Hyalohyphomycosis (hyaline septate molds) is a term used to encompass a variety of less common yet medically opportunistic mycotic pathogens.¹ They are non-dematiaceous molds or yeasts in which the tissue form is a colorless (hyaline) septate fungal hyphae with no pigment within the walls. This term is the counterpart to phaeohyphomycosis in which pathogens develop septate brown-walled hyphae in tissue. Hyalohyphomycosis does not represent a recognizable clinical syndrome, but in histologic tissue sections they can be misidentified as *Aspergillus*. Hyaline septate molds are identified by their macroscopic and microscopic morphology in culture. However, greater than 50% of hyaline molds indentified in tissue cannot be cultivated for definitive identification. The members of this group are extremely heterogeneous and include *Fusarium*, *Penicillium*, *Paecilomyces*, *Acremonium*, *Scopulariopsis*, and *Trichoderma*.

**Fusarium**

*Fusarium* species are common contaminants, ubiquitous soil saprophytes, important plant pathogens and are present in water worldwide.²³ *Fusarium* species can be pathogens in immunocompromised patients and have rarely been reported to cause disease in immunocompetent individuals. The two major risk factors for systemic *Fusarium* infection are neutropenia and corticosteroid therapy, usually occurring in hematologic malignancies (especially acute leukemia) and hematopoietic stem cell transplant (HSCT) recipients. Most fusarial infections occur in patients with prolonged (greater than 14 days) and severe neutropenia (less than 100 cells/mm³) that occurs mainly in acute leukemia. In the bone marrow transplant population the infection may occur in the early posttransplant period during neutropenia, at a median of 70 days after transplant among patients with acute graft versus host disease (GVHD) receiving corticosteroids and greater than 1 year postransplant during treatment of chronic extensive GVHD. Severe T-cell immunodeficiency is the major risk factor for fusariosis in these patients. Breakthrough fusarial infections in neutropenic patients receiving empiric therapy or anti-fungal prophylaxis (with itraconazole, voriconazole, or fluconazole) is rare.⁴ Fusarial infections that occur after solid organ transplantation tend to be localized and the outcome is better than in neutropenic patients. Infection is acquired by inhalation of spores, through traumatized skin of burn patients, following finger or toe cellulitis⁵⁻⁷ with or without onychomycosis or secondary to indwelling catheters.

*Fusarium* causes locally invasive infection in the immunocompromised host which may disseminate. The clinical scenarios for the portals of entry include: (1) localized cellulitis at an injection site or insect bite, (2) great toe cellulitis, (3) *Fusarium* paronychia especially in the setting of onychomycosis, (4) traumatic digital ulcer or eschar, (5) painful toe web sloughing with toe/foot cellulitis⁸ and (6) facial/peri orbital cellulitis from fusarial sinusitis (rhinocerebral infection). Disseminated infection by *Fusarium* species occurs almost exclusively in granulocytopenic cancer patients and recipients of bone marrow transplants who have indwelling central lines causing breaks in the skin barrier, disruptions in mucosal barriers from cytotoxic therapy and are receiving broad-spectrum antibiotics empirically or therapeutically.

The typical clinical presentations of *Fusarium* infection include persistent refractory neutropenic fever, pulmonary infiltrates (a wide spectrum of pulmonary involvement may be present from non-specific alveolar and interstitial infiltrates to nodules and cavities), sinusitis and painful skin lesions both primary and metastatic. The skin lesions evolve from painful disseminated red papules or nodules to violaceous purpuric necrotic or centrally ulcerated papules or nodules with concurrent severe...
myalgias and fevers. The characteristic lesion of *Fusarium* infection is a red or grey macule with a central ulceration or black eschar, which appears as a target lesion with necrosis within a rim of erythema. Skin lesions due to *Fusarium* are typically numerous and widespread and lesions at different stages of evolution may be present simultaneously in the same patient. Cutaneous lesions develop rapidly over days. The evolution of a skin lesion that later becomes necrotic in the center is a helpful clue to the diagnosis of *Fusarium* infection. Similar lesions can be produced by other angioinvasive opportunistic fungi including *Aspergillus* and *Mucor* species.

The clinical characteristics of disseminated *Fusarium* infections are similar to disseminated *Aspergillus*: (1) evolution of skin lesions from erythema to necrosis; (2) frequent sinopulmonary involvement (both sinus infections cause nasal and periorbital erythema often associated with black eschars on the bridge of the nose, nasal septum or palate); (3) propensity for vascular invasion and thrombosis leading to tissue infarction; (4) the spores of both can be cultured from routine air samples as well as from soil, plants and other environmental sources; and (5) appearance in tissues as acute branching (at 45° angles) broad septate hyaline hyphae. It is not possible to distinguish between *Fusarium* species and *Aspergillus* species simply by histopathologic examination of tissues. Diagnosis depends on confirmation by culture.

Important differences between *Fusarium* and Aspergillosis infections are that: (1) *Fusarium* species are frequently associated with widespread skin lesions which is uncommon in disseminated aspergillosis; (2) there is a high rate of isolation of *Fusarium* species from the blood (approximately 70%) in contrast to the rare detection of *Aspergillus* species in the blood; (3) skin lesions are common in disseminated *Fusarium* infections (75–90%) but are uncommon in disseminated aspergillosis; (4) mature skin lesions caused by *Aspergillus* species are characteristically few in number, large (2–3 cm in diameter), generally consist of a black eschar and adjacent lesions may coalesce; (5) *Fusarium* skin lesions are usually numerous, often widespread, smaller (1 cm in diameter), and demonstrate various stages of evolution simultaneously in the same patient; and (6) disseminated *Fusarium* infection has been almost uniformly fatal.

Clinical manifestations of disseminated *Fusarium* infection in the immunocompromised host diagnosed with histology and culture include: acral bullae in a 15-year-old with aplastic anemia and paranasal cellulitis; non-palpable purpura with a central flaccid pustule and multiple facial pustules with umbilicated centers and some with central necrosis in relapsed or refractory leukemia; painful, well-circumscribed round ulcers of the lower leg in a diabetic with non-Hodgkin’s lymphoma; sporotrichoid nodules on the arm of a 41-year-old with relapsed acute lymphocytic leukemia (ALL) and neutropenic fever; disseminated vesicles mimicking varicella or disseminated varicella-zoster virus (VZV) as the presentation of *Fusarium solani* sepsis on the day of stem cell transplant for leukemia with zero neutrophils; panniculitis-like tender red nodules on the legs of a neutropenic 11-year-old with ALL; the combination of vesicular and necrotic lesions in a 32-year-old with relapsing ALL, who was febrile, on broad-spectrum antibiotics, and neutropenic from chemotherapy; the combination of tender flaccid pustules, necrotic pustules, and tense hemorrhagic bullae of *F. proliferatum* sepsis in a 59-year-old with ALL and neutropenic fever post chemotherapy; and flaccid pustules on the scalp, tender intramuscular nodules, and a fluctuant subcutaneous nodule on the forehead of a 69-year-old with acute myelogenous leukemia (AML) who was febrile, neutropenic post chemotherapy, and on antibiotics with muscle tenderness in his extremities due to *F. solani*. *F. falciforme* produced numerous vesicular and pustular targetoid lesions which evolved into central necrotic nodules on the legs of a 58-year-old neutropenic woman following failed induction chemotherapy for AML.

Localized cutaneous *Fusarium* infections have been reported as a subcutaneous foot abscess, necrotic ulcers in the lower extremities and focally necrotic violaceous plaques on the lower leg in a renal transplant recipient. A similar forearm ulceration with a central black eschar due to *F. solani* was reported in a 43-year-old man with a stem cell transplant for Hodgkin’s disease.

Most systemic infections involve *Fusarium solani* (the most virulent and most commonly isolated species) followed by *Fusarium oxysporum*, *F. moniliforme* / *F. verticillioides*, and rarely *F. falciforme*.

The clinical course of *Fusarium* infection is either resolution associated with reconstitution of the white blood cell count or death secondary to overwhelming infection. Relapse was observed exclusively among patients who received additional myeloablative therapy after apparent resolution of the initial fusarial infection.
Figure 2.1. and 2.2. A necrotic subcutaneous nodule in the web space between the thumb and index finger developed in a febrile, neutropenic patient with end stage Hodgkin’s disease. Skin biopsy and culture demonstrated *Fusarium* species.
A 75-year-old man with refractory anemia developed acute myelogenous leukemia (AML). During chemotherapy, he developed multiple erythematous to violaceous nodules on his thumb, arms, chest, and abdomen. Skin biopsy and culture confirmed a diagnosis of *Fusarium* (Courtesy of Phillip Cohen, M.D.)
Figure 2.5. A 59-year-old diabetic with acute lymphocytic leukemia, on broad-spectrum antibiotics for Klebsiella and Staphylococcus epidermidis sepsis after chemotherapy-induced neutropenia, developed generalized erythematous macules and nonpalpable and palpable purpura with flaccid pustules. Potassium hydroxide (KOH) examination revealed septate hyphae. Skin biopsy demonstrated fungal vasculitis, and cultures grew Fusarium proliferatum (From Helm et al.17).

Figure 2.6. Erythematous macules, purpura, and necrotic pustules with concentric scales developed with worsening myalgias (From Helm et al.17).
Figure 2.7. Erythematous macules and papules, many with central necrosis, on the hand of a febrile, neutropenic 18-year-old with acute lymphocytic leukemia and severe myalgias (Courtesy of Amy S. Paller, M.D. From Alvarez-Franco M, Reyes-Mugica M, Paller AS. Cutaneous Fusarium infection in an adolescent with leukemia. Pediatr Dermatol 1992;9:62. Reprinted by permission of Blackwell Scientific Publications, Inc.)

Figure 2.8. Painful erythematous papules with vesicles and central erosions on the trunk. Skin biopsy demonstrated hyphal vascular invasion, a minimal inflammatory reaction, and cultured Fusarium (Courtesy of Amy S. Paller, M.D. From Alvarez-Franco M, Reyes-Mugica M, Paller AS. Cutaneous Fusarium infection in an adolescent with leukemia. Pediatr Dermatol 1992;9:62. Reprinted by permission of Blackwell Scientific Publications, Inc.)
Figure 2.9. Scattered erythematous and purpuric papules with central necrosis due to *Fusarium* in a febrile, neutropenic 19-year-old patient with acute myelogenous leukemia (Courtesy of Geetinder Chattha, M.D.)

Figure 2.10. Papulonecrotic skin lesion of *Fusarium* on the extremity of the patient depicted in Figure 2.9 (Courtesy of Geetinder Chattha, M.D.)
A 66-year-old with relapsed refractory acute monoblastic leukemia and pancytopenia developed redness and swelling of the fourth and fifth toes with a necrotic toe web due to *Fusarium*. He developed enlarging bilateral pulmonary nodules and died a few days later.
A 57-year-old man with a history of myelofibrosis status post matched unrelated donor allogeneic stem cell transplant with newly diagnosed AML presented with “toe cellulitis” (Fig. 2.13). The patient had completed idarubicin and cytarabine chemotherapy 7 days prior to dermatology consultation. He was neutropenic and febrile on broad-spectrum antimicrobials. Twelve days later the patient’s toenail demonstrated necrosis (Fig. 2.14), and he had numerous scattered erythematous papules on his head, abdomen, and lower extremities accompanied by myalgias. Magnetic resonance imaging (MRI) of his leg revealed intramuscular enhancing lesions (Fig. 2.15). KOH of his toe (Fig. 2.16) and skin biopsy of a forehead papule revealed the presence of Fusarium (Reprinted from Journal of the American Academy of Dermatology, Vol 65, King BA, Seropian S, Fox LP, Disseminated fusarium infection with muscle involvement, p. 235–237, 2011, with permission from Elsevier)
**Penicillium Marneffei (PM)**

*Penicillium marneffei* (PM) is a thermally dimorphic fungus endemic to Southeast Asia (particularly in Vietnam and Thailand) and the southern part of China (Guangxi Province). Humans and bamboo rats are infected with PM from a common source, most likely the soil especially during the rainy season from May to October. The incidence of penicilliosis has risen markedly since the first natural infection in a minister with Hodgkin’s disease reported in 1973. The increased incidence runs parallel to that of human immunodeficiency virus (HIV) infection and acquired immune deficiency syndrome (AIDS). Penicilliosis in HIV-infected patients has been classified as an AIDS-defining illness for those who live in or visit regions to which this fungus is endemic. In HIV-infected patients *Penicillium marneffei* usually occurs in the advanced stage when the CD4 count falls below 100 cells/mm$^3$. A significant increase in world travel and tourism across Southeast Asia has contributed to an increase in the number of cases of PM in other countries and demonstrated that penicilliosis is no longer confined to a specific region in Southeast Asia. The skin lesions are often the first indicator of PM dissemination as well as an HIV infection.

Reactivation of *Penicillium marneffei* occurs from a latent pulmonary focus in an immunocompromised host and spreads hematogenously. Visceral dissemination at the time of clinical presentation is common. *Penicillium marneffei* produces a clinical picture most commonly in HIV-infected males consisting of fever, weight loss, hepatosplenomegaly, generalized lymphadenopathy, pulmonary infiltrates, cough, symptomatic anemia, markedly elevated lactic acid dehydrogenase level, and skin lesions. Cutaneous involvement with numerous umbilicated papules with or without central necrosis, resembling molluscum contagiosum is characteristic but not diagnostic. The lesions occurred more frequently above the waist up, on the face, pinnae, upper trunk, and arms. Less often vesicular, necrotic, pustular, and acneiform lesions, subcutaneous nodules, and ulcerated papules are observed. Occasionally patients have papules on the palate, chronic genital or pharyngeal ulcers, soft tissue abscesses, or nodules.

Abnormal chest x-rays were commonly encountered in patients with respiratory symptoms showing reticulonodular patterns, interstitial or localized infiltrates, pleural effusions, and rarely single or multiple cavitory lesions. Clinically and histopathologically PM mimics disseminated histoplasmosis. Both proliferate within histiocytes and are similar in size (2–5 mm). PM differ by the presence of transverse septae, the absence of buds since the yeast form multiplies by fission and not by budding, and sausage shaped and tubular forms present outside of histiocytes. Histopathologic examination of skin biopsy specimens, touch smears of lymph node aspirates or bone marrow aspirates readily demonstrate the intracellular organisms of PM. Culture will provide the definitive diagnosis if microbiologists recognize *Penicillium* as a pathogen and not discard it as a saprophyte and common laboratory contaminant or simply report it as *Penicillium* species. Cultures from bone marrow, lymph node aspirates, skin biopsy, or blood are simple diagnostic tools. An enzyme-linked immunosorbent assay (ELISA) based antibody test with Mp1p, an antigenic cell wall mannoprotein of *Penicillium marneffei*, may be useful for the diagnosis.

Rapid diagnosis can be made in the AIDS patient with sepsis by carefully examining the peripheral blood smear for the presence of yeast cells within neutrophils. Demonstrating the organism in smears or scrapings of skin lesions can also result in prompt diagnosis and initiation of appropriate life saving therapy.
Figure 2.17. Numerous molluscum-like papules of disseminated *Penicillium marneffei* infection on the face of a human immunodeficiency virus (HIV)-positive man from Southeast Asia (Courtesy of Konrad E. Nelson, M.D., and Thira Sirisanthana, M.D.)

Figure 2.18. *Penicillium marneffei* infection on the face of an HIV-positive man from China (Courtesy of Toby Maurer, M.D.)
**Paecilomyces**

*Paecilomyces* is a rare emerging opportunistic saprophytic fungus found in soil, saunas, and contaminated medical materials. It can be an airborne laboratory contaminant or a contaminant in sterile solutions or moisturizing body lotions.\(^{30,31}\) *Paecilomyces* has been labeled the “bottle imp” because of its resistance to standard sterilization techniques and its propensity to contaminate sterile solutions.\(^{32}\) This explains why infections with this organism are often associated with surgical procedures.

*Paecilomyces* infections in immunocompetent hosts occur iatrogenically (with surgery or medical implants) or following minor injuries or previous trauma. Most reports of *Paecilomyces* have involved the eye after cataract extraction or intraocular lens implantation. The source of infection was the neutralizing solution used to bathe the lens prior to implantation which was contaminated with *Paecilomyces*. The majority of case reports on *Paecilomyces* infections are in the immunocompromised host with solid organ or bone marrow transplant, lymphoma, chronic granulomatous disease or immunosuppression secondary to chronic systemic corticosteroid use. The portal of entry for *Paecilomyces* usually involves breakdown of the skin barrier (onychomycosis or interdigital tinea pedis)\(^{33}\) or indwelling catheters.\(^{34}\) The fingernail or toenail may serve as the reservoir of *Paecilomyces* infection with contiguous spread of the infection, which explains the frequent involvement of the lower extremities, greater than upper extremities. *Paecilomyces* may cause extensive cutaneous infection of the arm or leg with a wide range of clinical features: erythematous macules, vesicles, pustules, or painful red nodules.\(^{35,36}\) It mimics bacterial infections, looking like cellulitis\(^{37,38}\) or furuncles.\(^{39,40}\) Wolfson et al. reported two renal transplant patients who developed an ulcerating cellulitis following lacerating trauma to the anterior tibial region virtually identical to a previously reported case.\(^{41}\) Satellite lesions or sporotrichoid nodules have been described in a renal transplant patient with *P. lilacinus*.\(^{42}\) *Paecilomyces* produced a sternal wound infection in a lung transplant recipient.\(^{43}\) Long-term cure was achieved by complying with the important surgical procedure of vigorous and adequate surgical debridement in addition to antifungal therapy. This is the same treatment principle in fungal infections associated with foreign body implants which includes removal of the device for a successful outcome.

Diagnosis of *Paecilomyces* infection is based on culture of the fungus and histology of the lesions. A peculiar characteristic of *P. lilacinus* is its ability to produce reproductive structures similar to those observed in vitro, including phialides and conidia in infected tissues. This type of sporulation in infected tissue, called adventitious sporulation, is a helpful diagnostic finding but also seen with *Fusarium* and *Acremonium*.\(^{44}\) Identification of *Paecilomyces* as a pathogen should be followed by species identification because antifungal susceptibilities vary. *P. lilacinus* and *P. variotii* are the two species most frequently reported as causes of infection. Other species reported to infect humans occasionally are *P. marquandii* and *P. javanicus* and *P. viridis*. Correct diagnosis of *P. lilacinus* is important because of its

![Figure 2.19](image-url)
intrinsic resistance to conventional antifungal drugs including amphotericin, flucytosine, and fluconazole. Most cases of Paecilomyces in immunocompromised patients were localized cutaneous infections and were cured with treatment.

**ACREMONIUM**

Acremonium (Cephalosporium) species are extremely common environmental fungal contaminants and soil saprophytes but are infrequent pathogens in humans. Since Acremonium rarely causes invasive disease in man, they are often considered as contaminants when isolated in the medical laboratory. The majority of infections have been mycetomas or corneal infections (mycotic keratitis) following penetrating cutaneous or ocular injuries in immunocompetent individuals. Acremonium species are being increasingly recognized as opportunistic fungal pathogens that cause a variety of infections in immunocompromised patients. These are organ transplant recipients, those with multiple myeloma, leukemia, or chronic granulomatous disease and those receiving chronic systemic corticosteroids.

Numerous species have been implicated in infections including A. falciforme, A. kilense, A. recifei, A. strictum, A. murorum, and A. roseogriseum. More than 80% of human infections are caused by the first three species. Acremonium species grow slowly and cultures must be kept for at least 2 weeks to ensure detection of a positive sample. The high frequency of positive blood cultures (similar to Fusarium, unlike Aspergillus) during Acremonium infections is explained by angioinvasion and adventitious sporulation with sustained release of fungal spores into the bloodstream.

The number and diversity of invasive infections caused by Acremonium species have increased in recent years. A two centimeter dark nodule developed on the index finger of a 62-year-old during induction chemotherapy for acute lymphoblastic leukemia. Multiple cutaneous nodules and muscle abscesses of both legs developed during induction chemotherapy induced neutropenia in a 15-year-old with acute myelogenous leukemia. A 34-year-old with myelodysplastic syndrome and neutropenia on high dose systemic steroids for severe GVHD following unrelated donor cord blood transplantation developed Acremonium pneumonia and multiple painful erythematous papules on her extremities and back. A similar case of painful, violaceous papules generalized over the extremities and body (about 30) with severe myalgias due to Acremonium strictum was reported in a febrile neutropenic leukemic. Acremonium or Fusarium should be considered if the clinical picture includes refractory fever, myalgias, and disseminated nodules or papules with necrotic centers in patients with profound neutropenia.

A case reported as mycetoma due to Acremonium falciforme in a renal transplant manifested as multiple large subcutaneous nodules and abscesses of the hands, forearms, and elbows. He continued to get new draining and ulcerated nodules on antifungal medications, with repeatedly positive Acremonium cultures for 16 months until he suffered a fatal cardiac arrest. A mycetoma of the foot due to Acremonium murorum/roseogriseum in a heart transplant recipient was neither aggressive nor distinctive despite immunosuppressive medications. It was locally invasive without systemic symptoms and did not disseminate. The Acremonium mycetoma responded to standard surgical and medical treatment.
Figure 2.20. and 2.21. *Acremonium mycetoma* developed 6 years after a heart transplant in a 46-year-old from Gambia.
**Figure 2.22.** *Acremonium* infection in a barefoot gardener with aggressive chronic lymphocytic leukemia (CLL) on chemotherapy.
**Scopulariopsis**

*Scopulariopsis* is a ubiquitous soil saprophyte also isolated from food, paper, California beaches, caves in Mexico, and sauna baths in the German Democratic Republic. Eight species of *Scopulariopsis* have been reported as causing infection in humans (*S. acremonium*, *S. asperula*, *S. flavus*, *S. fuscus*, *S. koningii*, *S. brevicaulis*, *S. brumptii*, and *S. candida*). Some species of *Scopulariopsis* have either *Microascus* or *Kernia* teleomorphs (sexual states, perfect form) and have been reported under these names as human pathogens. The majority of cases of *Scopulariopsis* species infections have been due to *S. brevicaulis*. *Scopulariopsis* species are keratinophilic and are most commonly associated with onychomycosis particularly involving the large toenails. A clinical clue to *S. brevicaulis* infection of the toenail (rather than the usual dermatophyte) is the absence of tinea pedis (a dermatophyte) or other toenails being affected.

Clinical manifestations of *Scopulariopsis* infection in the immunocompromised patient can vary. *Scopulariopsis* has presented as recurrent red-wine colored exophytic ulcerative subcutaneous nodules on the extremities of a liver transplant recipient. A case of locally invasive otomycosis and a case of paresthesias of the tip of the nose with fever and recurrent epistaxis both in leukemic patients have been described. Both were presumed to have aspergillosis until *Scopulariopsis* species was identified by culture. *Scopulariopsis* produced a black eschar or necrotic ulcer under an adhesive bandage for an intravascular catheter in a 10-year-old with graft versus host disease following stem cell transplant for acute myelogenous leukemia. This clinical picture has been also described for *Rhizopus* and *Aspergillus*. Several reports of inflammatory nodules of the extremities, histologically and mycologically positive for *Scopulariopsis*, have occurred in immunocompromised patients. The multifocal nature of the cutaneous infection suggested the possibility of either inoculation or hematogenous dissemination. The poor sensitivity of blood cultures for detection and identification of *Scopulariopsis* make it difficult to know the true mechanism. A 40-year-old with aplastic anemia on amphotericin for Candida esophagitis developed pain and periungual erythema of the big toe. The cellulitis developed a black necrotic lesion adjacent to the toenail which demonstrated angioinvasive *S. brevicaulis* histologically and by culture. Despite amphotericin the toe lesion progressed and required amputation. Histopathology revealed *Scopulariopsis* invading bone. This case illustrates how an immunocompromised host receiving antifungal prophylaxis can develop a rare relatively drug resistant opportunistic fungal infection. Most strains of *Scopulariopsis* are resistant to amphotericin, itraconazole, or 5-fluorocytosine. Successful eradication of invasive *Scopulariopsis* infection requires aggressive surgical débridement in addition to newer antifungal drugs.

![Figure 2.23. Paronychial and lateral nail fold necrotic ulcer surrounded by erythema due to biopsy and culture-proven *Scopulariopsis brevicaulis*. *Scopulariopsis* invaded into the bone requiring amputation of the great toe of this 40-year-old man with aplastic anemia who received a bone marrow transplant (Reprinted by permission of the publisher from Phillips et al. Copyright 1989 by Elsevier Science Inc.)](https://example.com)
Trichosporonosis is an uncommon but frequently fatal emerging opportunistic fungal infection in immunocompromised patients. The taxonomy of the genus *Trichosporon* (175 species) has been revised and the previously named single species *T. beigelii* (formerly *T. cutaneum*) in the most recent classification corresponds to six different species: *T. asahii*, *T. asteroides*, *T. cutaneum*, *T. inkin*, *T. mucoides*, and *T. ovoides*. All are recognized as potential human pathogens (as well as *T. pullulans* and *T. loubieri*) and each are associated with different types of infection: *T. cutaneum* and *T. asteroides*, superficial infections; *T. ovoides*, white piedra of the scalp; *T. inkin*, white piedra of the pubic area; *T. asahii* and *T. mucoides*, white piedra and deep seated infections. All species have been implicated in invasive infections in patients with hematologic malignancies, most frequently neutropenic acute leukemias. *T. asahii* is thought to be the most common cause of disseminated trichosporonosis. Invasive trichosporonosis also occurs in the setting of cytotoxic chemotherapy induced neutropenia, corticosteroids, underlying malignancy, hemochromatosis, and AIDS. *T. inkin* is a rare infection encountered almost exclusively in chronic granulomatous disease.

*Trichosporon* is a natural inhabitant of the soil and occasionally part of the normal flora of human skin. It colonizes the throat and lower gastrointestinal tract. The majority of patients with disseminated Trichosporon infection have acute leukemia and are neutropenic. Some granulocytopenic patients were receiving amphotericin B empirically for fever unresponsive to broad-spectrum antibacterial agents when they developed breakthrough trichosporonosis. Patients may present with a syndrome suggestive of disseminated candidiasis with fever, severe myalgias, endophthalmitis with multiple round white spots on fundus examination and multiple purpuric nodules that progress to centrally necrotic lesions. Compared to Candida, trichosporonosis is associated with higher positive blood culture yield, more frequent visceral involvement and a poorer prognosis. Cutaneous involvement occurs in 30–43% of patients with disseminated trichosporonosis. The most frequently documented skin lesions are purpuric papules and nodules with central necrosis and ulceration. The trunk, arms and face were most commonly involved. Other morphologies have been reported in immunocompromised hosts including: pink nodules on the face and scalp of a patient with AIDS; tender hemorrhagic bullous cellulitis in a pancytopenic man; sporo-trichoid purple nodules in a renal transplant patient; black necrotic lesions of the buccal mucosa in an acute leukemia patient; purpuric papules with pale centers in a bone marrow transplant recipient; erythematous papulopustules in a pancytopenic man with carcinoma of the lung; and multiple linear ulcerative hemorrhagic nodules due to *T. inkin* on the forearm of a steroid dependent woman with rheumatoid arthritis.

Skin biopsy and culture, like blood culture, is a high yield source of diagnosis. Although the microscopic appearance can be confused with Candida or *Aspergillus*, close observation of biopsy specimens containing *T. beigelii* by a skilled dermatopathologist reveals pseudohyphae, the presence of numerous rectangular arthroconidia and a few blastoconidia permitting an accurate diagnosis. *Trichosporon* shares cross-reactive antigenicity with the capsular polysaccharide of cryptococcus that results in a positive cryptococcal antigen test, as would be expected in cases of disseminated infection with either of these two pathogens. During the course of invasive Trichosporon infection, antigen positivity to *Aspergillus* galactomannan may also be positive potentially leading to misdiagnosis and inadequate treatment.

Fungal cultures of cutaneous lesions are positive in greater than 90% of cases and can minimize the possibility of mistaken histologic identification.

Disseminated Trichosporon infections are often fatal despite antifungal treatment. The death rate approaches 80%. In neutropenic patients the success of treatment was associated with resolution of neutropenia.
Figure 2.24. Tinea corporis, an unusual morphology for KOH and culture-positive *Trichosporon beigelii* in a patient with acquired immune deficiency syndrome (AIDS)

Trichoderma

*Trichoderma* infections in humans are rare but they are increasingly being reported in the immunocompromised patient. *Trichoderma* are ubiquitous saprophytic fungi with a worldwide distribution. They occur in soil, especially waterlogged soil, wood, decaying vegetation, cellulose containing substances and moisture damaged building materials. Six species have been identified as etiologic agents of infections in immunocompromised hosts: *T. harzianum*, *T. koningii*, *T. longibrachiatum*, *T. pseudokoningii*, *T. citrinoviride*, and *T. viride*. Risk factors for invasive *Trichoderma* include prolonged and severe neutropenia, prolonged treatment with broad-spectrum antimicrobial agents, steroid therapy, mucosal barrier damage, and transplantation. *Trichoderma* infection can be misdiagnosed as aspergillosis and other hyalohyphomycoses because the hyphae are morphologically similar on direct examination. Culture of biopsy material is needed for definitive diagnosis. *Trichosporum* is characterized by very fast growth. Blood culture does not appear to be a valuable diagnostic tool.

Three similar necrotic ulcerated plaques due to *Trichoderma* that developed on the extremities at the insertion site of intravenous cannulas have been reported. A 45-year-old bone marrow transplant recipient on amphotericin and fluconazole developed fatal disseminated *T. pseudokoningii* from an ulcer-necrotic skin lesion (histologic and mycologic positive skin, brain and lungs) at the entry point of a central venous catheter. A pediatric patient with aplastic anemia and prolonged neutropenia on fluconazole developed a painful two centimeter erythematous indurated centrally necrotic plaque at the site of a peripheral intravenous line. Skin biopsy and culture revealed *T. longibrachiatum* which was cured with a prolonged course of amphotericin. Another pediatric patient with ALL developed centrally necrotic plaques/nodules with erythematous halos on the extremities, “especially in canula entry of skin” during a neutropenic fever. Multiple cultures of pus from the skin lesions, sputum and throat grew *T. harzianum*. Two cases of invasive *Trichoderma* due to mucosal barrier damage, one in the oral cavity and the other in the intestinal wall were both fatal from overwhelming pulmonary infection and dissemination. A persistently neutropenic bone marrow transplant recipient (for ALL) on systemic steroids for GVHD and on amphotericin then itraconazole for *T. longibrachiatum* isolated from multiple stool surveillance cultures developed an enlarging perianal ulcer. It manifested as a necrotic lesion infiltrated with hyphae and cultured positive for *Trichoderma*. He developed multiple pulmonary nodules as the perianal ulcer continued to enlarge. *Trichoderma* was cultured from the liver, lung, brain and bowel at autopsy. *Trichoderma* has been isolated from grains and food suggesting acquisition of the “non-pathogenic” fungus through the gastrointestinal tract.

A fatal case of *T. longibrachiatum* rapidly disseminated from ulcerative necrotic gingiva covered by a violaceous pseudomembrane in a neutropenic patient with non-Hodgkin’s diffuse large B cell lymphoma.

Blastoschizomyces Capitatus

*Blastoschizomyces capitatus* (previously *Geotrichium capitatum* and *Trichosporon capitatum*) is an emerging opportunistic yeast pathogen that is rarely reported. *B. capitatus* is widely distributed in soil, feces of semi-domesticated pigeons, and is part of the normal human skin flora and the respiratory and digestive tract mucosa. *B. capitatus* has been documented in immunocompetent individuals as a cause of onychomycoses. Invasive infection occurs predominantly in severely neutropenic leukemic patients and especially in those receiving intensive chemotherapy. The clinical presentation is similar to that of invasive candidiasis. Initial gastrointestinal and respiratory tract colonization is followed by hematogenous dissemination and localization in the skin and lungs. The diagnosis is usually made by blood culture. The mortality rate (60% versus 24%) and percentage of patients who develop invasive organ involvement is much higher in *B. capitatus* infection compared to candidiasis (60–80% versus 10–20%). The incidence of skin involvement with *B. capitatus* in acute leukemia is approximately 26%, but well documented reports of cutaneous findings are rare.

Etienne et al. reported a 59-year-old patient neutropenic from chemotherapy for acute myelocytic leukemia with *B. capitatus* in blood culture, who developed bilateral nodular pneumonia and arm papules. Pérez-Sanchez described a pruritic rash, subcutaneous nodules, and gingival ulcers from which *B. capitatus* was cultured in a 44-year-old neutropenic patient with bilateral nodular pneumonia on chemotherapy for refractory anemia with excess of blasts. A 1 cm erythematous nodule developed on the arm of a 47-year-old neutropenic leukemic patient with bilateral bronchopneumonia and fatal disseminated *B. capitatus* infection. *B. capitatus* produced a chicken pox-like skin eruption in a febrile 6-year-old with refractory acute lymphocytic leukemia and neutropenic fever unresponsive to antibiotics. *B. capitatus* was cultured from blister fluid of skin lesions mimicking both the morphology and distribution of varicella.

Hepatosplenomegaly with microabscesses, elevated alkaline phosphatase, and bull’s-eye lesions with hepatic ultrasound or computerized tomography indistinguishable from hepatoplenic candidiasis is the most frequent manifestation of *B. capitatus*. The other frequently involved system is the respiratory tract where *B. capitatus* can produce pulmonary infiltrates with the crescent sign (mass/nodules surrounded by a halo of low attenuation, diagnostic of pulmonary mycetoma). This finding resembles angioinvasive fungal pneumonia which differentiates *B. capitatus* from *Candida pneumonia*. 
Paracoccidioidomycosis
(South American Blastomycosis)

Paracoccidioidomycosis (Lutz’ disease) is caused by the thermally dimorphic fungus *Paracoccidioides brasiliensis*, found in the soil of Latin America. It is geographically restricted and occurs mainly between the latitudes 23° north (Mexico) and 34° south (Argentina). *P. brasiliensis* is a rare infection worldwide but is an endemic deep mycosis most commonly found in Brazil followed by Columbia, Ecuador, and Venezuela. Infection with *P. brasiliensis* is acquired through inhalation of conidia, leading to pulmonary infection followed by extrapulmonary dissemination.

*P. brasiliensis* has not been classically considered an opportunistic mycosis of the immunocompromised host. *P. brasiliensis* has been described in patients receiving cancer chemotherapy, immunosuppressive medications such as azathioprine and systemic steroids, after renal transplantation, and in HIV/AIDS. However, *P. brasiliensis* is not as common as might be expected in immunocompromised patients. The relatively small number of cases of paracoccidioidomycosis associated with AIDS when compared with histoplasmosis and cryptococcosis among HIV-infected patients is striking because the prevalence of paracoccidioidomycosis is much higher in the non-immunosuppressed population. However, the rarity of cases of *P. brasiliensis* in patients with HIV/AIDS remains unexplained but it is consistent with the similarly low incidence of paracoccidioidomycosis among solid organ transplant recipients and patients with solid and hematologic malignancies. The scarcity of reported cases of paracoccidioidomycosis and AIDS might be explained by the widespread use of trimethoprim-sulfamethoxazole as prophylaxis for *Pneumocystis jirovecii*. This drug combination is also very effective against *Paracoccidioides brasiliensis*. It is not known whether paracoccidioidomycosis in HIV is explained by reactivation of latent infection or whether it begins from a recent exogenously acquired infection.

Paracoccidioidomycosis most commonly occurs as a chronic form with pulmonary lesions and ulcerations of the oral, nasal, or laryngeal mucosa and occasionally with skin and other visceral lesions. The most common manifestation in patients with AIDS is disseminated disease. The acute form, rapidly progressive with HIV disease, occurs with fever, generalized lymphadenopathy, hepatosplenomegaly, skin, and bone lesions. The lungs are the most common organ infected, followed by the skin and lymph nodes, with cutaneous lesions being the most common clinical presentation at the time of diagnosis. The cutaneous lesions of paracoccidioidomycosis in patients with HIV disease are multiple and widely disseminated. The skin lesions are in various stages of development including papules, nodules, nodules with central ulcerations, and ulcers.

The oral involvement in paracoccidioidomycosis commonly includes painful, infiltrated ulcerations, pronounced increase in thickness of the lips, and erythematous finely granular hyperplasia of the mucosa speckled with pinpoint hemorrhages and a mulberry-like surface. Although not uncommon, oral paracoccidioidomycosis can cause hard palatal perforation. Oral lesions are usually secondary to lung involvement and may be accompanied by laryngeal or esophageal involvement causing hoarseness, dysphagia, odynophagia, dysphonia, and/or cervical and submandibular lymphadenopathy. Paracoccidioidomycosis can also affect other mucosal surfaces causing nasal, conjunctival, or perianal lesions.
Hyalohyphomycosis


Fusarium


Penicillium marneffei (PM)


Paecilomyces

Hyalohyphomycosis


**Acremonium**


**Scopulariopsis**


**Trichosporon**


**Trichoderma**


**Blastochizomyces capitatum**


**Paracoccidioidomycosis (South American Blastomycosis)**


Cutaneous Manifestations of Infection in the Immunocompromised Host
Grossman, M.E.; Fox, L.P.; Kovarik, C.; Rosenbach, M.
2012, XIX, 309 p., Hardcover
ISBN: 978-1-4419-1577-1