneously over 1 to several years are sometimes resected to prevent future complications, especially if the cavity shows progressive enlargement or is immediately adjacent to the pleura and may cause pneumothorax. This potential benefit must be weighed against the risks of the surgical procedure, which vary according to the general health of the patient and the skill of the surgeon.

Pulmonary cavities occasionally produce symptoms, such as local pain, superinfection, or hemoptysis. When this occurs, treatment is usually instituted with oral antifungal azole therapy. This therapy often is accompanied by a diminution of symptoms, but recurrences are frequent if therapy is stopped. Antifungal treatment does not influence the size or disappearance of the cavity. For these patients, resection is a reasonable alternative to long-term suppressive medical therapy.[120] Extrapulmonary dissemination from a solitary pulmonary cavity is very uncommon.

Chronic Fibrocavitary Pneumonia

Persistent coccidioidal pneumonia is ordinarily treated with oral azole antifungal agents. Responses to these agents are approximately 55% to 60% as judged by improved symptoms and radiographic appearance. Treatment options for patients who do not respond include surgical resection of infection localized to a single lobe; switching to an alternative antifungal azole; for fluconazole, raising the dosage; or instituting amphotericin B therapy.

Extrapulmonary Dissemination

For most patients with nonmeningeal dissemination, initial therapy is with an oral antifungal azole. Exceptional patients with rapidly progressive infection or infection in critical locations, such as vertebrae, may respond faster to initial therapy with amphotericin B, but this has not been proved. As discussed previously, surgical débridement or drainage of selected lesions may be an important component of controlling infection.[221,222] As in chronic coccidioidal pneumonia, treatment is continued for at least 1 year and for 6 months past the point at which all evidence of further improvement has ceased. Even so, relapses occur in approximately one-third of patients when therapy is stopped, and some patients may require suppressive therapy indefinitely.

In the management of coccidioidal meningitis, most patients now are treated initially with fluconazole. This is a major departure from therapy with intrathecal amphotericin B, which until the early 1990s was still standard treatment.[223] Although there have been no comparative trials of intrathecal amphotericin B and fluconazole, the response rate of approximately 70% with fluconazole at 400 mg/day is probably at least as good as that achieved with intrathecal amphotericin B, and use of fluconazole avoids most of the toxicity associated with amphotericin B. Higher doses of fluconazole have produced responses in some patients who did not respond initially to 400 mg/day.[150] Similar results have been obtained in patients treated with itraconazole, although there is less clinical experience with this drug than with fluconazole.[202] Both posaconazole and voriconazole have been used as salvage therapy but offer no benefit to patients who have responded to fluconazole. The effect of azole treatment is to arrest fungal proliferation within the meninges and, as a result, inflammation resolves, as indicated by normalization of spinal fluid cell count and hypoglycemia, and this may produce a complete and lifelong remission of symptoms. However, azole therapy is not curative and dormant spherules persist, presumably indefinitely. It is a consensus opinion that patients who respond to azole therapy should continue suppressive treatment for life.[25] In one series in which 18 patients who had achieved an azole remission discontinued azole therapy, 14 relapsed and 2 died.[224] Moreover, it is recommended to use at least 400 mg/day of fluconazole as maintenance therapy, even in patients who are completely controlled on this dose.

Patients who do not respond to oral azole therapy may benefit from intrathecal amphotericin B.[225] Routes of administration include repeated percutaneous intracisternal injection, injection into Ommaya reservoirs that drain to either the cistern or a ventricle, lumbar puncture with medication in a hyperbaric glucose solution, and lateral cervical injection. The technique, frequency, and dosage of intrathecal amphotericin B vary widely among practitioners.

In addition to antifungal therapy to control the meningeal inflammation, surgical interventions are required for two other manifestations. One is hydrocephalus, a common complication of coccidioidal meningitis. Hydrocephalus ordinarily does not respond to antifungal therapy, and a shunting procedure is required. Ventriculoperitoneal shunts could become a conduit for *Coccidioides* spp. from the cerebrospinal space to the peritoneum, but this usually does not result in clinically apparent abdominal complications in patients on azole treatment. Fluid from a ventriculoperitoneal shunt is unreliable for assessing therapy because the whole blood cell count, protein, and glucose measurements are less abnormal during infection than is found in lumbar CSF.[226] A second and uncommon complication is intracerebral abscesses.[154] These lesions may necessitate drainage or resection, in addition to systemic antifungal drug therapy.

Another complication of coccidioidal meningitis is vasculitis.[155] In a retrospective series of 221 patients with meningitis, 18 (8.1%) had cerebrovascular accidents (CVAs), presumed to be a result of the infection.[227] Administering corticosteroids for this complication is controversial. In this series, 14 of the patients received dexamethasone at doses between 8 and 40 mg/day for 10 to 21 days, with the majority of these patients (9 of 14) receiving dexamethasone 10 mg intravenously once, followed by 4 mg four times daily. Steroid tapering ranged from 2 to 6 weeks. One patient received hydrocortisone (50 mg every 6 hours for 10 days). None of these 15 patients had subsequent CVAs, whereas the three patient who did not receive corticosteroids all had additional CVAs. These courses of steroids did not appear to interfere with the effectiveness of the antifungal therapy.

New Therapies

Because the fungal wall of *Coccidioides* organisms contains (1,3)-β-D-glucan and chitin,[39] antifungals that interfere with synthesis of these polysaccharides potentially could be therapeutic for coccidioidomycosis. Caspofungin (Cancidas; Merck & Co., Inc., Kenilworth, NJ) has been effective in treatment of experimental coccidioidal infections.[228,229] However, clinical experience is limited to combination therapy including an azole.[230,231]

Nikkomycin Z, a chitin synthase inhibitor discovered in the 1970s, was subsequently shown to be effective as a therapy against experimental murine coccidioidal infection.[232–234] Clinical trials were initiated in the 1990s but were soon interrupted because the sponsoring pharmaceutical company went out of business.[235] In 2005 the inactive project was transferred to the University of Arizona, which has reactivated the clinical studies.[236,237] A multidose phase I trial has been completed without identifying any safety concerns. Currently, new supplies of nikkomycin Z need to be manufactured to support phase II trials.

Olorofim is an inhibitor of dihydroorotate dehydrogenase that has recently been shown to have antifungal activity.[237a] Recently it has shown activity against an experimental central nervous system infection in mice[237b] and is in clinical trials as treatment for other fungal infections.

PREVENTION

Developing a vaccine as a means of preventing coccidioidomycosis has been an attractive goal for many years. This strategy might be useful because immunity develops in most persons who are infected naturally. A formalin-killed, whole-cell spherule vaccine was found to be exceptionally protective against lethal intranasal infections in mice.[238–243] The whole-cell vaccine also induced a great deal of local inflammation at the injection site, however, and thus the dose in humans is limited to 1.84 mg.[244] For an average human, this is approximately 1/1000 of the vaccine dose (milligrams per kilogram) required for protection in mice. When this dose of formalin-killed spherule vaccine was used in a human field trial, vaccination failed to result in significantly fewer symptomatic cases of coccidioidal pneumonia than were detected in placebo recipients.[245] One plausible explanation for the failure is that the inflammatory reactions to the whole-cell vaccine prevented use of a sufficient dose of the antigens responsible for protection. If this is the case, use of a purified or recombinant antigen might circumvent this limitation.

Several antigens have been expressed as recombinant proteins and, when used with Th1-based adjuvants, have evoked protection against

experimental coccidioidal infections in mice.[246] Unfortunately, the costs of developing a formulation of these vaccine candidates have been prohibitive, and this has prevented their further evaluation. Alternative approaches involve the development of a live-attenuated vaccine[247] or a vaccine with a live nonpathogenic fungus that engenders cross-species protection.[248] Recently, a heterologue of a gene identified to be involved in virulence for a corn pathogen, *Cochliobolus heterostrophus,* was deleted from *C. posadasii.*[28] This mutant causes no disease either in mice without an immune system or in those infected with millions of arthroconidia. Moreover, when this mutant is used as a live vaccine, it is very protective.[248a] This vaccine is now in active development as a candidate to prevent coccidioidomycosis in dogs. If safe and effective as a canine vaccine, this would provide further evidence that it might also be useful for humans.

The public health benefits from an effective preventive vaccine for coccidioidomycosis for the population at risk are roughly equivalent to that for the polio vaccine[246] and, if available, would be cost-effective.[249] That said, the population that would benefit from a Valley fever vaccine is relatively small and may not support commercial incentive to develop the product. Thus it is likely that other sources of support may be needed if a coccidioidal vaccine development program is to be successful.

Regarding preemptive or prophylactic use of prophylactic antifungal agents for visitors or residents of endemic regions, there is no evidence that this would be of benefit, even for highly immunosuppressed persons. A special case exists where an accidental laboratory exposure is identified. A detailed approach to managing such an occurrence has been published.[164] The recommended adult prophylactic dose of fluconazole or itraconazole is 400 mg daily. Drug interactions and pregnancy must be taken into account. There are specific recommendations for prophylactic antifungals for organ transplant recipients as outlined in the current IDSA practice guidelines.[25]

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The complete reference list is available online at Expert Consult.

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266 Dermatophytosis (Ringworm) and Other Superficial Mycoses

Roderick J. Hay

SHORT VIEW SUMMARY

Definition
- Dermatophyte infections are superficial infections of the stratum corneum of the skin or of keratinized appendages, such as hair or nails, arising from it. Other superficial infections are caused by *Candida* and *Malassezia* spp. or less common organisms (e.g., *Piedraia*).

Epidemiology
- Globally, the superficial fungal infections of the skin affect more than 900 million individuals. Most have no underlying abnormality, although individual conditions such as seborrheic dermatitis and oropharyngeal candidiasis may be early signs of human immunodeficiency virus infection.

Microbiology
- The main fungi involved are dermatophyte species of the genera *Trichophyton, Microsporum,* and *Epidermophyton,* and yeasts such as *Candida* or *Malassezia* spp. Less commonly, other mold fungi (e.g., *Neoscytalidium*) are implicated.

Diagnosis
- Direct microscopy of the skin and culture is diagnostic. Molecular diagnostic techniques are in development.

Therapy
- Topical treatments include azole antifungal agents and terbinafine. Selenium sulfide and zinc pyrithione have specific activity against *Malassezia.* Oral therapies include itraconazole and fluconazole; oral terbinafine is the preferred drug for many dermatophyte infections (see Table 266.3).

Prevention
- There are no major preventive programs, although early identification of infection limits spread in communities, such as schools.

The superficial fungal infections include some of the most common infectious conditions, such as ringworm, tinea corporis, and pityriasis versicolor, and rare disorders such as tinea nigra. Their prevalence varies in different parts of the world, but in many tropical countries they are the most common causes of skin disease. Dermatophyte infections and other superficial mycoses are described in this chapter. Superficial candidiasis is discussed in Chapter 256.

DERMATOPHYTOSIS

The dermatophytes are molds that can invade the stratum corneum of the skin or other keratinized tissues derived from epidermis, such as hair and nails. They may cause infections (dermatophytoses) at most skin sites, although the feet, groin, scalp, and nails are most commonly affected.[1] The dermatophytes are among the earliest microorganisms that were found to cause infections in humans. *Trichophyton schoenleinii,* the cause of the scalp infection favus, was isolated from a patient and the culture was shown to reproduce the typical lesions after inoculation onto human skin as early as 1841. Dermatophyte infections had been described many years before this, although the identity of the cause had not been recognized. The ancient Greek physicians knew about ringworm, and there are descriptions of the manifestations of dermatophytosis in more unlikely sources, such as the records of the early explorers of the 16th century who reported a strange disease of the skin, subsequently known as *tinea imbricata,* caused by *Trichophyton concentricum,* in the islanders of the western Pacific.

Dermatophytes

There are four main genera of dermatophyte fungi pathogenic in humans: *Trichophyton, Microsporum, Nannizzia,* and *Epidermophyton.* The last genus is represented by only a single species, *Epidermophyton floccosum.* These keratinophilic organisms probably arose as saprophytic soil fungi, and some dermatophytes, which have been isolated only from soil, have not been shown to cause disease in either animals or humans. Most of the dermatophyte species, however, are parasitic and can cause disease in either humans or animals, often being adapted to a single or narrow range of host species. The dermatophytes are referred to as *zoophilic, anthropophilic,* or *geophilic,* depending on whether their primary source is an animal, human, or soil, respectively. The most common geophilic species found in human infections is *Nannizzia* (previously *Microsporum*) *gypseum.* Other soil genera such as *Paraphyton* do not appear to cause human infections

The exact taxonomic status of dermatophytes remains a subject of debate, although the wider use of molecular tools to determine species has enabled a scientifically based classification and consensus to evolve.[2] The most recent version has the merit of restricting changes to established species names to a minimum.[2]

The relationships among different dermatophytes are not simply a subject for intellectual dispute. To understand the spread of infections, for instance, it is important to attempt to differentiate strains of the same species. Significant advances have been made both in the molecular taxonomy of these organisms and in the development of schemes for strain differentiation through the use of molecular tools.[2] Attempts have also been made to classify the dermatophytes according to their protein spectra, most recently using matrix-assisted laser desorption ionization time-of-flight (MALDI-TOF) techniques [3] Another new technique for identification is surface-enhanced Raman spectroscopy (SERS) coupled with principal component analysis (PCA).[4]

Such techniques have also contributed to our understanding of key issues in pathogenesis, such as spread of infection in populations and relapse after apparently successful treatment. Proteinases produced by dermatophytes are inducible by, for instance, amino acids.[5] Dermatophytes secrete a number of enzymes with different protein affinities, including keratin, the largest of which is a 200-kDa glycosylated metalloprotease, and the genes encoding subtilisin proteinases in *Microsporum canis* (*Sub1, Sub2,* and so on) have been identified.[6] Other significant gene products are heat shock proteins, thiol carbonases, and transporters. These have been shown to be expressed in vivo.[7]

Epidemiology

The factors affecting the distribution and transmission of dermatophytosis are largely dependent on the source of the infection[8]: animal, soil, or human.

Zoophilic Dermatophyte Infections

The main zoophilic dermatophyte fungi are listed in Table 266.1. Each organism is primarily an animal pathogen that sometimes causes human infection. In each case there is usually a range of host specificities, from organisms such as *Microsporum nanum,* whose natural host is the pig and which does not infect other animals, to *Trichophyton mentagrophytes,* which affects a range of different rodent species or, rarely, cats, dogs, and horses.

The host preferences of *T. mentagrophytes,* coupled with small clinical and cultural differences, have led many mycologists to subdivide this group. Under this classification, *T. mentagrophytes quinckeanum (T. quinckeanum)* is used to describe the fungus that causes the clinical pattern of favus in mice, an infection associated with the formation of epithelial crusts. However, the organisms are difficult to distinguish genetically. In most temperate countries, *Trichophyton verrucosum,* the cause of cattle ringworm, and *M. canis,* a dermatophyte that causes infections in cats or dogs, are the most common zoophilic dermatophytes that cause human infections, such as tinea capitis.

Of all the zoophilic dermatophytes, *M. canis* is the most prevalent throughout the world, in both temperate regions and some tropical regions.[8] On occasion, the distribution of zoophilic dermatophytes may appear to be difficult to explain, but usually it reflects the distribution of the animal host. For instance, *Trichophyton erinacei* (part of the *Trichophyton benhamiae* series) is confined mainly to Europe and New Zealand. It is carried by hedgehogs, which were introduced into New Zealand in the 19th century from England. *T. benhamiae* (previously *Arthoderma benhamiae*) is increasingly recognized as a cause of scalp and skin infection acquired from guinea pigs, *Trichophyton simii* is associated with monkeys in India and the Far East, and infections in humans are observed only in these areas.[8]

Geophilic Dermatophyte Infections

Dermatophytes originating from soil, such as *N. gypseum,* are infrequent causes of human disease, although they may be seen more commonly in certain parts of the tropics such as the western Pacific and Central America. In other areas, they usually cause sporadic infections, although on occasion they are responsible for outbreaks of disease among humans in appropriately exposed occupational groups, such as gardeners or farmworkers.[8]

TABLE 266.1 Classification of the Main Dermatophytes (*Trichophyton, Microsporum, Nannizzia,* and *Epidermophyton*)

ORGANISM(S) AND THEIR SOURCES			
HUMAN ORIGIN	**SOIL ORIGIN**	**ANIMAL ORIGIN**	**MAIN ANIMAL SOURCE**
Trichophyton concentricum	*Nannizzia gypseum*	*Trichophyton benhamiae*	Guinea pigs
Trichophyton interdigitale		*Trichophyton erinacei*	Hedgehogs
Trichophyton rubrum		*Trichophyton equinum*	Horses
Trichophyton schoenleinii		*Trichophyton mentagrophytes*	Rodents
Trichophyton soudanense		*Trichophyton quinckeanum*	Mice
Trichophyton tonsurans		*Trichophyton simii*	Monkeys
Trichophyton violaceum		*Trichophyton verrucosum*	Cattle
Microsporum audouinii		*Microsporum canis*	Cats, dogs
Microsporum ferrugineum		*Nannizzia nana*	Pigs
Epidermophyton floccosum		*Nannizzia persicolor*	Bank voles

Anthropophilic Dermatophyte Infections

Dermatophytes that are natural pathogens of humans are the most common cause of human dermatophytosis. They include organisms that mainly cause infections of glabrous skin of the feet or hands and a range of pathogens whose invasion may involve penetration of the hair shaft. The most common of these organisms in most parts of the world is *Trichophyton rubrum,* which causes tinea pedis or tinea cruris in temperate climates and, particularly in the tropics, tinea corporis. Cases of infection that are caused by *T. rubrum* were once rare in the Western Hemisphere, but the infection has spread rapidly since the 1960s. In the feet, among other sites, this dermatophyte can cause noninflammatory chronic infections that are easily transmitted; this is probably an important factor that has determined its spread.[8] The large population movements during World War II are also thought to have contributed to the spread of the disease. Despite this, a variant with distinct morphologic appearances may be isolated from patients with tinea corporis,[9] particularly in the tropics, which suggests that although endemic disease caused by this species has been present for a considerable time, the key adaptation leading to spread was the appearance of strains capable of causing indolent and noninflammatory infections of peripheral skin sites.

The organisms that infect glabrous skin spread largely through contact with infected desquamated skin scales. Classically, this occurs in bathing areas or shower rooms where large numbers of individuals share common facilities—for instance, in military camps or factories.[10] Workers in heavy industries such as mines or nuclear fuels may have a high frequency of foot infection, mainly caused by *T. rubrum,* although *Trichophyton interdigitale* (part of the *T. mentagrophytes* complex) may also be isolated.[11] Changing rooms used by the police and armed forces, schools, and public swimming pools are also sites for infection. In contrast, transmission within the home as a reflection of conjugal or familial cases is not common, although it has been suggested that some patients show immunologic and genetic susceptibility.[12] *E. floccosum* may also cause foot infections, although it is particularly associated with tinea cruris either as a sporadic disease or in institutions, such as prisons and military barracks. These infections are not geographically restricted, even though there are variations in different countries. In many tropical areas, particularly the Far East, *T. mentagrophytes* is less commonly a cause of interdigital foot disease, and patients are infected by the zoophilic variety of this species on sites other than the feet.[13]

Tinea imbricata (a variant of tinea corporis), caused by the anthropophilic dermatophyte *T. concentricum,* has an unusual distribution confined to remote parts of the humid tropics.[14] The main endemic areas are the western Pacific islands, Malaysia, Northeast India, and parts of the Amazon Basin in Brazil. Infants may be affected shortly after birth, and spontaneous recovery is unusual. Large numbers of viable organisms can be cultured from the houses of infected families. Visitors to areas in which the condition is endemic are rarely infected.

The distribution of some of the other anthropophilic dermatophytes that cause tinea capitis in children, and other clinical forms of disease such as tinea corporis or onychomycosis, may be more restricted. The reasons for this are not entirely clear, except that because these infections are prevalent in children, who form a relatively stable population with little opportunity for travel, the spread of the disease within the continent may be limited to certain localities. Whatever the reason, these scalp infections are often found in defined endemic areas (Table 266.2). The situation is best illustrated by the distribution of *Trichophyton* spp. that cause tinea capitis in West Africa, where the endemic areas for *Trichophyton soudanense* and *Trichophyton yaoundei,* members of the *T. rubrum* complex, are distinct, although there is some overlap.[15] However, this pattern is changing as *Trichophyton tonsurans* is now found increasingly in the region. The predominant cause of scalp infection is *T. tonsurans* in the United Kingdom, United States, and Mexico and *Trichophyton violaceum* in India, East Africa, and the Middle East. The situation does not always remain stable, and the slow increase in numbers of *T. tonsurans* in the United States was followed by spread to the United Kingdom and some parts of Europe, Latin America, and Africa.[8] In addition,

TABLE 266.2 Distribution of *Trichophyton* and *Microsporum* Species That Cause Tinea Capitis

DERMATOPHYTE	DISTRIBUTION
Trichophyton tonsurans	North, Central, and South America, Europe, Africa
Trichophyton soudanense	West and Central Africa
Trichophyton schoenleinii	North Africa United States, Middle East, South Africa, South America (sporadic)
Trichophyton verrucosum	Europe
Trichophyton violaceum	Indian subcontinent, Middle East, North and East Africa
Microsporum audouinii	Central America, West Africa Europe (uncommon)
Microsporum canis	Worldwide but uncommon in India and Far East
Microsporum ferrugineum	Central Africa, Far East

other anthropophilic *Trichophyton* infections such as *T. violaceum* and *T. soudanense* are seen in immigrants in Europe and elsewhere. Endemic anthropophilic scalp infections that are caused by *Microsporum* spp. are less common. For instance, *Microsporum ferrugineum* is now seldom found. The most widely distributed of this genus is *Microsporum audouinii.* Once common throughout Europe, it almost disappeared but has been reintroduced by immigration from regions in which it remained endemic, such as West Africa, and it is still a major cause of tinea capitis in Africa.

Favus—the infection caused by *T. schoenleinii*—has characteristic clinical manifestations. It was once common in Europe but has now largely disappeared from many areas, although pockets of infection still exist in parts of sub-Saharan Africa. One of the features of this disease is the development of crusts, or scutula, on the scalp. Hairs are invaded, but shedding is delayed because they are not structurally damaged until late in the course of the infection. Although tinea capitis is normally a disease of children, occasionally women have favus.

Dermatophytes causing scalp disease may be carried on the skin surface without invading the skin or hair. A small proportion of carriers develop infections within 6 months; in others the fungus disappears. Members of an infected individual's family can also become carriers.[16] It is likely, however, that some carriers have limited but undetected infections.

Age Incidence

Tinea capitis is mainly a disease of childhood, and cases rarely occur after puberty. However, this infection may occur in adults and may also be associated with scarring alopecia. The reason for the preponderance of the disease in children is thought to be the presence of medium-chain fatty acids (C_8 to C_{12}) in sebum that inhibit the growth of dermatophytes in postpubertal individuals. In contrast, tinea pedis is usually seen in older children or young adults.[17] Foot infections occasionally occur in young children, but in this age group the nails may be invaded without concomitant skin infection.

Pathogenesis

Transfer of infecting organisms from soil, animals, or humans is accomplished by means of arthrospores, which are vegetative cells with thickened cell walls formed by dermatophyte hyphae in vitro and in vivo. These structures are probably shed by the primary host with skin scales or hair. It has been shown that dermatophyte arthrospores can survive for considerable periods outside the host, in some cases for more than 15 months. Direct contact between the infected individual and another individual is not necessary for the development of dermatophytosis in the latter. The process of transfer itself is little understood, but invasion of the skin appears to follow adherence of fungal cells to keratinocytes in vitro, a process that is maximal after about 2 or 3 hours. Keratinocytes from different sites do not appear to differ in their binding capacity for arthrospores. Subsequent germination leads to invasion.[18]

Susceptibility to infection is not universal. In humans it has been suggested that susceptibility to tinea imbricata is mediated through an autosomal recessive gene. Mutations in genes that convey increased susceptibility to unusual forms of dermatophytosis such as those associated with chronic mucocutaneous candidiasis *(STAT1)*[19] or deep dermatophytosis[20] *(CARD9)* are being identified and are associated with reduced interleukin (IL)-17 production.

However, at the point of contact between fungus and stratum corneum there are endogenous epidermal cell defense mechanisms, such as antimicrobial peptides, including human β-defensin, that are inhibitory to dermatophytes.[21] After contact with the skin, virulence genes that aid penetration, such as the subtilisins or proteinase genes, are expressed.[22] In experimentally infected mice and guinea pigs, the inflammatory response to dermatophytosis is maximal after 9 to 16 days, and after this stage there is resolution of the infection. The main efferent limb of immunologic resistance is the T lymphocyte. Studies of mice with *T. quinckeanum* infections have shown that resistance can be transferred to sublethally irradiated mice with T cells bearing the phenotype of helper-inducer T cells.[23] Suppressor lymphocyte activity can be detected in cells from the draining lymph nodes at the peak of infection. Immunity cannot be transferred with antibody to uninfected animals. Although it is difficult to extrapolate these data to infected humans, there is evidence that the kinetics of the immune response in humans is similar. For instance, the development of delayed-type hypersensitivity in children with naturally acquired scalp ringworm caused by *T. tonsurans* is correlated with recovery. Experimentally infected humans develop both delayed-type skin reactions to trichophytin and T-lymphocyte blastogenic responses at the time of recovery.[23] Patients with chronic *T. rubrum* or *T. concentricum* infections appear to have defective T-lymphocyte–mediated responses, and patients with persistent dermatophyte infections elicit a cytokine profile suggestive of a helper T-cell type 2 response.[24] These observations suggest that appropriate T-lymphocyte activation is crucial for recovery in dermatophytosis.

The afferent limb of the immune response is provided by epidermal Langerhans cells, which have been shown to act as antigen-presenting cells in mixed cultures with human lymphocytes. The mechanisms by which T lymphocytes affect recovery are less well understood. Phagocytes—mainly neutrophils and, to a lesser extent, macrophages—can kill dermatophytes both intracellularly and extracellularly, mainly through oxidative pathways.[19] Dermatophyte antigens have been shown to be chemotactic to human leukocytes and may activate the alternative pathway of complement activation. However, other mechanisms of fungal clearance must also be involved. It has been shown that increased epidermal turnover occurs during infection. Although this also occurs in heterologous skin grafted onto T-cell–deficient *(nunu)* mice, which suggests that an intrinsic response is involved, it is maximal at the time of development of the maximal immune responses.[25] It is possible that elimination of dermatophytes is also accomplished by means of increased shedding of the stratum corneum and that the immune system amplifies an endogenous epidermal response to infection.

Different dermatophyte species vary in their ability to elicit an immune response; some organisms, such as *T. rubrum,* cause chronic or relapsing infections, and others, including *T. verrucosum,* lead to long-term resistance to reinfection. Some dermatophytes produce glycopeptides, which are capable of reversibly inhibiting T-lymphocyte blastogenesis in vitro.[5] There is variation in the ability of different dermatophyte species to stimulate release of cytokines such as IL-12 from keratinocytes in vitro, which may provide an explanation of the differences in inflammatory responses in the skin.[26]

Clinical Manifestations

The archetypal lesion of dermatophytosis is an annular scaling patch with a raised margin that exhibits a variable degree of inflammation; the center is usually less inflamed than the edge. The word *tinea* is used to refer to dermatophyte infections, and it is usually followed by the Latin description of the appropriate site. Hence, tinea pedis is an infection of the feet and tinea capitis is an infection of the scalp. The term *tinea incognito* is used to describe infections that do not have any of the usual characteristic features of dermatophytosis, often because of inappropriate application of corticosteroid creams. Disease associated with immunosuppression,

including infection with the human immunodeficiency virus (HIV) and acquired immunodeficiency syndrome (AIDS), affects the clinical expression of dermatophytosis; the result is often diminished scaling but prominent folliculitis and the formation of pustules.

The clinical appearances of the infection vary with the site, the fungal species involved, and the host's immune response. Zoophilic fungi often cause inflammatory lesions, and in some cases large pustular lesions (kerions) may develop. In contrast, lesions caused by anthropophilic dermatophytes often exhibit little inflammation and may become chronic (see "Pathogenesis").

Tinea Pedis

Tinea pedis is usually caused by infection with either *T. rubrum* or *T. interdigitale* (part of the *T. mentagrophytes* complex) or, less commonly, with *E. floccosum.* The infection usually starts in the lateral interdigital spaces of the foot or on the undersurface of the lateral aspects of the toes. The main symptom is itching, although the severity is variable. The skin usually cracks and may become severely macerated. In some cases, often when *T. mentagrophytes* is the causative organism, bullae are formed and itching is severe. The infection may also spread onto the dorsum of the feet, usually on the lateral side of the foot. Involvement of the sole is common in *T. rubrum* infections, and part of or the entire sole becomes erythematous and covered with dry scales. This is most noticeable along the lateral borders of the sole, where the appearance is often characterized as "moccasin" or "dry-type" infection. Blisters may also be formed in small clusters on the sole. The course of infection is variable. In noninflammatory forms, the interdigital scaling is often chronic or intermittent, whereas if blisters are formed, the infection usually resolves but may recur several months later. The main complications of tinea pedis are bacterial cellulitis and fungal invasion of the toenails (onychomycosis) or the skin of the dorsum of the foot and leg.

Tinea pedis usually occurs in young adults or teenagers. It is particularly common in institutions or places where common bathing facilities are used. The clinical manifestations of infection are altered in patients with T-lymphocyte abnormalities, in whom there is often extensive spread of the lesions onto the dorsal surface of the foot.

Scaling between the toes is often referred to as *athlete's foot,* but similar clinical signs may be produced by a variety of organisms. Erythrasma that is due to *Corynebacterium minutissimum* may manifest as scaling and, in particular, maceration of the toe webs. Gram-negative bacteria such as *Pseudomonas* and *Proteus* spp. may contribute to interdigital disease in patients with closely apposed web spaces or whose work involves immersion in water. These organisms may replace the original dermatophytes in this site, an infection known as *dermatophytosis complex.*[27] *Staphylococcus aureus* may cause secondary infections of the foot, but this characteristically starts on the dorsum of the foot over the first two digits. The mold fungi *Neoscytalidium dimidiatum* (formerly known as *Hendersonula toruloidea*) and *Neoscytalidium hyalinum* may cause interdigital scaling, nail disease, and sole involvement that is indistinguishable from dry-type infections caused by dermatophytes. Cracking between the toes is conducive to cellulitis in predisposed patients, such as those with chronic lymphedema.

Tinea Cruris

The most common dermatophytes associated with groin infections are *T. rubrum* and *E. floccosum.* This infection is also called *jock itch.* The infection starts with scaling and irritation in the groin. The rash usually involves the anterior aspect of the thighs, less commonly the scrotum. The leading edge extending onto the thighs is prominent and may contain follicular papules and pustules. The infection may also spread to the anal cleft. Although tinea cruris is mainly a disease of young men, it may affect women, particularly in the tropics, where the infection may spread in a band around the waist area.

As with tinea pedis, there may be clustering of cases of tinea cruris in institutionalized groups, such as those in military camps. The toe webs are also often infected in patients with tinea cruris.

Erythrasma of the groin may also cause a localized rash with itching. However, here the leading edge is less prominent than in tinea cruris and the rash is covered with fine wrinkles. Erythrasma fluoresces pink under Wood light. Candidiasis of the groin may also mimic tinea cruris, but an important clue to the presence of *Candida* is the appearance of small satellite pustules beyond the free margin of the rash. Flexural psoriasis causes a vivid red and uniformly scaling rash in the groin, and there is usually at least one other site with typical psoriatic plaques.

Tinea Corporis

Tinea corporis is one of the most commonly misdiagnosed skin diseases. Cases of this infection are not common in temperate climates, although it is seen more frequently in the tropics. This form of dermatophytosis has various clinical manifestations. Most lesions have a prominent edge that may contain pustules or follicular papules, and the center of the lesion is often less inflamed and scaly (Fig. 266.1). Sites commonly involved are the trunk and legs. Itching is variable, and lesions may be single or multiple. In general, infections caused by anthropophilic dermatophytes such as *T. rubrum* are less inflammatory and less clearly demarcated, and in some patients it is necessary to search for the margin carefully to delineate the rash. Lesions are usually hyperpigmented in pigmented skins. An outbreak of very extensive tinea corporis (and tinea cruris) infection, refractory to treatment, has been highlighted in many areas of India. An association with the use of high-strength topical steroid antifungal-antibacterial combinations has been identified. Zoophilic infections such as those caused by *M. canis* and *T. verrucosum* are more inflammatory, and lesions may become elevated and contain pustules. Infections caused by *N. gypseum* are also usually inflammatory and may have a brick-red appearance.

These clinical patterns vary with the site of infection. In patients with defective T-lymphocyte function, scaling is often minimal, and the rash of tinea corporis consists of grouped papules or pustules without significant erythema. *T. rubrum* infections on the lower parts of the legs may lead to the formation of single or multiple deep nodules that may mimic erythema nodosum.[28] The overlying skin is dry, red, and scaly, which is a useful clue to the correct diagnosis. This form of infection, *nodular folliculitis,* follows follicular penetration of the hair follicles of the lower portions of the legs by the fungus. It occurs mainly in women.

Tinea corporis can occur at any age.

A number of different conditions should be considered in the differential diagnosis of tinea corporis, including eczema, psoriasis, and annular erythema. The important points to look for are the annular scaling margin of lesions and follicular prominence, which are features of dermatophytosis. However, it may be necessary to take scrapings for laboratory culture when there is doubt.

Tinea Imbricata

Tinea imbricata is a variant of tinea corporis that is caused by *T. concentricum.* The geographic distribution of the disease is shown in Table 266.2. Patients may be infected at any age, although infants and young children are most frequently affected. The main characteristic of the rash is the formation of concentric rings of scales (Fig. 266.2) that amalgamate to form waves of scaling over large parts of the body.[14] Other clinical varieties of tinea imbricata include the diffuse scaling variety, in which large flakes of skin are prominent. The disease gets its

FIG. 266.1 Inflammatory tinea corporis caused by *Trichophyton erinacei* (part of the *Trichophyton mentagrophytes* complex).

FIG. 266.2 Early lesions of tinea imbricata, showing the first signs of concentric rings.

FIG. 266.3 Tinea faciei caused by *Trichophyton rubrum.*

name *imbricata* (Latin, "tiled") from this clinical pattern. Other patients may have itchy lichenified lesions on the forearms. The face may be affected, as may the sides of the fingers, but the feet, scalp, axillae, and groin are usually spared. Tinea imbricata is seldom mistaken for other diseases, and the inhabitants of areas in which the condition is endemic easily recognize the appearance of the infection and have specific names for it. In Papua New Guinea it is called *sipoma* or *grille.*

Tinea Manuum

The term *tinea manuum* is used for dermatophyte infections involving the hand. In some patients, the dorsum of the hand may be affected, but most commonly the disease occurs on the palmar surface. A characteristic of dry-type infections at this site is involvement of only one palm, although in some patients both may be affected. The clinical manifestations are identical to those seen with dry-type infections of the sole. The usual cause is *T. rubrum,* and the feet are often involved, in addition to the hands.

Dermatophytosis affecting the palm may be confused with eczema, but the unilateral distribution of the infection and the common accompanying findings of onychomycosis and tinea pedis are helpful clues. Patients with palmoplantar keratoderma (tylosis) are particularly susceptible to superinfection of the palms and soles with dermatophytes.[29] This complication may be difficult to identify, but the skin may blister and the hand usually itches. In such patients, fungi other than *T. rubrum* may be implicated.

Tinea Faciei

Dermatophyte infections of the face are usually caused by the same organisms associated with tinea corporis. Infections with *T. rubrum* at this site are often particularly difficult to recognize. The facial skin becomes itchy and red, but the margin of the rash may be difficult to discern (Fig. 266.3). Some patients report that the facial rash is exacerbated by sun exposure. In other instances, lesions are more readily noticeable and affect the ears. Tinea faciei has been reported more frequently in patients with AIDS.

Tinea barbae (infection of the neck and beard area) may be pustular and inflamed because it is often caused by zoophilic organisms such as *T. verrucosum.* It is more localized than sycosis barbae, which is caused by *S. aureus*; this difference is helpful in distinguishing the two conditions.

FIG. 266.4 Scalp ringworm in which an ectothrix infection of the hair is caused by *Microsporum canis.*

Tinea Capitis

Scalp ringworm, or tinea capitis, is a disease of childhood. Its prevalence varies considerably in different parts of the world. The disease is widespread in some urban areas in the United States, Africa, and Europe. Tinea capitis is also common in parts of India. In northern Europe the disease is sporadic. The main reasons for these differences in the prevalence of infection in different localities are the nature of the infecting organisms and the availability of control measures. Endemic infections affecting large numbers of children are associated with anthropophilic organisms; sporadic disease is associated with zoophilic fungi. Tinea capitis is usually classified by the pattern of hair shaft invasion. Dermatophyte infections in which arthrospores are formed on the outside of the hair shaft are known as *ectothrix* infections; those in which the spores develop within the hair itself are known as *endothrix* infections. In *T. schoenleinii* infections, the fungi invade the hair medulla but then regress and leave tunnels containing air within the hair shaft (the "favic" pattern). Although it is identified as a childhood disease, adults exposed to *T. tonsurans* infections and patients with AIDS may develop tinea capitis.

The main clinical feature of dermatophyte scalp infections is the appearance of scaling of the scalp skin that is associated with a variable degree of erythema, inflammation, and alopecia. In some cases, the infection closely resembles seborrheic dermatitis or dandruff of the scalp. The infection is often accompanied by itching. A pathognomonic feature is hair loss. In ectothrix infections, hairs often break a few millimeters or more above the skin surface (Fig. 266.4). Broken or infected hairs are also slightly swollen and have a dull appearance. In endothrix infections, parasitized hairs break at the skin level. In some endothrix infections, scattered stumps can be seen within areas of hair loss (black-dot ringworm). In such cases, inflammation may be minimal. A further element in tinea capitis is the variable amount of inflammation, but in some cases the whole area becomes pustular and covered with a thick scale or exudative crust. Often one of these elements dominates the clinical pattern. For instance, in some children there is little overt hair loss; the whole infection resembles seborrheic dermatitis. Likewise, in some ectothrix infections, a pustular form of dermatophytosis (kerion) develops. This is less common in endothrix infections. In most kerions, the pustules are not a sign of secondary bacterial infection,[30] although this may occur under adherent crusts.

Tinea capitis is uncommon in adults, although it has been reported with a variety of fungi such as *T. tonsurans* or *T. violaceum.* It has been associated with scarring alopecia of unknown etiology (pseudopelade) in adults.

In favus the same processes occur, but an important clinical characteristic is the formation of an inflammatory crust, or scutulum, composed of neutrophils and serous exudate around individual hair shafts. With time, these amalgamate over the surface of the scalp, so that the hair appears to be matted together with a thick crust that is said to have a musty odor. In many patients, the signs are indistinguishable from those seen with other forms of scalp ringworm. Two other characteristics of favus are late shedding of hairs and a tendency to develop scarring alopecia. The infection may persist into adulthood.

Untreated scalp ringworm usually remits spontaneously after puberty. Permanent hair loss is uncommon unless the response has been severely inflammatory or the patient has favus. A surprising degree of recovery of hair growth occurs, even in children with severe kerions.

Tinea capitis must be distinguished from seborrheic dermatitis, which usually occurs in older children and does not cause hair loss. Alopecia areata also causes circumscribed areas of hair loss but does not scale, and the "exclamation mark" hairs seen in this condition—broken hairs tapering from the fractured end toward the skin surface—are pathognomonic.

Onychomycosis Caused by Dermatophytes

Onychomycosis, or fungal infection of the nails, usually occurs in individuals with infections of adjacent toe or palmar skin, except in rare cases of childhood nail infection in which nail plate invasion may develop without skin involvement. There are several different patterns of nail plate invasion.[31]

The most common clinical pattern of onychomycosis is distal and subungual onychomycosis, in which the nail plate is invaded from the distal and lateral borders. There is usually associated thickening of the nail, which becomes white, yellow, or brown. Occasionally, *T. rubrum* results in fungal melanonychia or black pigmentation of the nail. In onychomycosis caused by endothrix scalp fungi such as *T. soudanense,* the thickening may be minimal and the nail surface is pitted with small fissures.[32] The most common cause of onychomycosis is *T. rubrum,* which often accompanies long-standing disease, and the infection involves the entire nail plate.

Superficial white onychomycosis occurs when the nail plate is invaded from the top surface, which is eventually covered with white crumbly plaques. Other fungi, such as *Fusarium* spp., more commonly cause this pattern of nail invasion, but this may be followed by deeper penetration. However, in its pure form, superficial white onychomycosis can occur with *T. interdigitale,* and it may accompany distal and subungual onychomycosis in some *T. rubrum* infections. It may also accompany proximal subungual onychomycosis (described later).

In rare cases, invasion appears to originate from the proximal nail plate as patchy or linear discoloration. This is usually a feature of relapse of treated nails, but rapidly spreading proximal nail plate invasion or full-thickness nail penetration has also been described in patients with AIDS.[33] Patterns of infection differ with striate or continuous areas of infection. They may be caused by dermatophytes and by nondermatophyte fungi such as *Fusarium* spp.

Onychomycosis can occur at any age, although it is more common with increasing age. Men and women are affected in equal numbers.

Onychomycosis caused by dermatophytes must be distinguished from that caused by *Candida,* in which there is little nail plate thickening but toenail infection is rare. *Neoscytalidium* infections may also lead to nail plate invasion. These are similar to infections caused by dermatophytes, but the nail plate is often not grossly thickened and may be severely undermined, and invasion affects predominantly the lateral border of the plate in the early stages of disease. Psoriasis of the nail also causes onycholysis, but the nail plate is typically covered with fine pits.

Deep Dermatophyte Infections

On rare occasion, patients known to be immunocompromised or otherwise healthy individuals develop dermatophyte infections in which the fungi invade deep dermal structures or produce a disseminated infection. In the first and more localized form, dermatophytes invade subcutaneous tissues after hair shaft penetration, producing a deep nodule described previously as nodular folliculitis or a granuloma (Majocchi granuloma), or it may spread via the lymphatic vessels, causing clusters of granulomas, lymphedema (Fig. 266.5), and draining sinuses. Sometimes aggregates of fungal hyphae resembling those found in eumycetomas may be observed in histologic sections. These dermatophyte "pseudomycetoma" grains may be surrounded by neutrophil abscesses, but the fungal hyphae are often engulfed by giant cells in tissue sections. Deep dermatophyte infections may extend farther and result in widespread cutaneous lesions; these may progress to involve draining lymph nodes or disseminate to other sites, including the liver and brain, and they may be fatal. Individual patients and members of families with some forms of deep dermatophytosis have been found to have mutations within the *CARD9* gene.[20] Patients homozygous for mutations in this gene are also more predisposed to deeply invasive candidiasis, phaeohyphomycosis, and aspergillosis. Case reports of deep infection caused by dermatophytes are rare, but, in addition to the *CARD9* cases described previously, isolated examples are regularly described, often in immunodeficient patients.[34]

Dermatophyte "Id" Reactions

The immune mechanisms in dermatophytosis may lead to the appearance of secondary rashes called *id reactions.* The most common of these is acute vesicular eczema or pompholyx that occurs on the hands and feet in patients with inflammatory ringworm of the feet, mainly caused by *T. mentagrophytes.* These events are thought to be causally linked if the original dermatophyte infection becomes inflamed before the appearance of the secondary rash, if the latter is maximal on the affected foot. A second form of id reaction, seen in patients with inflammatory tinea capitis or tinea corporis and usually caused by zoophilic organisms, consists of small follicular papules, some of which appear necrotic. This is a form of cutaneous vasculitis that usually subsides spontaneously. Both reactions may be triggered by antifungal therapy. Less common types of id reactions include annular erythema and erythema nodosum.

Point of Care and Laboratory Diagnosis

In some cases it is possible to screen patients with scalp infections by using a filtered ultraviolet light source (Wood light). Infections caused by some *Microsporum* spp. fluoresce green. However, *Trichophyton* infections do not fluoresce, apart from favus, in which the hairs appear yellowish. Because fluorescent hairs are infected, Wood light examination may be helpful as a method of selecting hairs for microscopy and culture. The dermatoscope, a skin surface handheld microscope, is very useful because it may show specific patterns indicating fungal invasion in patients with tinea capitis or nail infections.[35]

The laboratory diagnosis of dermatophytosis depends on the examination and culture of scrapings or clippings from lesions.[1] It is important

FIG. 266.5 Deep dermatophytosis in which *Trichophyton rubrum* infection is causing unilateral lymphedema after invasion of the lymphatic vessels.

to sample the edge of skin lesions and infected nails. In the case of infected hairs, it is best to select broken stubs, which can be removed with forceps without undue trauma. Material should be allowed to soften in 10% potassium hydroxide before being examined under the microscope. Nails often take up to 2 hours to soften, although the process can be hastened by gentle warming. Fungal hyphae can be seen as chains of arthrospores in cleared scales or clippings. The fluorescent whitener calcofluor may also be used to stain fungi, but preparations have to be viewed with fluorescence microscopy; however, it may enhance the yield of positive samples.

Dermatophytes infecting hair have characteristic direct microscopic appearances that are helpful in recognition. Some form arthrospores on the outside of the hair shaft (ectothrix infections). The small spores can be seen by focusing the microscope on the edge of the epilated hair shaft. With most of the pathogenic *Microsporum* spp. that cause tinea capitis, small arthrospores are clustered around the outside of hair. By contrast, few *Trichophyton* spp. form ectothrix spores, but those that do, such as *T. verrucosum,* produce large arthrospores. The majority of *Trichophyton* spp. causing scalp ringworm form arthrospores within the hair shaft (endothrix infection). With some practice, it is possible to make a preliminary identification of the likely genus of invading fungus from the findings of the microscopic study of infected hair. *T. schoenleinii* invades hair, but hyphae regress and leave airspaces within the hair shaft.

Skin scrapings or nail clippings may also be cultured. Primary isolation is carried out at room temperature, usually on Sabouraud agar containing antibiotics (penicillin-streptomycin or chloramphenicol) and cycloheximide (Acti-Dione), an antifungal agent that suppresses the growth of environmental contaminant fungi. In the case of nail disease, it is important to use media without cycloheximide because certain fungi, such as *Neoscytalidium,* that may infect nails are sensitive to the latter. Most dermatophytes can be identified within 2 weeks, although *T. verrucosum* grows best at 37°C and may have formed into only small and granular colonies at this stage. Identification depends on the gross colonial and microscopic morphologic features. In some cases, other tests involving nutritional requirements and hair penetration in vitro are necessary to confirm the identification. Molecular diagnosis of dermatophytosis using defined polymerase chain reaction (PCR) assay probes are also used in dermatophytosis,[36] although at present there are few commercially available molecular test kits. Direct microscopy is still a necessary part of the diagnosis. Likewise MALDI-TOF is an alternative method of diagnosis.

Therapy

Ringworm of the Glabrous Skin (Tinea Pedis, Corporis, Manuum)

Topical Therapy

The usual approach to the management of these dermatophyte infections is topical therapy if possible, although most nail and all hair infections and widespread dermatophytosis are best treated with oral drugs (Table 266.3).[37] The main topical agents used for dermatophytosis are compounds with specific antifungal activity. The keratolytic agents such as Whitfield ointment (salicylic and benzoic acid compound) are now rarely used. Currently, a large group of specific antifungal agents are used in treatment of dermatophytosis, although some of these are largely confined to the treatment of tinea pedis. The most frequently used medications are the topical azole antifungal agents, which include miconazole, clotrimazole, econazole, tioconazole, ketoconazole, luliconazole, efinaconazole, bifonazole, and isoconazole.[37] These are active against all the common skin fungi, and many can be used once daily. Other potent topical antifungal agents used in the treatment of dermatophytosis are ciclopirox olamine, tavaborole, terbinafine, and naftifine. It is difficult to choose among the different groups of these agents on the basis of well-constructed comparative studies. A Cochrane Review of topical treatments for tinea cruris and corporis (126 studies with 18,086 participants) found many biases and poor-quality evidence but concluded that data suggested that topical terbinafine and naftifine were effective.[38] In addition, older preparations, such as chlorphenesin, undecylenate, and tolnaftate, are available in cream or, in some cases, powder form and are effective in uncomplicated cases.

TABLE 266.3 Treatment of Dermatophytosis

DERMATOPHYTOSIS, CLINICAL DISEASE PATTERN	TREATMENT
Tinea pedis	
Interdigital	*Topical cream/ointment:* terbinafine, imidazoles (e.g., miconazole, econazole, clotrimazole), undecenoic acid, tolnaftate
"Dry type"	*Oral:* terbinafine, 250 mg/day for 2–4 wk; itraconazole, 400 mg/day for 1 wk/mo (repeated if necessary); fluconazole 200 mg weekly for 4–8 wk
Tinea corporis	
Small, well-defined lesions	*Topical cream/ointment:* terbinafine, imidazoles (e.g., miconazole, econazole, clotrimazole)
Larger lesions	*Oral:* terbinafine, 250 mg/day for 2 wk; itraconazole, 200 mg/day for 1 wk; fluconazole, 250 mg weekly for 2–4 wk
Tinea capitis	Griseofulvin, 10–20 mg/kg/day for minimum 6 wk Terbinafine <20 kg: 62.5 mg/day 20–40 kg: 125 mg/day >40 kg: 250 mg/day Itraconazole, 4–6 mg/kg pulsed dose weekly Fluconazole, 3–8 mg/kg pulsed dose weekly
Onychomycosis	
Fingernails	Terbinafine, 250 mg daily for 6 wk Itraconazole, 400 mg/day for 1 wk each month, repeated for 2–3 mo Fluconazole, 200 mg weekly for 8–16 wk
Toenails	Terbinafine, 250 mg daily for 12 wk Itraconazole, 400 mg/day for 1 wk each month, repeated for 2–4 mo Fluconazole, 200 mg weekly for 12–24 wk

In general, topical therapy for tinea pedis has to be continued for at least 2 and possibly 4 weeks. Topical terbinafine can be used to clear lesions of tinea pedis in 7 days and is also available as a single-dose film-forming solution applied to the soles of the feet. Tinea cruris usually responds within 2 or 3 weeks of the outset of treatment. Some of the azole agents can be used only once daily.

Systemic Therapy

The main oral antifungal agents used for dermatophytosis are terbinafine, itraconazole, and fluconazole. Griseofulvin is an older alternative treatment but is still used in tinea capitis caused by *Microsporum* species.[39] Adverse effects include headache, nausea, and abdominal discomfort. Less common reactions are urticaria, diarrhea, and photosensitivity. Newer triazoles, such as posaconazole and voriconazole, are expensive and not widely used. Terbinafine is given in dosages of 250 mg daily for 2 weeks for tinea cruris or corporis. It produces rapid and long-lasting remissions for dry-type dermatophytosis and other skin infections. Itraconazole can be given continuously in doses of 200 mg daily and is curative for tinea cruris or corporis after 1 week. Fluconazole can also be used as a treatment for dermatophytosis, but current regimens entail 150 to 300 mg weekly for infections of the skin. All three drugs are well tolerated and have evidence of efficacy in ringworm of the glabrous skin.[40,41] Drug interactions in patients with comorbidities can limit use of itraconazole or terbinafine. With terbinafine, interactions with antidepressants and β-blockers may contraindicate use. With itraconazole, drug interactions are even more numerous. Risk of hepatic injury is very low (<1 per 70,000) with all three antifungals.

Tina Capitis

Oral therapy is used for scalp ringworm. Itraconazole and terbinafine are effective in treating scalp disease, and pediatric formulations are available in some countries.[42] Terbinafine is effective against *Trichophyton* scalp infections and usually requires only 2 to 4 weeks of therapy. Terbinafine is less active against tinea capitis caused by *Microsporum* species, for which griseofulvin is preferred and used for 8 to 12 weeks. Griseofulvin is given in doses of 10 to 20 mg/kg daily for the microsize

formulation in either tablet or syrup form. It is often useful to use a topical azole cream or shampoo in addition to systemic therapy for tinea capitis and, if crusts are present, to remove these with saline soaks.

It is important to attempt to identify the organism causing scalp infection because if the infection is of human origin, it can spread to other contacts, and it may be necessary to screen classmates or members of the families of children with anthropophilic infections. Zoophilic infections do not usually spread from child to child, although several family members exposed to the same source of infection may develop scalp disease.

Onychomycosis

Topical treatment of onychomycosis or nail mycosis is generally ineffective. Nevertheless, several topical preparations are of potential value in the management of nail disease. One, a topically applied nail solution containing 28% tioconazole, has been found to produce some mycologic and clinical remissions. Another preparation is a combination of 40% urea and bifonazole. Urea is a potent hydrating agent and softens nails after application under occlusion. The 40% urea paste may be used to remove residual areas of infection after oral therapy for onychomycosis.[43] This combination may also prove useful in addition to oral therapy for nail disease. Solutions with penetration enhancers, such as ciclopirox olamine and amorolfine, are widely used as nail lacquers. They are effective in a proportion of early cases of dermatophyte and *Candida* nail infection. They are applied once or twice weekly and are increasingly being used in combination therapy with oral drugs in severe infections.[44]

Three new topical antifungal agents have been used for the treatment of onychomycosis. Luliconazole 5%, efinaconazole 10% solution, and tavaborole 5% solution are applied to the nail daily for 48 weeks. They are effective in some patients but have not greatly improved on the cure rates seen with other topical nail agents,.[45]

Several pulsed laser treatment regimens using intermittent pulses have been applied to the treatment of onychomycosis. Treatment is expensive, and efficacy when used alone appears to be modest, usually leading to only temporary improvement.[39,46] Other new treatment approaches include the use of photodynamic therapy, iontophoresis of terbinafine, and application of nail antifungal solutions after drilling multiple holes on the nail.[47]

When the entire nail matrix is involved, atraumatic removal of infected nails using 20% to 40% urea, applied under occlusion, can significantly improve results of topical or systemic therapy.[39]

Systemic treatment of onychomycosis is preferred. Terbinafine and itraconazole have replaced griseofulvin for this indication. Treatment is given for 6 weeks for fingernail infections and 12 weeks for toenail infections. In 70% to 80% of patients, terbinafine 250 mg once daily produces cure in 6 weeks for fingernails and 12 weeks for toenails.[48] Itraconazole is also effective against toenail infections and can be given at a dosage of 200 mg daily for 3 months. However, for nail infections, it is usually administered as a "pulsed" treatment given for 1 week of each month at a dosage of 400 mg daily, the week's course being repeated once more for fingernail infections (two pulses) and two or three times for toenail disease (three or four pulses).[49] Reported remission rates are above 60%. Intermittent regimens with fluconazole (300 and 450 mg weekly) are also used in the treatment of onychomycosis.[50] There have been no large comparative studies of fluconazole versus the other two treatments for nail disease. However, in one large double-blind study of patients with toenail onychomycosis, terbinafine, given continuously at 250 mg daily for 12 or 16 weeks, was compared with pulsed itraconazole, at 200 mg twice a day for 1 week each month repeated three or four times. The results revealed significantly better responses for both terbinafine groups than for itraconazole in both mycologic and clinical remission rates.[51] To date, in vitro resistance to drugs used in dermatophytosis has not proved to be a significant problem.

NEOSCYTALIDIUM INFECTIONS

Infections caused by the pigmented fungus *N. dimidiatum* closely resemble dry-type dermatophytosis caused by *T. rubrum*. *N. dimidiatum* was originally described as a pathogen in plants, but it appears to be a genuine cause of human infection. A similar infection has been ascribed to the related nonpigmented mold *N. hyalinum*. In both cases, the affected patients come from the tropics.[52]

The precise mechanisms of infection with either organism are unknown. *N. hyalinum* has never been isolated from the environment, and although *N. dimidiatum* is a pathogen of certain plants such as fruit trees, patients do not usually give a specific history of exposure. It has been found that healthy individuals in some tropical areas carry these organisms on the feet but do not have overt disease, which suggests that asymptomatic carriage may, under the appropriate conditions, be followed by infection. Infections have been described in immigrants from tropical areas to the United Kingdom, Canada, and France. They have also been identified in the southern United States, Trinidad, West Africa, Colombia, Ecuador, and India, and it is likely that it is more widespread. On occasion, it may be seen in patients who have paid short visits to the tropics.

Clinical Manifestations

The clinical signs of skin infection with both *Neoscytalidium* species are identical to those associated with dry-type *T. rubrum* infections.[52] There is scaling of the lateral interdigital spaces, over the soles, and on one or both palms. Itching is usually minimal. Onychomycosis may also develop. Often there is early invasion of the lateral border of the nail without significant thickening of the nail plate (Fig. 266.6), but eventually the whole nail plate may be undermined and onycholysis may lead to shedding of the complete nail. Hyperpigmented streaks may occur in the nails, although these are not pathognomonic for these infections and can be seen with other forms of inflammatory nail dystrophy. Deep infections such as sporotrichoid *Neoscytalidium* infections and a brain abscess have rarely been reported, mainly in immunocompromised patients.[53]

Diagnosis

Scrapings or nail clippings examined after treatment with potassium hydroxide contain sinuous fungal hyphae. Close inspection reveals that the structure is different from that normally seen with dermatophyte hyphae, but accurate discrimination requires experience. Both organisms grow on Sabouraud agar but are inhibited if cycloheximide (Acti-Dione) is incorporated in the medium.

Therapy

There is no satisfactory therapy for either infection. Whitfield ointment (6% benzoic acid and 3% salicylic acid) may be used to treat *Neoscytalidium* infections of the sole or the palm. However, none of the specific antifungal drugs currently available produces consistent results.

OTHER FORMS OF ONYCHOMYCOSIS

A number of other fungi may cause onychomycosis. The most common of these is *Scopulariopsis brevicaulis,* which usually causes infection of the great toenails. Some patients with this form of infection have previously abnormal toenails (e.g., onychogryphosis). *Scopulariopsis* infections of the nails have a typical cinnamon color that is caused by the presence

FIG. 266.6 Onychomycosis caused by *Neoscytalidium dimidiatum*.

of fungal spores seen on direct microscopic views of the nail. The fungus is easy to isolate in culture. Treatment may be difficult, but chemical nail removal with 40% urea may be useful.

Superficial white onychomycosis may be caused by *Fusarium* species. These infections are similar to those caused by *T. mentagrophytes,* and the identity of the causative organisms should be confirmed with culture.

On occasion, other fungi are isolated from nail material. In many cases they appear to be colonizing the undersurface of dystrophic nail plate. On rare occasions, however, they may contribute to the nail disease by invasion. This is best established through repeated attempts at culture; if the organism is isolated on numerous occasions and if hyphae are present in the nail, it is likely that the organism is involved in the nail disease. Examples of infections caused by a range of different organisms, such as *Aspergillus* and *Fusarium* spp., have been recorded. *Fusarium* is now known to cause a range of fungal nail infections from superficial white onychomycosis to paronychia and proximal subungual disease. In severely neutropenic patients, nail infection may be followed by systemic dissemination of this fungus. It may also cause toe web infection. Oral antifungal therapy is unpredictable against these infections,[53] and nail removal with 40% urea is often used as an adjunctive treatment.

PITYRIASIS VERSICOLOR

Pityriasis versicolor, or tinea versicolor, is a superficial infection caused by *Malassezia* species, which are lipophilic yeasts that are normal commensals on the skin surface.[54] The infection is confined to the trunk or proximal aspects of the limbs. It does not cause hair and nail plate invasions.

Organisms

The normal skin is colonized in late childhood and adult life by lipophilic yeasts. Morphologically, these are either oval (most common on the scalp) or round (mainly on the trunk), and they were previously called *Pityrosporum ovale* and *Pityrosporum orbiculare,* respectively. These organisms have now been reclassified as members of the genus *Malassezia,* among which there are seven common pathogenic species: *Malassezia furfur, Malassezia pachydermatis* (not associated with human skin infections), *Malassezia sympodialis, Malassezia globosa, Malassezia restricta, Malassezia obtusa,* and *Malassezia slooffiae.*[55] Round yeasts, usually *M. globosa,* are seen in lesions of pityriasis versicolor accompanied by short, stubby hyphae; *M. furfur* may also produce filaments but is less common in adults. *Malassezia* species dominate the skin fungal microbiome in core scalp, body, and arm sites of adults.[5]

Pathogenesis

The infection is associated with transformation of yeast-phase organisms into hyphal forms, although occasional patients with pityriasis versicolor have only oval yeasts. The stimulus for this phase change is unknown. Infections are more common in the tropics and may appear after sun exposure, which may therefore be a trigger factor. Patients with Cushing syndrome may also develop this infection, but diseases related to T-lymphocyte suppression, such as HIV infection and AIDS, are not necessarily associated with pityriasis versicolor.[56] *Malassezia* yeasts grow in the presence of medium-chain fatty acids.

Different species of *Malassezia* obviously play a role in the development of disease, although it is not known why, for instance, *M. globosa* in particular should be associated with pityriasis versicolor.

Clinical Manifestations

Pityriasis versicolor is usually seen on the trunk or proximal portions of the limbs, although more extensive infections involving the face and waist area occur in the tropics. Lesions may be hypopigmented or hyperpigmented macules that amalgamate to cover the affected area with scaling plaques. The lesions are usually not itchy. In some patients, lesions may remit spontaneously. Rare clinical variants include some infections that result in anetoderma (localized skin atrophy).

The diagnosis can be confirmed through direct microscopic study of lesions, on which the characteristic round yeast forms and short hyphae can be seen. The scrapings can be viewed after clearing with potassium hydroxide. Lesions fluoresce yellow-green under Wood light, although this may not be seen on all affected areas. *Malassezia* yeasts are difficult to culture unless oil or Tween 80 is added to the medium.

Therapy

The most appropriate therapy for pityriasis versicolor is a topical azole or terbinafine cream[55]; less expensive alternatives, now less often used, are 2% selenium sulfide lotion or 20% sodium thiosulfate applied daily for 10 to 14 days. These alternative preparations may be irritative. In some cases, intermittent applications of 50% propylene glycol in water prevent a relapse.[57] In severe cases, oral itraconazole produces remissions. Among oral treatments, itraconazole 200 mg daily for 5 or 7 days and fluconazole 300 mg weekly for 2 weeks are effective.

Patients usually have to be warned that the pigmentary changes may return to normal only after many months, even when the infection has been successfully treated.

OTHER *MALASSEZIA* INFECTIONS

Two other skin conditions are associated with *Malassezia* yeasts: *Malassezia* folliculitis and seborrheic dermatitis. In addition, this fungus has caused catheter-acquired sepsis (see Chapter 268).

Malassezia Folliculitis

There are three main forms of *Malassezia* folliculitis. The first is a folliculitis on the back or upper part of the chest that consists of scattered follicular papules or pustules. These are itchy and often appear after sun exposure. In the second form, which is seen in patients with seborrheic dermatitis, there are numerous small follicular papules over the upper and lower portions of the back and chest. Erythema and greasy perifollicular scales are often seen in these patients. In the third form, multiple pustules are seen on the trunk and face in patients with HIV infection. This type is similar to the second form, and affected patients usually have severe seborrheic dermatitis.

Scrapings or biopsy specimens from lesions show numerous yeasts occluding the mouths of follicles. Treatment with topical azole antifungal agents may be effective, but oral therapy with itraconazole is often necessary.

Seborrheic Dermatitis

In the early part of the 20th century, seborrheic dermatitis and dandruff of the scalp were thought to be caused by *Malassezia* yeasts because numerous organisms were present in skin scales. This view was subsequently superseded by the belief that the yeasts were secondary to a hyperproliferative state. However, evidence suggests that *Malassezia,* mainly *M. globosa* and *M. restricta,* is implicated in the pathogenesis of the condition.[58]

In most cases, seborrheic dermatitis responds to oral or topical azole antifungal agents. Improvement is associated with disappearance of the organisms, and relapse is associated with recolonization. Furthermore, the clinical appearances can be mimicked in animals with the application of both live and killed organisms to the skin. Some patients with seborrheic dermatitis have high titers of antibody to *Malassezia* species. Two newly described potential pathogenetic mechanisms are the production of irritants, such as oleic acid, or of *Malassezia* metabolites that are immunomodulatory, such as indolocarbazole and malassezin, on affected skin of seborrheic dermatitis patients.[59] Lipase production by *Malassezia* isolated from affected skin can be enhanced by exposure to β-endorphin.[60]

Seborrheic dermatitis can appear in any individual, although it is said to be particularly common in patients with neurologic disease, such as parkinsonism. In patients with AIDS, the onset of seborrheic dermatitis may be sudden and the rash more extensive than in other individuals.[61] The histology of seborrheic dermatitis shows acanthosis and hyperkeratosis with elongation of dermal papillae. An infiltrate of polymorphs in the epidermis above the dermal papillae is also often seen. HIV-positive patients tend to have more plasma cells in the infiltrate. These changes are similar to those seen in some forms of psoriasis.

Clinical Manifestations

The classic features of seborrheic dermatitis make up a range of different clinical appearances. These include erythema and scaling of the central part of the anterior aspect of the chest and the upper part of the back

that are accompanied by a variable degree of itching. On the face, there is erythema with greasy scales in the eyebrows, around the alae nasi, behind the ears, and in the external ears. Scaling may also appear in the presternal areas of the chest and on the back. Scaling on the scalp is accompanied by the appearance of pustules in some patients. The clinical appearances are typical, and fungal scrapings are unnecessary.

Other forms of skin disease, including severe erythroderma in infants and an intertriginous rash in adults, have also been called "seborrheic dermatitis," but these lesions do not appear to be related to the variety discussed here.

Therapy

The main therapy involves the use of topical azole creams or oral azoles such as itraconazole and weak topical corticosteroids such as 1% hydrocortisone.[54] Relapse is common, but repeated treatment when necessary is the simplest approach to management.

Malassezia is also associated with a form of atopic dermatitis affecting the face in young adults. It is believed that immunoglobulin E (IgE)–mediated sensitization by allergenic proteins produced by *Malassezia* (e.g., Mala s1 to Mala s9) may play a role in exacerbating the inflammatory responses in eczematous skin.[62]

TINEA NIGRA

Tinea nigra is a superficial form of phaeohyphomycosis caused by *Phaeoannellomyces werneckii* (also called *Hortaea werneckii* and *Exophiala werneckii*). The infection is confined to the stratum corneum of the palms or soles and occurs mainly in the tropics or subtropics in children or young adults.

The typical lesion of tinea nigra is a superficial, scaling, brown or black macule on the palms or soles. The pigmentation is irregularly distributed over larger lesions. Spread of the infection to other sites is rare, and lesions remain asymptomatic.

The main differential diagnosis is a superficial form of melanoma or a pigmented nevus. The pigmented hyphae can be seen by direct microscopic study of skin scrapings treated with potassium hydroxide. The organism can also be cultured from scrapings, but a dermatoscope can show the very typical pigmented hyphae on the skin.

The best therapy is treatment with a topical azole or a keratolytic agent such as Whitfield ointment or 5% to 10% salicylic acid ointment.

WHITE PIEDRA

White piedra is an uncommon infection caused by yeasts of the genus *Trichosporon,* namely, *Trichosporon ovoides* (scalp hair), *Trichosporon inkin* (pubic hair), and *Trichosporon asahii* (rare in piedra). The infection occurs in both the tropics and temperate zones. It is a superficial infection of the hair shafts of the scalp, body, or pubic hair. *Trichosporon* species may also cause a systemic infection in neutropenic patients (see Chapter 268).

The organisms may be carried on the skin or around the anus. In some patients, the infection appears to be sexually transmitted. White piedra is asymptomatic and manifests as small yellow concretions on the hair shafts.[63] The pathogenesis of this infection is still unclear, but it is likely to result from synergy between the fungi and coryneform bacteria.[64] The lesions are circumscribed and appear as small nodules, unlike the more diffuse coating of axillary or pubic hair[65] seen in trichomycosis axillaris, which is caused by the presence of bacteria on the hair.

The diagnosis may be confirmed by examining an epilated hair mounted in potassium hydroxide. Each nodule contains fungal hyphae, and the organisms can be cultured from infected hairs without difficulty.

Treatment is difficult. Nodules may be removed simply by shaving. Otherwise, coating the hairs with an azole such as econazole or treating the patient with oral itraconazole may cure the infection. Relapse is common after therapy.

BLACK PIEDRA

Black piedra is another infection of the hair shafts that is caused by a black yeast, *Piedraia hortae*.[66] The disease is rare and confined mainly to parts of the humid tropics. The infection manifests as small black nodules on the hairs of the scalp and less commonly elsewhere. These have to be distinguished from pediculosis, but itching is usually absent in black piedra. With direct microscopy, these nodules can be shown to be composed of hyphal elements and small ascospores of the causative agent within a dark cement-containing stroma. Treating hairs with a topical salicylic acid or an azole cream is usually sufficient, although relapse is common.

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