Angioinvasive fungal infections impacting the skin

Background, epidemiology, and clinical presentation

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Learning objectives
After completing this learning activity, participants should be able to identify and describe the epidemiology, initial presentation and subsequent clinical manifestations of angioinvasive fungal infections; characterize at-risk populations for angioinvasive fungal infection; and classify frequently encountered opportunistic organisms in dermatology and compare their distinguishing cutaneous features.

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Angioinvasive fungal infections cause significant morbidity and mortality because of their propensity to invade blood vessel walls, resulting in catastrophic tissue ischemia, infarct, and necrosis. While occasionally seen in immunocompetent hosts, opportunistic fungi are emerging in immunosuppressed hosts, including patients with hematologic malignancy, AIDS, organ transplant, and poorly controlled diabetes mellitus. The widespread use of antifungal prophylaxis has led to an "arms race" of emerging fungal resistance patterns. As the at-risk population expands and new antifungal resistance patterns develop, it is critical for dermatologists to understand and recognize angioinvasive fungal pathogens, because they are often the first to encounter the cutaneous manifestations of these diseases. Rapid clinical recognition, histopathologic, and culture confirmation can help render a timely, accurate diagnosis to ensure immediate medical and surgical intervention. Superficial dermatophyte infections and deep fungal infections, such as blastomycosis and histoplasmosis, have been well characterized within the dermatologic literature, and therefore this article will focus on the severe infections acquired by angioinvasive fungal species, including an update on new and emerging pathogens. In the first article in this continuing medical education series, we review the epidemiology and cutaneous manifestations. The second article in the series focuses on diagnosis, treatment, and complications of these infections. (J Am Acad Dermatol 2019;80:869-80.)

Key words: angioinvasive fungus; aspergillosis; mucormycetes; Candidiasis; Fusarium; Scedosporium.

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EPIDEMIOLOGY AND CLINICAL PRESENTATION

Many of the causative organisms of angioinvasive fungal infections are ubiquitous in the environment and rarely cause clinical infection in patients with an intact immune system, but have the potential to result in serious, often fatal disease in immunocompromised patients.[1-4] Fungi previously thought to be nonpathogenic are becoming increasingly medically significant as the incidence of invasive fungal infections rises along with extended survival in critically ill patients.[5] The widespread use of antifungal prophylaxis in immunosuppressed individuals is further altering the resistance patterns of these organisms.[6] The medical community is called upon to recognize individuals who are at risk for infection, identify variations in clinical presentation, and understand factors involved in prevention and treatment.[7] Invasive fungal organisms have a propensity to invade blood vessels, and can either be inoculated from local trauma or reach the skin via dissemination in the blood stream.[8,9] Cutaneous manifestations include pink to purple macules, papules, patches, and plaques, regardless of the causative agent or underlying etiology (Fig 1, *A-C*). Hemorrhagic, ecthyma gangrenosum–like lesions can occur in infection with systemic candidiasis,[10] aspergillosis,[9] mucormycetes,[11] phaeohyphomycosis, and *Fusarium* infection.[12-14] Necrotic papulonodules and deep subcutaneous nodules are common to candidiasis,[15,16] aspergillosis,[17] mucormycosis,[18] and hyalohyphomycosis.[13,19,20] Patients with mucormycosis[18,21] and hyalohyphomycosis[19,22] can both present with cellulitic plaques as well. Unique clinical manifestations of each angioinvasive fungus will be detailed in their individual sections.

CANDIDIASIS

Key points

- **Invasive candidiasis is the leading cause of mycosis-associated mortality in the United States**
- **There is a growing number of medically relevant *Candida* species, including the recently recognized *Candida auris***
- **Disseminated candidiasis is more severe in immunocompromised hosts and neonates**

Invasive candidiasis is the leading cause of mycosis-associated mortality in the United States and is globally recognized as a cause of significant morbidity.[23] The majority of invasive disease is caused by *Candida albicans*, *Candida glabrata*, *Candida tropicalis*, *Candida parapsilosis*, and *Candida krusei*. While *C albicans* remains the most common cause of invasive candidiasis, *C glabrata* has now emerged as the second most common pathogen in the United States, and *C parapsilosis* and *C tropicalis* remain the second most common causative agents of blood stream infections in other countries.[23] As microbial detection methods become more sensitive, the number of clinically relevant candida species continues to grow.[23] Changing fungal resistance patterns, specifically the development of multidrug resistance in *C glabrata*, makes its rise especially problematic.[24] A new angioinvasive species, *Candida auris*, has been recently recognized and exhibits multidrug resistance and reduced susceptibility to fluconazole and amphotericin B.[25,26]

Humans are known carriers of commensal candidal species within the gastrointestinal tract and vagina, while a subset of the population also carries oral candida asymptomatically.[27] Colonizing candida from the oral and gastrointestinal mucosa in the setting of immunosuppression related to chemotherapy can result in invasive infection. Disseminated candidiasis has been cited as the fourth leading cause of hospital-acquired bloodstream infection in the United States[28] and has been touted as the causative agent of the majority of cases of invasive fungal infections worldwide.[29] The incidence of candidemia in the United States varies by region at 14 per 100,000 people in the Baltimore area and 10 per 100,000 in the Atlanta area.[30] The high incidence of infection has been attributed to the increased use of aggressive immunosuppressive therapy, blood transfusion, total parenteral nutrition,[31] central venous catheters, and immune modifying drugs in well-developed nations,[29] with the risk in developing countries attributed to limited medical care, difficulties in implementing infection control in hospitals, and less aggressive antifungal treatments in at-risk patients.[32]

Candida spp are not a known commensal organism of the skin and when present are able to trigger an inflammatory response via Toll-like receptor 2, altering keratinocyte expression of key defense cytokines.[33,34] Interleukins, such as interleukin-17 (IL-17), are recognized for their ability to fight *Candida spp* infection.[35-37] In addition, certain genetic mutations, including those seen in autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy, can predispose to infection with *Candida spp*. There has been an association between the development of autoantibodies against IL-17A with severity of candidal infection in patients with autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy.[38] In addition, the use of IL-17 inhibitors (secukinumab and ixekizumab) also can increase the risk of *Candida spp* infections.[39]

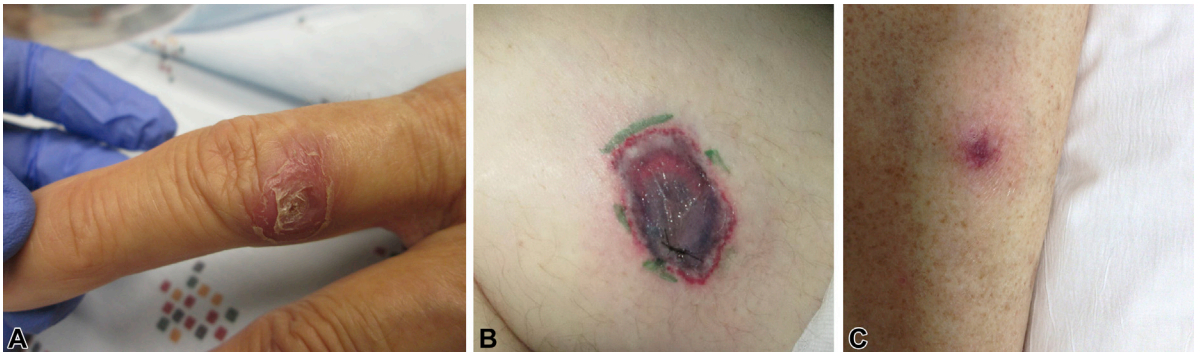

Fig 1. Variable cutaneous manifestations of angioinvasive fungal infections. Presentations include pink to red and violaceous papules and plaques. **A**, *Fusarium* infection involving the left index finger. **B**, *Lichtheimia* on the right thigh. **C**, *Aspergillus spp* infection on the left thigh.

Common cutaneous manifestations caused by *Candida spp* are highlighted in Table I.[40-102]

In individuals with underlying immunosuppression, candidiasis can be much more severe. Disseminated candidiasis generally presents as a triad of fever, rash, and diffuse muscle tenderness[103]; however, it can involve any organ, including the kidneys, liver, spleen, myocardium, eyes, and brain.[29] Cutaneous findings in disseminated disease are broad, but the most commonly reported are asymptomatic, erythematous to violaceous papules with pale, vesicular centers (Supplemental Fig 1; available at http://www.jaad.org) that can progress to necrotic, purpuric plaques and tense hemorrhagic bullae.[15] Less common clinical presentations of adult and pediatric candidiasis are shown in Table I. Clinicians should always consider candidemia in the differential when areas of central necrosis and hemorrhage are present.

ASPERGILLOSIS

Key points

- **Invasive aspergillosis infections have increased since 1980**
- **Infection often occurs at sites of skin breakdown, trauma, adhesive dressings, venipuncture or catheter insertion sites, and burn scars**
- **Presentation in disseminated disease can be atypical in immunocompromised hosts**

Aspergillus spp are omnipresent in the environment and inhaled as conidial spores daily.[2] Aspergillosis infection is most commonly caused by *Aspergillus fumigatus*, *Aspergillus flavus*, *Aspergillus terreus*, and *Aspergillus niger*, all of which generate the clinically distinct entities of allergic bronchopulmonary aspergillosis, allergic fungal rhinosinusitis, chronic pulmonary aspergillosis, chronic necrotizing pulmonary aspergillosis, and primary cutaneous aspergillosis. Slow-sporulating, difficult-to-culture species *Aspergillus lentulus*, *Aspergillus calidoustus*, and *Neosartorya (Aspergillus) udagawae* are emerging pathogens that have also been implicated in causing invasive infection.[104] Angioinvasion by hyphae is usually rapid and causes necrosis and tissue hemorrhage. Invasive disease was estimated at 1 to 2 cases per 100,000 people in the San Francisco Bay area in one of the first population-based estimates.[105]

Cutaneous manifestations can vary depending on whether they are the result of primary inoculation or secondary infection caused by dissemination. Primary cutaneous aspergillosis is rare and is most frequently encountered in immunocompromised patients as described in Table I. Primary cutaneous aspergillosis is also seen in those with chronic granulomatous disease who have a predisposition to acquiring refractory infections caused by *Aspergillus nidulans*, an otherwise rare species.[2,49] Infection is often nosocomial, occurring at sites of trauma, such as adhesive tape dressings, venipuncture or catheter insertion sites, or burn scars.[9,50,53,106,107] Burn victims most frequently experience infection between 10 and 35 days postinjury, and environmental triggers have been questioned, with almost 60% of cases of aspergillosis attributed to hospital construction or air conditioner ducts and filters being serviced, according to some reports.[108,109]

Premature neonates often exhibit some level of mechanical cutaneous barrier dysfunction via the use of adhesives and pulse oximetry. Neonates have diminished phagocytic ability, greatly increasing their risk of aspergillosis. Primary cutaneous infections typically occur between 5 and 30 days after

Table I. Common cutaneous manifestations caused by *Candida spp*

Fungus	Host risk factors	Cutaneous features
Candida spp	Immunosuppression, blood transfusion, total parenteral nutrition[31] central venous catheter, immune-modifying medications,[29] limited medical care and infection control in developing countries,[31] genetic mutations,[38] interleukin-17 inhibitor use,[39] and autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy[38]	Adult: ecthyma gangrenosum–like lesions,[10] diaper and perianal dermatitis, oral and vaginal thrush, intertrigo, balanitis, angular cheilitis, erosio interdigitalis blastomycetica,[18,40-43] pink erythematous and violaceous papules and vesicles, necrotic purpuric plaques, tense hemorrhagic bullae,[15] folliculitis-like eruption,[44] and subcutaneous nodules[16] Pediatric: erythematous dermatitis with vesicles and desquamation with collarettes of scale[45,46] and ecthyma gangrenosum–like lesions[47]
Aspergillus spp	Immunosuppression, hematologic malignancy, HIV/AIDS, solid organ transplantation, burns, corticosteroid use, diabetes mellitus, neonates,[48] chronic granulomatous disease,[2,49] and trauma[9]	Ecthyma gangrenosum–like lesions,[9] necrotic papulonodules,[17] deep subcutaneous nodules with central eschar,[50,51] violaceous macules, papules, or plaques,[9,52] pinpoint pustules,[52] molluscum contagiosum–like lesions, dermatophyte-like lesions,[53] panniculitis,[54] subcutaneous granulomas and abscesses,[55] erythematous macules with hemorrhagic, and necrotizing ulcerations[17]
Mucormycetes (*Rhizopus spp*, *Mucor spp*, *Rhizomucor spp*, *Lichtheimia spp*, *Saksenaea spp*, *Cunninghamella spp*, and *Apophysomyces spp*)	Hematologic malignancy, hematopoetic stem cell transplant, renal disease, malnutrition, neutropenia, immunosuppressive medication use (chemotherapy, tumor necrosis factor inhibitors, and corticosteroids),[56] iron overload,[57,58] diabetes mellitus, burns, traumatic injury, infected tape, wooden splints,[56,59-61] toxic epidermal necrolysis,[62] and autoimmune disease[21]	Ecthyma gangrenosum–like lesions,[11] mucocutaneous ulceration and eschar,[21] necrotic papulonodules,[18] gangrenous lesions,[63] cellulitic plaques,[21] pink erythematous papules, pustules, vesicles, and subcutaneous nodules, "bull's-eye infarcts,"[64] targetoid plaques with central necrosis,[64] "cotton-like" appearance within wounds,[65] pyoderma gangrenosum–like lesions,[66] dermatophyte-like lesions,[67] and cutaneous vasculitis–like lesions[68]
Fusarium spp	Immunosuppression, neutropenia, lymphopenia, graft versus host disease, hematologic abnormalities, immunosuppressive medications,[7] trauma, burns, and foreign body[69]	Ecthyma gangrenosum–like lesions,[12,70,71] necrotic papulonodules, deep subcutaneous nodules, tinea pedis, intertrigo, onychomycosis,[12,13] granuloma annulare–like plaques,[14] facial granulomas,[72] cellulitis, abscesses, and umbilicated or necrotic papules and pustules[18,19]

Continued

Table I. Cont'd

Fungus	Host risk factors	Cutaneous features
Scedosporium spp	Immunosuppression, neutropenia, malignancy, hematopoetic or solid organ transplantation,[73] lymphopenia, corticosteroid use, serum albumin <3 mg/dL, cytomegalovirus reactivation, and diabetes[74]	Eumycetomas with erythematous and necrotic papules,[20] ulcerations, subcutaneous nodules,[2,75] cellulitis,[22] sporotrichoid spread, thrombophlebitis,[76,77] diffuse papules and pustules,[75] cutaneous abscesses,[75] pyoderma gangrenosum–like lesions,[78] and malignant otitis externa[79]
Paecilomyces spp	Immunosuppression,[80] postoperative,[81-83] and HIV/AIDS[84,85]	Subcutaneous swellings and nodules,[84,86] septic bursitis,[87] red-brown papules, plaques, papules, abscesses,[88] and eumycetoma[89]
Other hyalohyphomycoses (*Acremonium spp* and *Trichoderma spp*)	Immunosuppression, intravenous catheters, and trauma[90]	Cellulitic plaques, tender red papules,[90] mycetoma,[90,91] and ulceronecrotic plaques at catheter sites[92]
Phaeohyphomycoses (*Alternaria spp*, *Bipolaris spp*, *Wangiella spp*, *Fonsecaea spp*, *Cladophialophora spp*, *Curvalaria spp*, *Exophiala spp*, and *Phialophora spp*)	Immunosuppression, malignancy, diabetes mellitus, corticosteroid use, HIV/AIDS,[73,93,94] solid organ transplantation,[95] and hypercortisolism[96]	Ecthyma gangrenosum–like lesions,[97] verrucous papulonodules,[98,99] eumycetoma,[2] granulomatous nodules,[98,100,101] sporotrochoid spread,[98] multiple pyogenic granuloma–like nodules, dematophytosis-like plaques,[102] subcutaneous cysts,[102] cutaneous erythema, desquamation, eczematous patches that ulcerate and erode,[97] and onychomycosis[2]

birth and may present with papules, nodules, pustules, and ulcers.[9]

As the population of immunocompromised individuals expands, it is likely that the prevalence of primary cutaneous aspergillosis will increase.[110] In primary lesions, the skin exhibits red to violaceous, broad, flat, hard, macules, papules, or plaques that may be painful or entirely asymptomatic.[9] Aspergillosis disease progression leads to the development of vesicles with central hemorrhage, which subsequently ulcerate (Fig 2, *A*). Primary infection is usually limited to a few lesions but may rapidly expand and develop disseminated lesions with variable morphologies as outlined in Table I. In patients with AIDS or who are otherwise immunocompromised, atypical presentations can be seen as outlined in Table I. In immunocompetent patients, disease can arise from surgical wounds, traumatic inoculation, or via exposure to high spore counts, which are frequently encountered in farming.[9]

Dissemination of primary cutaneous lesions remains a risk in the immunocompromised host. Accompanying systemic symptoms, including respiratory disease, fever, stroke, and seizure, are observed in disseminated disease, which usually occurs from hematogenous spread from the lungs.[2] The Centers for Disease Control and Prevention report an increase in invasive aspergillosis infection of 357% since 1980.[48,111] In systemic infections that

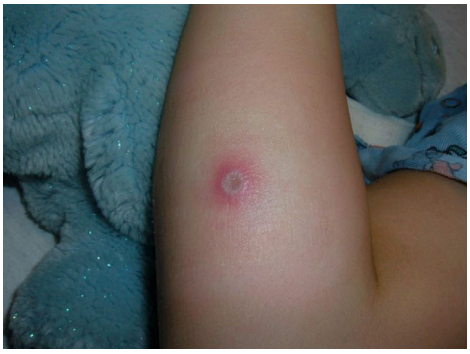

Fig 2. Cutaneous manifestations of *Aspergillus spp* infection. Primary cutaneous *Aspergillus spp* infections on the right forearm presenting as an impending ulcerated violaceous plaque.

secondarily involve the skin, widespread lesions with deep, multiple, subcutaneous nodules, with or without central eschar, can be seen (Fig 2, *B*; Supplemental Fig 2, available at http://www.jaad.org).[50,51] Importantly, cutaneous findings can be the first indicator of underlying systemic infection, and a high clinical index of suspicion is key to making this diagnosis in a timely fashion.[50]

These patients should be treated rapidly because disseminated disease can be fatal. Prognosis can improve with discontinuation of immunosuppressant medications or reversal of neutropenia.[112] While aspergillosis in patients undergoing allogenic hematopoietic stem cell transplants used to be rare, the incidence of invasive disseminated aspergillosis amongst this patient population has increased along with a shift from early to late postengraftment aspergillosis.[113] Treatment with fludarabine or rituximab during the pretransplant period are extremely high risk factors for invasive aspergillosis, and these patients should be regularly assessed for this complication.[114] Similarly, there are reported cases of transition from aspergilloma to invasive aspergillosis after therapy with sunitinib.[115]

MUCORMYCOSIS

Key points

- **Mucormycetes, previously referred to as zygomycetes, includes several genera: *Rhizopus*, *Mucor*, *Rhizomucor*, *Lichtheimia*, *Saksenaea*, *Cunninghamella*, and *Apophysomyces***
- **Diabetes is a major risk factor for disseminated mucormycosis**
- ***Mucor spp* sequester iron from their hosts, indicating iron overload syndromes as an additional risk factor in disseminated disease**

Mucormycetes include the genera *Rhizopus*, *Mucor*, and *Rhizomucor*,[21] as well as *Lichtheimia spp*, *Saksenaea spp*, *Cunninghamella spp*, and *Apophysomyces spp*, and are so named for their ability to cause systemic mucormycosis. Previously referred to as zygomycetes after the phylum Zygomycota (which is no longer accepted), a genetic reconsideration of taxonomy suggests that mucormycosis (after the order *Mucorales*) is more appropriate than zygomycosis when referring to these fungi and constellation of symptoms.[116]

Mucormycetes are abundant in the environment and are routinely encountered by humans via direct contact with soil and decaying vegetation or through the inhalation of conidial spores.[117] Mucormycetes are frequently implicated pathogens in patients with underlying immunocompromise as outlined in Table I. A well-known virulence factor of the *Mucorales* is the ability to sequester iron from host organisms.[118] Iron overload syndromes, including those in patients requiring frequent red blood cell transfusions in the setting of transplant or hematopoietic disorders[57,58] or medications that chelate iron, such as deferoxamine, represent potential risk factors for infection; however, the novel iron chelators deferasirox and deferiprone do not predispose to mucormycosis.[21] Although most often seen as a disease of the immunosuppressed host, reports of these species causing infection in healthy hosts without identifiable risk factors have been published.[119-121] While epidemiologic data are difficult to obtain, small case reviews have cited the incidence of mucormycosis between 10.8%[119] and 22.2%[120] in hosts without known risk factors for disease.

Recent epidemiologic research suggests that an environmental component also contributes to the infectivity of these organisms, citing natural disasters, contaminated adhesive dressings, water supplies, tongue depressors, hospital linens, and building construction in outbreaks of mucormycosis.[122-125] Lower levels of economic and industrial development in the community serve as an appreciable risk for infection in individual hosts.[21] This may be related to sanitation practices, temperature differences, stagnant water supplies, or another unidentified factor.

Mucormycosis can exhibit 5 main clinical presentations, including pulmonary, gastrointestinal, rhinocerebral, cutaneous, and disseminated infections.[126] Pulmonary disease arises after the inhalation of conidial spores, and pulmonary mucormycosis can develop into chest wall cellulitis via direct extension.[21,127] Gastrointestinal mucor localizes to the stomach, ileum, and colon and typically affects malnourished patients, premature neonates, and neutropenic adults. The rapid fatality of gastrointestinal disease makes it frequently diagnosed postmortem[128] (Supplemental Fig 3, available at http://www.jaad.org). Rhinocerebral infection is most frequently encountered in patients with poorly controlled diabetes when infection of the paranasal sinuses occurs after the inhalation of sporangiospores.[21] As rapid spread to contiguous structures occurs, patients exhibit facial pain, nasal discharge, periorbital cellulitis, blurred vision, proptosis, headache, mucocutaneous ulceration, and eschar, with a risk for cerebral extension.[21]

Disease is considered localized when it is limited to the skin and subcutaneous tissue and is considered disseminated when involvement includes muscle, tendon, bone, and noncontiguous organs.[67]

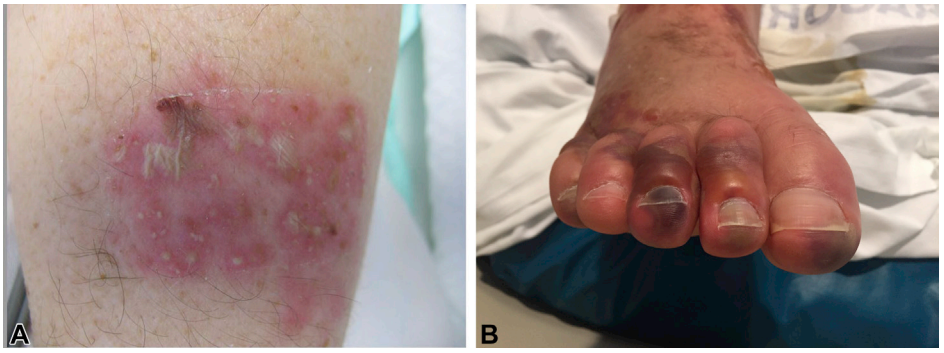

Fig 3. *Mucorymycosis spp* can present in a variety of ways. Purpuric plaques in the perinasal and periocular locations, which are concerning for extension from sinonasal locations, and in occluded areas such as (**A**) on the left forearm and (**B**) hemorrhagic bullae on the toes.

When cutaneous mucormycosis occurs secondarily, as a consequence of hematogenous dissemination, skin findings are the result of hyphae invading blood vessels, with rapid necrosis and tissue hemorrhage. The skin can exhibit pink, erythematous papules, pustules, and vesicles with suppurative inflammation and rapid ulceration that evolves to central crusting and eschar (Fig 3, *A* and *B*; Supplemental Fig 4, available at http://www.jaad.org). Coloration can be variable, ranging from pink-yellow nodules to black necrosis in immunosuppressed patients.[129,130] A predilection for areas of trauma and distal extremities frequently occurs.[117]

OTHER HYALINE MOLDS

Key points

- **Cutaneous involvement can be seen in approximately 75% of cases of disseminated *Fusarium* infection**
- **Hyalohyphomycoses often present with eumycetoma**

Hyaline molds, or hyalohyphomycoses, include lightly pigmented, septate, branching filamentous fungi. *Fusarium spp*, *Scedosporium spp*, *Paecilomyces spp*, *Acremonium spp*, and *Trichoderma spp* are the most frequently encountered infectious agents. Infection can result from inhalation or traumatic implantation from the environment, including soil, wood, or contaminated water sources. It is often difficult to distinguish between true infection and colonization in immunocompromised patients.[2] Cutaneous hyalohyphomycosis can be difficult to detect clinically, presenting with numerous clinical morphologies and frequently evolving with time and host immune status as described in Table I.

Tissue breakdown is the primary risk factor in immunocompetent individuals, and *Fusarium* can exhibit virulence via attachment to prosthetic material and suppression of the immune system by production of mycotoxins, such as trichothecenes.[131] Table I outlines the risk factors for fusariosis. Inhalation of airborne conidial spores, as well as skin and mucosal membrane bypass, serve as the primary portals of entry for *Fusarium*; however, these species have been uncovered in hospital water systems,[132] and it has been suggested that water-related activities could serve in acquisition of infection.

Cutaneous involvement can be seen in approximately 75% of cases of disseminated *Fusarium* infection, and manifestations include diffuse, erythematous to violaceous papules and nodules, often with central necrosis and gray eschar, which can resemble ecthyma gangrenosum (Fig 4; Supplemental Fig 5, available at http://www.jaad.org).[12,70,71] Lesions can be exquisitely tender and evolve quickly over the course of a few days, likely because *Fusarium spp* have the ability to generate collagenases and proteases that result in tissue breakdown.[133] Hematogenous and lymphangitic spread of deep lesions may progress to disseminated fusariosis.[134] The prognosis for immunocompromised patients with widespread disease is poor, but an intact immune system serves to increase survival rates drastically.[13]

There are two medically significant *Scedosporium* species, including, *Scedosporium apiospermum* (*Pseudallescheria boydii*) and *Scedosporium prolificans*.[7] Scedosporiosis is most frequently found in immunocompromised patients as reviewed in Table I. Targeted organs include the lungs, central nervous system, skin, and eyes. The lungs are the most frequently infected with *S apiospermum*, and patients with cystic fibrosis and chronic pulmonary disease are at an elevated risk of pulmonary infection.[135] In patients with pulmonary scedosporiosis, development of secondary brain abscesses has been

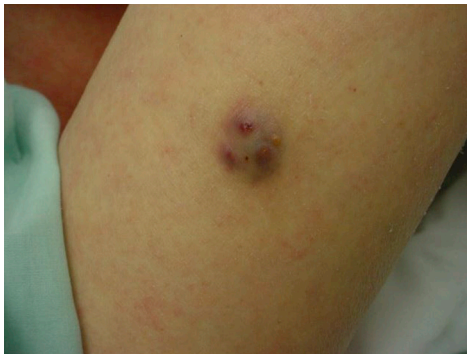

Fig 4. *Fusarium* infection presenting in the skin as a purpuric plaque on the right thigh.

reported.[136] Endophthalmitis, presenting as ocular floaters and decreased visual acuity, can be the first clinical manifestation of scedosporiosis, and clinicians should be wary of this symptom in immunocompromised hosts.[137] Cutaneous findings can be primary or caused by dissemination. In primary lesions, traumatic implantation can result in white-grain mycetomas leading to the variable clinical presentations highlighted in Table I.[2] If nodules develop they can ulcerate and crust, mimicking syphilitic gummas.

Paecilomyces spp are encountered in foods, soil, and wood; however, their ascospores are strongly heat- and treatment-resistant, making them a contaminant of pasteurized and treated food products and laboratory cultures.[138,139] Infection most commonly occurs in immunocompromised individuals and after surgical procedures or implantation of cardiac valves,[81,140] intraocular lenses,[82,141] and dialysis catheters.[80,83] Disseminated *Paecilomycosis* infection often presents with tender, subcutaneous, ulcerated nodules.[84] Cases of *Paecilomyces* infections are also reported in immunocompetent hosts, with features outlined in Table I. Coinfection with *Alternaria* also has been reported.[142,143] Given their frequency as contaminants, *Paecilomyces* infections have been initially misdiagnosed as lupus on histopathology, so clinician awareness of this organism's potential for infection is important.[139]

Trichoderma spp are most frequently responsible for peritonitis in patients undergoing peritoneal dialysis; however, reports of disseminated infection have surfaced more recently. Cutaneous presentations have included perianal ulceration and ulceronecrotic lesions at the sites of intravenous catheters.[92]

Infections caused by *Acremonium spp* occur most frequently in the settings of immunosuppression, penetrating trauma, and intravascular catheters.[90] There are reports of cutaneous *Acremonium* presenting with mycetoma in both immunocompromised and immunocompetent hosts after trauma.[90,91] Less common presentations of *Acremonium* infection are outlined in Table I.

PHAEOHYPHOMYCOSIS

Key points

- **Phaeohyphomycoses are rare but can cause infection in both immunocompetent and immunocompromised hosts**
- **Melanin production in these organisms plays a key role in fungal infectivity and virulence**

Dematiaceous molds, also known as phaeohyphomycoses, encompass the genera *Alternaria spp*, *Bipolaris spp*, *Wangiella spp*, *Madurella spp*, *Fonsecaea spp*, *Cladophialophora spp*, *Curvularia spp*, *Exophiala spp*, and *Phialophora spp*. They are termed for their natural melanin pigment and subsequent colored cell walls. Their ability to produce melanin serves as an important virulence factor in fungal infectivity, presumably by reducing susceptibility to host defense mechanisms and antifungals.[2,144] Much like the mucormycoses, they are ubiquitous in nature, present in soil and vegetation worldwide, with traumatic implantation frequently related in these infections. Risk factors for infection are described in Table I.

While most notable for their role in allergic fungal sinusitis, phaeohyphomycoses can cause the skin and soft tissue infections outlined in Table I. These fungal species also have a predilection for invasion of vessels with risk for hematogenous and lymphatic dissemination as well as invasion of bone, causing osteomyelitis.[145] In a review of 56 stem cell and solid organ transplant patients with identified phaeohyphomycosis, 55.4% of them exhibited disseminated disease, with *Alternaria* being the more frequent causative agent,[95] highlighting the importance of immune compromise as a risk factor for generalized disease. One of the main predisposing factors to alternariosis is hypercortisolism or Cushing syndrome.[97] Less frequent cutaneous manifestations of phaeohyphomycoses are outlined in Table I.

Disseminated *Cladophialophora* infection is rare but is notable for the formation of skin lesions and brain abscesses, and cases have been reported in both healthy and immunocompromised hosts.[146,147] *Curvalaria spp* have reportedly caused ecthyma gangrenosum–like lesions,[97] disseminated erythematous papules and nodules,[148] and deep, soft tissue abscesses with ulceration.[149] There are few reports of disseminated *Bipolaris* infection with cutaneous

involvement; however, this organism is known to cause localized cutaneous disease. Unfortunately, recent reports of brain abscesses and biliary tree invasion in an immunocompetent patient with *Bipolaris*[150] and brain abscesses in an immunocompetent patient with *Cladophialophora*[151] make it clear that healthy hosts can be affected with phaeohyphomycoses.

In conclusion, the clinical presentations of the angioinvasive fungi can vary depending on a patient's immune status, but early recognition for prompt diagnosis and the fast initiation of therapy are imperative to prevent morbidity and high mortality in these conditions. Diagnostic work-up, therapies, and potential complications will be discussed in the second article in this continuing medical education series.

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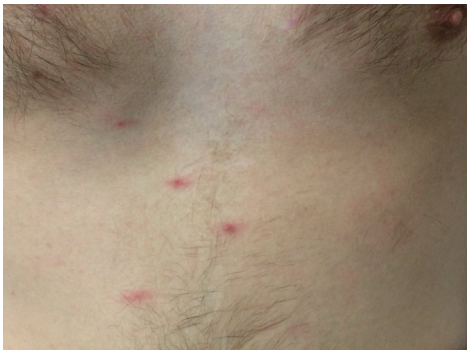
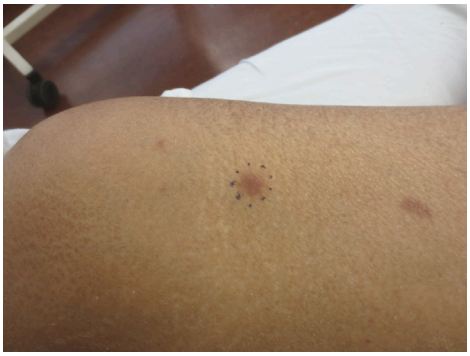
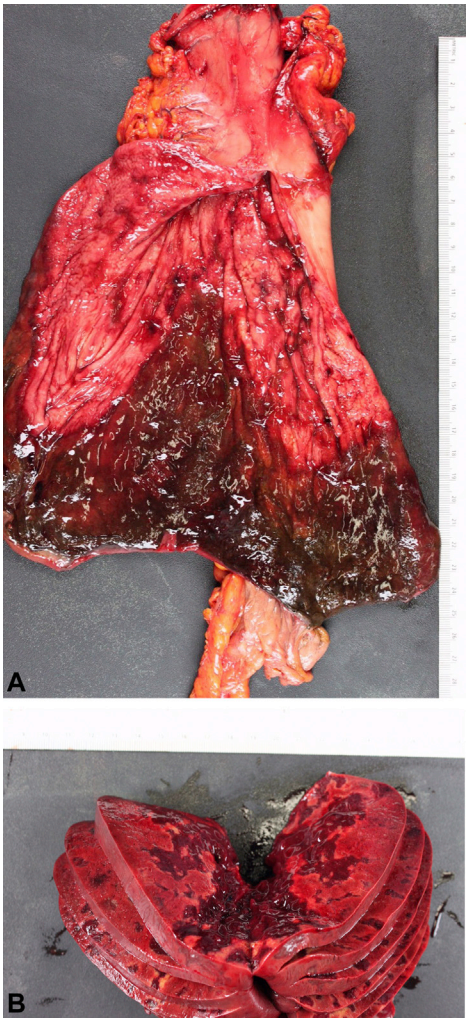


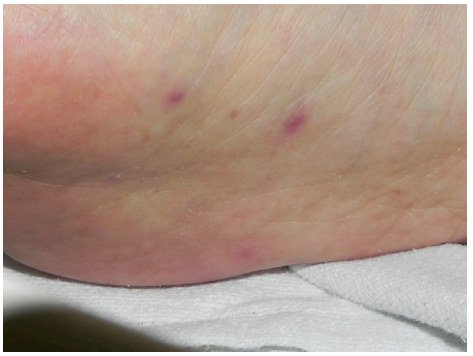
Supplemental Fig 1. Disseminated *Candida spp* infection, clinically characterized by several red papules and pustules in an immunosuppressed patient.



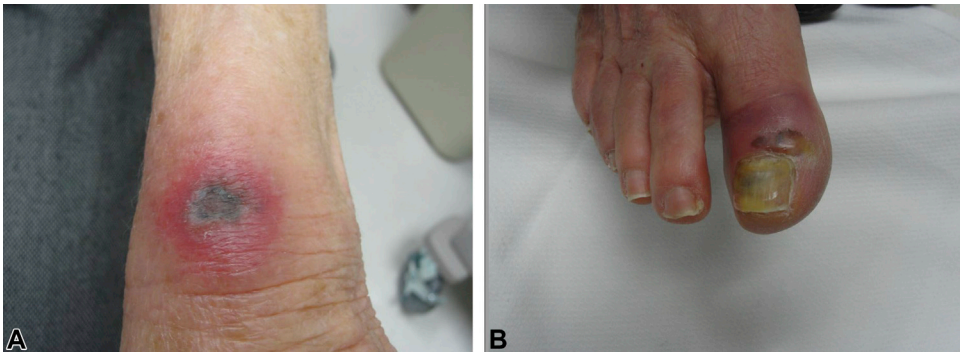
Supplemental Fig 2. Disseminated *Aspergillus spp* presenting as a firm nodule on the right thigh.



Supplemental Fig 3. Postmortem diagnosis of disseminated *Mucormycosis*. Involvement of the gastrointestinal tract resulted in hemorrhagic necrosis of the (**A**) stomach and (**B**) spleen. Photograph courtesy of Amanda Barrett, MD, and Stuti Shroff, MD.



Supplemental Fig 4. *Mucorymycosis spp* can present in a variety of ways, including red papules on the foot.



Supplemental Fig 5. *Fusarium* infection presenting in the skin. **A**, On the left wrist, infection presented as an erythematous nodule with central eschar. **B**, An erythematous nodule with overlying bullae on the right great toe.