Infectious Diseases: Deep Fungal Infections

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Subcutaneous Mycoses: Sporotrichosis, Chromoblastomycosis, Mycetoma, Rhinosporidiosis

Clinical Features

Sporotrichosis is chronic infection caused by the dimorphic fungus *Sporothrix schenkii*, which is transmitted by direct inoculation of soil through skin. The most common form of sporotrichosis is lymphocutaneous, characterized by the development of an erythematous papule or nodule at the site of inoculation. Subsequently, additional lesions, with or without ulceration, occur proximally along lymphatic channels. The most common site of involvement is the upper extremity (Fig. 17.1). Fixed cutaneous lesions, in the form of verrucous or ulcerative plaques, may occur on the face or extremities. In immunocompromised states, visceral spread, such as pulmonary disease, may occur [1].

Chromomycosis is caused by inoculation of a dematiaceous fungus from the soil into skin. Typical lesions of chromomycosis in children or adolescents are erythematous nodules or verrucous plaques, most often located on the upper extremity. This is of notable contrast to disease presentation in adults, which usually occurs on the lower extremity. In one study of chromomycosis in South American children, *Cladophialophora carrionii* was the most common cause, while most studies in adults have show *Fonsecaea pedrosoi* to be the most common cause [2, 3].

Eumycetoma is a chronic mycotic infection of the skin and soft tissue. Infection follows inoculation injury from a contaminated thorn or splinter. At least 30 species of molds are implicated; *Pseudallescheria boydii* is the most common causative species in the United States, while *Madurella mycetomatis* is the most common cause worldwide. Infection most often involves the feet or lower extremities, and is characterized by large verrucous nodules with abscesses, sinus tracts, and macroscopic grains (Fig. 17.2). Eumycetomas are usually confined to subcutaneous tissues, but can involve fascia, bone, and regional lymph nodes via contiguous dissemination. Fibrosis, deformity, and lymphedema eventually result if untreated [4].

Rhinosporidiosis is a non-contagious chronic granulomatous infection caused by *Rhinosporidium seeberi*, and is characterized by polyps which are sessile or pedunculated, and mainly affect the nasal mucosa and, less commonly, the conjunctival or ocular mucosa. Cutaneous lesions may occur due to spread from adjacent mucosa, direct inoculation, or hematogenous spread. Infection in adolescents and young adults is common [5, 6].

Specific Investigations

For diagnosis
Fungal culture
KOH
Histopathology
For treatment
CBC, LFTs, lipid panel, metabolic panel (potassium, blood glucose), kidney function tests (BUN and creatinine), EKG
Thyroid function tests (TFTs)

Fungal culture is the most sensitive method for the diagnosis of sporotrichosis. Aspirate from a nodule or tissue from a punch biopsy should be inoculated onto Sabourad dextrose agar; growth occurs within 5 days at room temperature. Histopathology may be supportive, but is rarely diagnostic, given the difficulty of finding the sparse organisms, which are 3 μm or smaller in diameter. Nonspecific findings, including suppurative granulomas and asteroid bodies, are often present [7]. An enzyme immunoassay for serologic testing of *S. schenkii* has demonstrated up to 90 % sensitivity and 80 % specificity, but is not available widely [8].

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J.M.C. Teng et al. (eds.), *Therapy in Pediatric Dermatology*, DOI 10.1007/978-3-319-43630-2_17

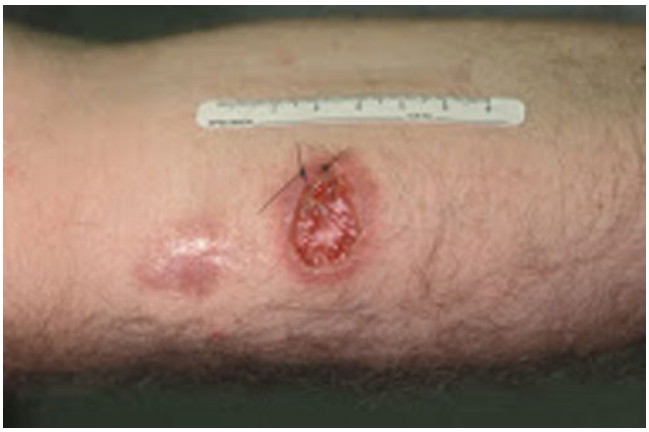

Fig. 17.1 Lymphocutaneous sporotrichosis. Erythematous nodule and ulceration present along the lymphatics of the upper extremity (Photo courtesy of Sylvia Hsu, MD)

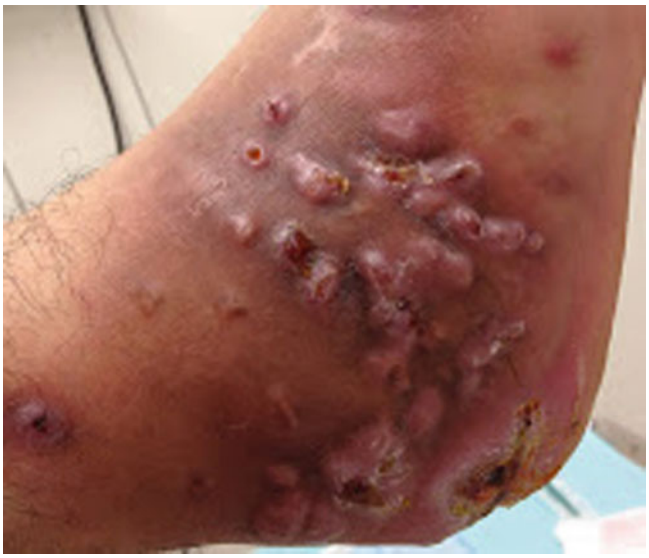

Fig. 17.2 Eumycetoma. Multiple coalescent verrucous nodules with sinus tract formation on the foot, resulting in deformity (Photo courtesy of Sylvia Hsu, MD)

In chromomycosis, KOH is highly sensitive in identifying the characteristic sclerotic or medlar bodies. Fungal culture on Sabourad or Mycosel agar is sensitive and specific. Histopathology often demonstrates granulomatous inflammation, pseudocarcinomatous hyperplasia, and pigmented yeast forms with single septations [9].

Eumycetoma can be diagnosed by the clinical findings in combination with black macroscopic grains, which are only found with fungal infections; yellow or white grains indicate fungal or bacterial infection. KOH demonstrates broad, septate, and branching hyphae. Culture should be performed but requires 6–8 weeks for growth. Histopathology is also helpful and demonstrates hyaline or pigmented hyphae in microscopic grains. Radiography, including X-ray, computed tomography, and magnetic resonance imaging should be considered in extensive cases, to exclude bony and soft tissue involvement [10].

In rhinosporidiosis, KOH or histopathology are diagnostic, demonstrating large sporangia 200 μm in diameter and filled with smaller endospores. Culture is not helpful, as *R. seeberi* is intractable to isolation or growth in microbiologic culture media [11].

Given the lengthy duration of systemic azole therapy required for theses diseases, baseline and periodic evaluation of CBC and LFTs is recommended. In the case of itraconazole, periodic evaluation of serum lipids is recommended, given the risk of hypertriglyceridemia. SSKI therapy requires monitoring of thyroid function tests, including TSH and FT4. Kidney function tests as well as potassium levels should be monitored during amphotericin B treatment; EKG is also recommended, given the risk of arrhythmia.

Table 17.1 First-line therapy for sporotrichosis [12–14]

Medication	Dosing	Evidence level
Itraconazole	6–10 mg/kg/day up to maximum daily dose 400 mg daily × 3–6 months (2–4 weeks after clinical clearance)	B

Clinical cure was obtained in almost 95 % of patients with cutaneous sporotrichosis, including children, treated with oral itraconazole. In another study, clinical response rate to itraconazole was over 80 %.

Table 17.2 Second-line therapy for sporotrichosis [15, 16]

Medication	Dosing	Evidence level
Saturated solution of potassium iodide (SSKI)	One drop in juice or milk three times daily, increased weekly to a maximum of one drop per kg or 40–50 drops three times daily	B

In a randomized non-blinded study, clinical cure rates were high and similar (above 89 %) for pediatric patients treated with either daily dosing or four times daily dosing of SSKI.

Table 17.3 Third-line therapies for sporotrichosis [17]

Medication	Dosing	Evidence level
Amphotericin B deoxycholate followed by itraconazole	Amphotericin B: 0.7 mg/kg/day until improved Itraconazole: 6–10 mg/kg/day up to maximum daily dose 400 mg × 12 months	E*

Initial treatment with intravenous amphotericin B followed by long-term therapy with itraconazole is reserved for disseminated sporotrichosis and based on case reports.

Table 17.4 First-line therapies for chromomycosis [2, 9]

Medication	Dosing	Evidence level
Itraconazole	100 mg/day for 1 month	E*
5-Fluorouracil (5-FU) 1 % cream	Once daily for 3 weeks to 3 months	D*

Complete clinical and mycologic remission was achieved in 85 % of the patients treated with itraconazole or 5-FU cream. Similar results were obtained for electrodesiccation or fulguration, but given the more invasive nature and potential for scarring, this is considered an alternative to itraconazole or 5-FU. Ajoene gel (isolated from alcoholic extracts of garlic) also demonstrated a high rate of efficacy, but may be difficult to obtain.

Table 17.5 Second-line therapies for chromomycosis [2, 9]

Medication	Dosing	Evidence level
Electrodesiccation or fulguration		E*
Cryosurgery		D*

Low cure rates (31 %) were observed in a study of 51 cases, but cryosurgery and itraconazole produced the best results overall, sometimes in combination.

Table 17.6 Third-line therapies for chromomycosis [2, 9]

Medication	Dosing	Evidence level
Ajoene 0.5 % gel		D*

Table 17.7 First-line therapies for eumycetoma [18, 19]

Medication	Dosing	Evidence level
Itraconazole	× 12 months	E*
Voriconazole		E
Posaconazole		E*

In one study, itraconazole was moderately efficacious, associated with improvement in 42 % of cases, although none showed mycologic or clinical remission. Voriconazole is the treatment of choice for eumycetoma caused by *P. boydii*. Posaconazole can be used as an equally effective alternative to itraconazole and voriconazole.

Table 17.8 Second-line therapies for eumycetoma [20–24]

Medication	Dosing	Evidence level
Surgery	Preceded by at least 6 months of antifungal therapy	E*
Ketoconazole	× 6 months	C

Radical surgical procedures should be avoided, but combined medical therapy and conservative excision have produced good results. Relapse rates after surgery alone are high (over 50 %), so antifungals should be administered for at least 6 months prior to surgery, and then in the post-surgical period to reduce recurrence. In a small study of oral ketoconazole, 5 of 13 patients were completely cured, and 4 improved following at least 6 months of treatment. Despite its historical role as the preferred agent for this disease, toxicity limits its use, and it is now only considered an alternative agent.

Table 17.9 First-line therapies for rhinosporidiosis [25]

Medication	Dosing	Evidence level
Surgery		E*

Local surgical excision is the treatment of choice, but has been associated with 10 % recurrence rate. Concurrent medical treatment with dapsone has been used to decrease this risk.

Table 17.10 Second-line therapies for rhinosporidiosis [26, 27]

Medication	Dosing	Evidence level
Dapsone		E*

Case reports have described long courses of dapsone being used as monotherapy or in combination with surgery. It has also been used in combination with surgery or other antimicrobials such as cycloserine and ketoconazole for disseminated disease.

Systemic Mycoses: Blastomycosis, Coccidioidomycosis, Paracoccidioidomycosis, Histoplasmosis

Clinical Features

Blastomycosis is caused by inhalation of the conidia of the dimorphic fungus *Blastomyces dermatitidis*. The lungs are the most common site of disease, and infection may be asymptomatic or severe. Cutaneous disease results from hematogenous spread from the lungs, and occurs in up to one-fifth of patients. Verrucous lesions with irregular borders and microabscesses, ulcerative plaques with elevated borders, subcutaneous nodules, and cold abscesses may be seen [28].

Coccidioidomycosis is caused by the dimorphic fungi, *Coccidioides immitis*, or *Coccidioides posadasii*, which are endemic to arid regions. Patients of African or Filipino ancestry or those with a history of immunosuppression are at increased risk of infection. Cutaneous lesions are either due to disseminated disease via hematogenous spread from a pulmonary nidus or, less commonly, primary infection.

Organism-specific manifestations include nodules, pustular lesions, verrucous plaques, abscesses, and fistulae. Reactive cutaneous manifestations include erythema nodosum, erythema multiforme, an acute exanthem, Sweet's syndrome, and interstitial granulomatous dermatitis [29, 30].

Paracoccidioidomycosis is a systemic mycotic disease caused by the dimorphic fungus *Paracoccidioides brasiliensis*. It is endemic in Central and South America, where it is widely present as a soil saprophyte. Exposure is often occupational, and the main portal of entry is inhalation. Acute or subacute disease is most often seen in children and adolescents: features include lymphadenopathy, hepatosplenomegaly, fever, and bone marrow dysfunction, but skin and pulmonary involvement are uncommon. In contrast, the chronic form of the disease involves the lungs, mucosa, skin, lymph nodes, and adrenal glands. Mucosal and skin findings simulate those of leishmaniasis. Painful ulcers with ragged borders and petechiae are seen most often in the mouth or larynx. Ulcerative or verrucous nodules or plaques are seen in the skin [31, 32].

Histoplasma capsulatum is a dimorphic intracellular fungus found worldwide. Cutaneous lesions are present in up to 15 % of patients with disseminated histoplasmosis (Figs. 17.3 and 17.4). A variety of manifestations are seen, including nodules, plaques, ulcers, pustules, abscesses, erythroderma, cellulitis and panniculitis, and purpura [33].

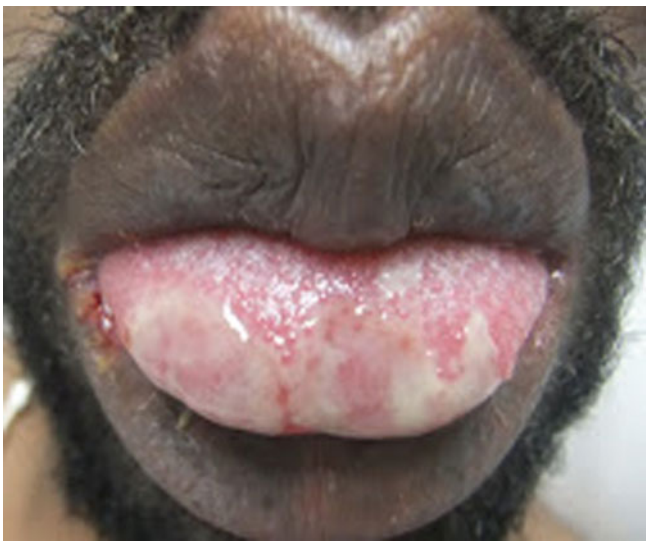

Fig. 17.3 Disseminated histoplasmosis. Erosive plaques of the oral mucosa in a patient with AIDS

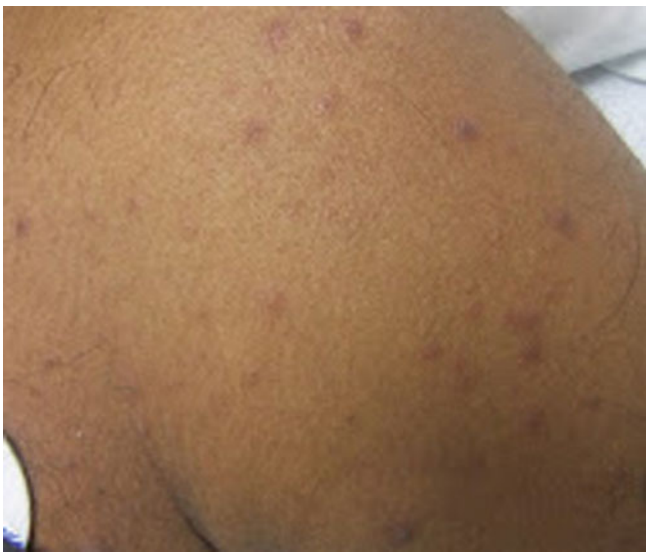

Fig. 17.4 Disseminated histoplasmosis. Violaceous papules distributed over the trunk and extremities in a patient with AIDS

Specific Investigations

For diagnosis
KOH
Fungal culture
Histopathology
Antigen detection (EIA)
Serology (EIA, immunodiffusion, complement fixation)
Skin testing (Coccidioidomycosis)
Imaging (Computed tomography or x-ray, for paracoccidioidomycosis)
For treatment
Repeat serology to monitor treatment response (paracoccidioidomycosis)
CBC, LFTs, lipid panel, metabolic panel (potassium, blood glucose), kidney function tests (BUN and creatinine), EKG

For blastomycosis, KOH preparation has a diagnostic yield of less than 50 %, despite multiple specimens. Histopathology demonstrates suppurative granulomas, but yeast forms may be difficult to visualize. When identified, they are 8–15 μm in diameter, with refractile walls and single broad-based buds. Definitive diagnosis requires fungal culture, and *B. dermatitidis* grows within 1–4 weeks [34]. Antigen detection assays for blastomycosis demonstrate overall sensitivity of 90 %, but specificity is less than 80 % due to cross-reactive antigens in histoplasmosis, paracoccidioidomycosis, and penicilliosis. Sensitivity is higher in urine than in serum. Given the lower specificity, culture is still the gold standard [35].

Cutaneous coccidioidomycosis should be diagnosed either by direct visualization of the organism or by culture. *Coccidioides* spp will grow on routine media, but may take more than 1 week to isolate. Spherules of *Coccidioides* are large, up to 70 μm in diameter, and can be detected with KOH prep or in histologic sections. Despite their size, organisms are often sparse, so multiple level sections should be examined by the dermatopathologist [36]. Overall, serologic tests for the detection of IgG and IgM antibodies against

Coccidioides are highly specific, but sensitivity is variable in early infection, as antibody production may not occur for weeks to months after illness onset. Immunodiffusion testing is the most specific serology available, while enzyme-linked immunoassay (EIA) has a sensitivity of 100 %. Thus, EIA should be used a screening test and immunodiffusion should be used for confirmation [37–39]. Complement fixation and tube precipitin-type assays are less accurate than these two newer methods. EIA for antigenuria is over 70 % sensitive, but also detects *Histoplasma* antigen. Skin testing for coccidioidomycosis is not recommended to diagnose current illness. Skin tests are positive for life, even in healthy patients with adequate prior treatment. In contrast, skin tests can be negative in infected patients with anergy. Thus, it is more useful as a prognostic test [40].

Paracoccidioidomycosis is diagnosed via direct microscopic visualization and/or by culturing *P. brasiliensis* from clinical specimens. KOH prep is positive in over 90 % of cases. Skin biopsy may be obtained in chronic disease, and demonstrates suppurative granulomas in most cases; *P. brasiliensis* is seen as a round or oval yeast 4–40 μm, with two or more narrow-necked budding cells (resembling a "pilot's wheel" or "Mickey mouse head"). Quantitative immunodiffusion is the most useful serologic test for diagnosis and for monitoring response to therapy, given its high sensitivity and specificity—up to 97 and 100 %, respectively. Cultures are positive in up to 80 % of cases, but can take up to 30 days to grow. In addition to imaging of affected areas (computed tomography or X-ray) to evaluate lymphadenopathy and pulmonary lesions, all patients with suspected paracoccidioidomycosis should have specimens submitted for direct microscopy, culture, and serology [41].

In a study of HIV-infected patients with disseminated histoplasmosis, skin biopsy with special stains for fungi (gomori methenamine silver or PAS) allowed direct visualization of *Histoplasma* in over 86 % of cases. The most common histologic pattern is a diffuse infiltrate of macrophages parasitized by yeast 2–3 μm in size. However, organisms may also be extracellular [42, 43]. EIA antigen testing in disseminated histoplasmosis demonstrates a sensitivity ranging from 75 % to 100 %, with increased sensitivity in serum compared to urine, and in immunocompromised patients. However, false-positive tests can occur in patients with blastomycosis or coccidioidomycosis [44]. PCR is positive in over 70 % of culture-positive tissue samples [45]. Immunodiffusion and complement fixation methods detect anti-*Histoplasma* antibodies in 70 % of immunocompromised and 90 % of immunocompetent patients with disseminated infection, but are often negative in patients on tumor necrosis-alpha inhibitor therapy [46]. Blood cultures are positive in 65 % of patients with disseminated histoplasmosis; tissue cultures from skin biopsy specimens can also be submitted.

Blastomycosis

Table 17.11 First-line therapies for blastomycosis [28, 47–52]

Medication	Dosing	Evidence level
Liposomal amphotericin B	3–5 mg/kg/day IV	D/C*
Amphotericin B deoxycholate	0.7 mg/kg/day IV	D/B*
Itraconazole	2–5 mg/kg/dose po twice daily for 6 months, with maximum single dose 200 mg	B*

For patients with severe disseminated infection, amphotericin B should be used. Pooled retrospective data show that amphotericin B is up to 91 % effective for blastomycosis. Although liposomal amphotericin B does not have as much supportive data, it should be used when available, and is particularly preferred in cases with CNS involvement. Itraconazole may be used in patients with mild to moderate disease not involving the CNS. In an open study, 90 % of patients with blastomycosis demonstrated clinical response to treatment with 6 months of itraconazole, making this a first-line therapy for blastomycosis. Although ketoconazole has strong supportive trial data for its curative success in blastomycosis, its use can be associated with severe hepatotoxicity as well as infection relapse. Therefore it is not recommended for the treatment of any endemic mycosis, including blastomycosis.

Table 17.12 Second-line therapies for blastomycosis [53–56]

Medication	Dosing	Evidence level
Fluconazole	For 6 months	B*
Voriconazole	9 mg/kg/dose every 12 h IV with maximum daily dose 350 mg	D*
Posaconazole	12 mg/kg/day in 3 divided doses	D*

Fluconazole was 65 % effective at doses under or equal to 400 mg/day, but was successful in 87 % of patients treated with doses above 400 mg/day for 6 months in open studies. Voriconazole has been successful in small series for the treatment of refractory blastomycosis with CNS involvement. Posaconazole has also been used.

Coccidioidomycosis

Table 17.13 First-line therapies for coccidioidomycosis [57]

Medication	Dosing	Evidence level
Itraconazole	For 12 months	C/A*
Fluconazole	For 12 months	C/A*

A randomized, controlled trial demonstrated 72 % response rate for itraconazole and 57 % response rate for fluconazole after 12 months of treatment. While the majority of patients included were adults, there were a few cases in children as young as 6 years old.

Table 17.14 Second-line therapies for coccidioidomycosis [58, 59]

Medication	Dosing	Evidence level
Posaconazole	For 12 months	C*
Voriconazole	For 6 months	C*

Case series support the use of posaconazole, which has shown up to 73 % efficacy in refractory infections. Voriconazole demonstrated similar results for the treatment of resistant disease, albeit following a shorter treatment course.

Table 17.15 Third-line therapies for coccidioidomycosis [60]

Medication	Dosing	Evidence level
Liposomal amphotericin B	3–5 mg/kg/day IV	D
Amphotericin B deoxycholate	0.7 mg/kg/day IV	D

Amphotericin B treatment is reserved for patients with rapidly worsening or CNS disease. Otherwise, treatment with oral azoles is preferred. Of note, in children with primary cutaneous disease and solitary lesions in whom disseminated disease has been excluded, observation or conservation excision, if feasible, can be considered.

Paracoccidioidomycosis

Table 17.16 First-line therapies for paracoccidioidomycosis [61–63]

Medication	Dosing	Evidence level
Itraconazole	5 mg/kg po once daily for 6–12 months	A

Oral antifungal therapy can be used in most (mild to moderate) cases of paracoccidioidomycosis. Among children and adults with paracoccidioidomycosis treated with itraconazole for an average of 6 months, 91 % of patients showed either marked improvement or resolution. In a small randomized trial, itraconazole, ketoconazole, and sulfadiazine were roughly equivalent in efficacy following treatment for at least 24 months. For patients with severe infection, including hypotension, respiratory failure, or severe malnutrition, therapy should be started with amphotericin B and then transitioned to oral therapy once improved.

Table 17.17 Second-line therapies for paracoccidioidomycosis [64, 65]

Medication	Dosing	Evidence level
Voriconazole	9 mg/kg/dose every 12 h IV with maximum daily dose 350 mg	B*
Trimethoprim/sulfamethoxazole (TMP-SMX)	10 mg/kg/day based on the TMP component, for at least 24 months	B*

Measured in terms of complete or partial treatment response, itraconazole was over 94 % effective compared to voriconazole, which was over 88 % effective. Voriconazole also has excellent in vitro activity against *P. brasiliensis*, but better data is available to support the use of itraconazole as a first-line therapy. In a separate open study, TMP-SMX was as effective as itraconazole, but treatment duration was four times as long with TMP-SMX.

Table 17.18 Third-line therapies for paracoccidioidomycosis [66]

Medication	Dosing	Evidence level
Liposomal amphotericin B	3–5 mg/kg/day IV	D*
Amphotericin B deoxycholate	0.7 mg/kg/day IV Duration: 20–40 days or until clinical improvement then transition to oral therapy	D*

Therapy with amphotericin B is reserved for severe or refractory disease, and retrospective reviews have supported the use of this agent in this context.

Histoplasmosis

Table 17.19 First-line therapies for histoplasmosis [67–70]

Medication	Dosing	Evidence level
Liposomal amphotericin B	3 mg/kg/day IV	A
Amphotericin B deoxycholate	1.0 mg/kg/day IV For 2 weeks or greater duration until clinical improvement, then step down to itraconazole	A
Itraconazole	2–5 mg/kg/dose po tid for 3 days then bid for 12 months, with maximum single dose 200 mg	B

In adult patients with AIDS and moderate-severe disseminated histoplasmosis, liposomal amphotericin B demonstrated better clinical success (88 %) than conventional amphotericin deoxycholate (64 %), in addition to improved survival and reduced nephrotoxicity; however, in children,

amphotericin B deoxycholate is usually well tolerated, and the lipid preparations are not preferred. If liposomal formulations are not available, then amphotericin B deoxycholate should be used for induction.

Itraconazole demonstrated 85 % clinical response in adult patients with AIDS and histoplasmosis. However, patients with moderate to severe disease responded poorly. Additionally, clearance of fungemia is slower with itraconazole than with amphotericin B. Therefore, itraconazole is reserved as induction therapy for patients with mild disease without fungemia, and for maintenance therapy after successful induction. Maintenance therapy should continue for 1 year, to reduce the risk of relapse.

Table 17.20 Second-line therapies for histoplasmosis [71–75]

Medication	Dosing	Evidence level
Fluconazole	3–6 mg/kg/day po or IV for maintenance therapy	B
Posaconazole	12 mg/kg/day in 3 divided doses	D*
Voriconazole	9 mg/kg/dose every 12 h IV with maximum daily dose 350 mg	D/C*

Itraconazole is superior to fluconazole in terms of clearance of fungemia as well as clinical response. Additionally, fluconazole is not as active as itraconazole against *H. capsulatum* in vitro. Although 74 % of patients responded to induction therapy with fluconazole in a large open study, almost half of patients demonstrated a relapse of their disease at 1 year while on maintenance therapy. Thus, fluconazole is reserved as a second-line therapy when amphotericin B and itraconazole cannot be tolerated. In a small case series, posaconazole has been effective for severe refractory infection as salvage therapy. Posaconazole demonstrates high *in vitro* activity against *H. capsulatum*. Voriconazole has also been used successfully as salvage therapy in disseminated histoplasmosis, but has inferior *in vitro* activity compared to itraconazole, and like posaconazole, has not been evaluated in a high-quality study.

Opportunistic Mycoses: Aspergillosis, Cryptococcosis, Fusariosis, Mucormycosis

Clinical Features

Aspergillus species are ubiquitous, and inhalation occurs often without sequelae in healthy hosts. In the setting of immunosuppression, most often during treatment for hematologic malignancies, or stem cell or solid organ transplantation, *A. fumigatus*, *A. flavus*, and *A. terreus* invade pulmonary or cutaneous tissue and may disseminate widely in the presence of angioinvasion. Neutropenia, high-dose corticosteroids, burns, and the neonatal period are also risk factors. Cutaneous aspergillosis may be primary, resulting from inoculation from trauma, or secondary, resulting from contiguous or hematogenous spread. Primary cutaneous aspergillosis may present as acute paronychia, necrotic plaques or nodules at the site of catheter insertion, or an erythematous edematous plaque. Secondary cutaneous aspergillosis may present with inflammatory or necrotic nodules, periorbital cellulitis, or ulcers [76, 77].

Cryptococcus neoformans and *Cryptococcus gattii* are encapsulated yeasts found worldwide in soil and bird guano that cause infections predominantly in patients with immunosuppression: HIV/AIDS, corticosteroids, organ transplantation, sarcoidosis, and malignancy. Following inhalation, meningoencephalitis, pulmonary infection, or disseminated disease may occur. Cutaneous lesions are seen in up to 15 % of patients with disseminated cryptococcosis. Plaques, purpura, ulcers, abscesses, cellulitis, and molluscum contagiosum-like lesions in patients with HIV may be seen [78]. Primary cutaneous disease is also possible following inoculation by minor trauma and, unlike secondary cutaneous lesions, may occur in immunocompetent hosts and is associated with favorable prognosis [79, 80].

Fusarium species are hyaline fungi present worldwide in soil, plant parts, and water. Superficial infections such as keratitis, onychomycosis, and intertrigo occur in immunocompetent hosts, while invasive infections occur only in patients with immunosuppression including neutropenia, hematologic malignancy, stem cell transplantation, and corticosteroid therapy. Sinusitis, pneumonia, fungemia, and dissemination can occur. Invasive infections occur via inhalation, direct inoculation, or spread from a superficial infection [81]. In this context, cutaneous lesions may be localized, as in cellulitis, or disseminated, with multiple necrotic painful lesions resembling those of ecthyma gangrenosum. Lesions at different stages of evolution, lymphangitic spread, target lesions, and blisters may be seen. Primary cutaneous disease in otherwise healthy hosts occurs at sites of burns or trauma, and presents with cellulitis, ulcers, verrucous nodules, and abscesses [82].

Rhizopus, *Mucor*, and *Rhizomucor* are genera of ubiquitous fungi that belong to the order Mucorales and cause most mucormycosis infections. Almost all infections occur in the context of immunosuppression, including poorly-controlled diabetes with ketoacidosis. Other risk factors include corticosteroid treatment, stem cell transplantation, hematologic malignancy, iron overload or deferoxamine treatment, HIV/AIDS, and burns. Inhalation of spores in susceptible individuals can lead to rhino-orbital-cerebral and pulmonary

infections, the most common forms of the disease [83]. In contrast, cutaneous disease is always due to direct inoculation, and may occur following minor iatrogenic trauma such as intravenous line placement. Rarely, primary cutaneous disease may occur in immunocompetent individuals. Cutaneous disease usually presents with single cellulitis-like or ecthyma-like lesion. As with other forms of mucormycosis, rapidly progressive tissue necrosis often ensues due to infarction resulting from angioinvasion. Dissemination from cutaneous lesions can also occur [84].

Specific Investigations

For diagnosis
Culture
Histopathology with GMS, PAS, mucicarmine, alcian blue, or India ink
EIA for galactomannan or beta-D-glucan polysaccharides
Cryptococcal antigen testing (EIA, latex agglutination, lateral flow assays)
PCR
Imaging (computed tomography)
For treatment
CBC, LFTs, lipid panel, metabolic panel (potassium, blood glucose), kidney function tests (BUN and creatinine), EKG
Flucytosine levels (for induction treatment in cryptococcosis)

Definitive diagnosis of aspergillosis requires culture in combination with the histopathologic demonstration of tissue invasion by hyphae. Organisms are observed in biopsy specimens as narrow (3–6 μm wide), septate, and hyaline hyphae, with branching at an acute angle (45°). GMS or PAS may be useful to recognize hyphae, which can be seen invading blood vessels of the dermis or subcutis. It is important to note that histopathology alone is very nonspecific, since other hyaline molds such as *Scedosporium* and *Fusarium* have the same appearance, although Mucorales can be distinguished morphologically. The polysaccharide galactomannan can be detected in serum by EIA, which has demonstrated up to 71 % sensitivity and 93 % specificity in cases of aspergillosis [85]. False-positive results may occur in patients with infections due to *Fusarium*, *Penicillium*, *or Histoplasma* species, or in patients who have received intravenous piperacillin-tazobactam. The beta-D-glucan assay is less specific (positive in candidiasis), but more sensitive than EIA for galactomannan; both tests are useful detecting invasive aspergillosis prior to the onset of clinical findings in susceptible patients [86]. PCR demonstrates sensitivity up to 84 %; when two PCR tests are positive, the specificity is 95 % [87]. Given that the lungs are the most common site in invasive aspergillosis, CT imaging is an important component of evaluation.

Cutaneous cryptococcosis is best diagnosed by visualization of encapsulated yeast forms (5–7 μm in diameter) and isolation in culture. Mucicarmine and alcian blue highlight the capsule, while Fontana-Masson highlights the cell wall. In contrast, india ink demonstrates the yeast as halos against a black background [87]. Depending on the host response, histopathology may demonstrate suppurative granulomas with fewer organisms, or abundant organisms with minimal inflammation (gelatinous). Various methods are available for the evaluation of disseminated or systemic infection: serum cryptococcal antigen, culture, imaging, and PCR. The sensitivity of serum cryptococcal antigen testing is over 94 % for CNS disease and 90 % for lung disease; the sensitivity of CSF testing is over 87–100 % with a specificity of 100 %. Of note, cryptococcal antigen testing cannot distinguish between *C. neoformans* and *C. gattii* and is not useful for monitoring response to treatment. Standard assays utilize EIA or latex agglutination, while lateral flow assays offer rapid screening and are also highly sensitive [88]. Blood, sputum, CSF, and tissue from skin biopsies can be cultured on standard media. Cerebral and lung CT should be performed if disease in those locations is suspected. PCR is sensitive and can distinguish between *C. neoformans* and *C. gattii*, but is reserved for use in cases where direct visualization and culture are negative [89].

Histopathology and culture are the best methods for diagnosis of cutaneous fusariosis. In tissue, *Fusarium* species appear similar to *Aspergillus* and *Scedosporium*: septate hyaline hyphae branching at acute angles (45°). Thus, the finding of an angioinvasive hyalohyphomycosis by histopathology is nonspecific, and definitive diagnosis requires culture. Cutaneous lesions are present in over 80 % of patients with disseminated disease, are the only source of diagnostic material over half of cases, and often precede fungemia. Thus skin biopsies should always be performed, and submitted for histology and culture, when this diagnosis is entertained. Fusarium grows rapidly on media that lack cycloheximide; blood cultures are positive in 40 % of patients with invasive disease [90]. Beta-D-glucan is released by *Fusarium* but also by *Candida*. Galactomannan antigen assay has a sensitivity of 83 % but a specificity of 67 %, since it is also positive in aspergillosis [91].

Given that attempted cultures of Mucorales often yield no growth, the need for rapid diagnosis, and the importance of empiric therapy, histopathologic identification may provide the only direct evidence of mucormycosis. Presumptive diagnosis is made based on the presence of broad (up to 15 μm in diamater) aseptate hyphae with irregular branching patterns. While speciation should not be attempted by the dermatopathologist, distinction from *Aspergillus* is helpful, if possible, as Mucorales are not sensitive to voriconazole, the treatment of choice for aspergillosis [92]. PCR may also be helpful when cultures are negative, and can be applied with high sensitivity to histologic specimens [93].

Aspergillosis

Table 17.21 First-line therapies for aspergillosis [94–97]

Medication	Dosing	Evidence level
Voriconazole	Loading dose: 6 mg/kg twice daily IV for 1 day	A
	Maintenance: 4 mg/kg daily IV or 9 mg/kg po twice daily for several months	

In a large open trial of patients with invasive aspergillosis, voriconazole treatment resulted in survival rate over 70 %, while amphotericin B deoxycholate achieved a survival rate of less than 60 %. Voriconazole is also the preferred treatment given the lower risk of severe adverse effects.

Table 17.22 Second-line therapies for aspergillosis [96–99]

Medication	Dosing	Evidence level
Liposomal amphotericin B	3–5 mg/kg IV daily	B
Amphotericin B deoxycholate	1 mg/kg IV daily	B
Posaconazole	4 mg/kg po three times daily for several months	A
		B*
Isavuconazole (Isavuconazonium sulfate 372 mg = Isavuconazole 200 mg)	Loading dose: 200 mg TID × 2 days, then 200 mg daily	A*
	Maintenance: for several months	(No dosing guidelines for pediatric patients yet)

In patients who are intolerant of, or refractory to, therapy with voriconazole or amphotericin B, posaconazole is an alternative treatment; in one open trial, posaconazole was successful in 42 % of patients treated. Isavuconazole was non-inferior to voriconazole in a randomized, controlled trial of patients with invasive aspergillosis; however, this study also evaluated patients with infections due to filamentous molds other than *Aspergillus*.

Table 17.23 Third-line therapies for aspergillosis [100–106]

Medication	Dosing	Evidence level
Itraconazole	5–10 mg/kg/day in two divided doses daily for several months	B*
Echinocandins (concurrently with voriconazole):		
Caspofungin	70 mg/m2 on day 1 then 50–70 mg/m2 daily IV with maximum single dose 70 mg	B*
Anidulafungin	200 mg IV on day 1 then 100 mg IV daily (adolescents)	B*
Micafungin	1.5–3 mg/kg daily IV	B*

Itraconazole has demonstrated efficacy comparable to that of amphotericin B, but has inferior activity *in vitro* against *Aspergillus*. Caspofungin is approved for the treatment of aspergillosis, and has equivalent activity to that of the other echinocandins micafungin and anidulafungin. In patients intolerant of or refractory to standard treatment, overall clinical response to caspofungin was 45 %.

Echinocandins should not be used as monotherapy for aspergillosis, but can be used in combination with other treatments, including voriconazole. Several trials have produced data supportive of therapy combining voriconazole with echinocandins over monotherapy with voriconazole or amphotericin B alone. Similarly, the combination of liposomal amphotericin B and echinocandins has also demonstrated superiority to polyene therapy alone. However, retrospective data and *in vitro* studies do not support the use of amphotericin B in combination with azoles. In fact, azole therapy may be antagonistic toward the mechanism of action of amphotericin B.

Cryptococcosis

Management Strategies

Therapy regarding treatment of pediatric cryptococcosis is based on data from studies in adults. Given that most children with cutaneous cryptococcosis have underlying disseminated disease, the following treatment recommendations are best-suited for children with disseminated disease, but without a history of HIV or organ transplantation [107–109].

Table 17.24 First-line therapies for cryptococcosis [110–117]

Medication	Dosing	Evidence level
Liposomal amphotericin B	5 mg/kg/day IV	A*
OR		
Amphotericin B deoxycholate AND Flucytosine	1 mg/kg day IV	A*
	100 mg/kg/day po in 4 divided doses	
	Duration of induction: 2 weeks then transition to consolidation therapy	A*
Fluconazole	Consolidation: 10–12 mg/kg/day po for 8 weeks	A*
	Maintenance: 6 mg/kg/day po for 6–12 months	

Several high-quality studies of HIV-infected patients with cryptococcosis have demonstrated that higher dose amphotericin B in conjunction with flucytosine provides improved clinical response, sterilization of cerebrospinal fluid, and survival benefit compared to induction monotherapy with

lower dose amphotericin B and without flucytosine. Given the risk of myelosuppression with flucytosine induction, flucytosine peak levels should be maintained between 30 and 80 mcg/mL, and CBC should monitored regularly.

Consolidation and maintenance therapy should follow induction in order to reduce the risk of relapse. Comparative studies have shown that risk of relapse of cryptococcosis is 15–20 times greater without consolidation therapy. Fluconazole is preferred over itraconazole, due to it superior ability to sterilize the cerebrospinal fluid. Itraconazole is used for consolidation and maintenance when fluconazole cannot be tolerated.

Table 17.25 Second-line therapies for cryptococcosis [111, 114, 118, 119]

Medication	Dosing	Evidence level
Itraconazole	Consolidation: 2.5–5 mg/kg po 3 times daily for 3 days (maximum daily dose 600 mg) followed by 2.5–5 mg/kg po 1–2 times daily (maximum daily dose 400 mg) for at least 8 weeks	A*
	Maintenance: 5 mg/kg po daily for 6–12 months	
Voriconazole	Consolidation: 9 mg/kg po twice daily for 10–12 weeks with maximum dose 350 mg	B*
Posaconazole	Consolidation: 4 mg/kg po 3 times daily	B*

For patients with persistent or relapsed infection that is not susceptible to fluconazole, voriconazole or posaconazole may be used for salvage consolidation therapy. Several open trials have supported the use of these alternative agents in this context.

Fusariosis

This section focuses on invasive infection associated with cutaneous lesions, rather than primary superficial infections such as onychomycosis.

Table 17.26 First-line therapies for fusariosis [49, 111, 114, 118, 119, 120–123]

Medication	Dosing	Evidence level
Liposomal amphotericin B	3–5 mg/kg/day IV	D/C*
	Duration: several weeks or until clinical improvement with immune reconstitution (resolution of neutropenia)	
Voriconazole	Loading dose: 6 mg/kg twice daily IV for 1 day	D/C*
	Maintenance: 4 mg/kg IV daily	
	Step-down therapy:	
	9 mg/kg po twice daily for several months, with maximum single dose 350 mg	

Retrospective data supports the use of liposomal amphotericin B for fusariosis, and this is the first-line preferred therapy for invasive or disseminated infection, demonstrating improvement or cure in 46%. Conventional amphotericin B deoxycholate should not be used for fusariosis, as it is associated with a higher case-fatality rate.

Voriconazole treatment was associated with up to 52% clinical response rate in retrospective studies. Voriconazole may be used as monotherapy, as step-down therapy following induction treatment, or as combination treatment with amphotericin B. Strictly speaking, retrospective data do not demonstrate a clear benefit for combination therapy, but survival of patients with invasive fusariosis has improved in recent years with an increased use of voriconazole and combination therapy.

Table 17.27 Second-line therapies for fusariosis [124, 125]

Medication	Dosing	Evidence level
Posaconazole	Step-down therapy:	C
	4 mg/kg po three times daily for several months	
Isavuconazole	Step-down therapy:	D*
	Po daily for several months	

In open studies, posaconazole salvage treatment was associated with a successful outcome in 48% of patients with fusariosis refractory to standard treatment. In small series and reports, isavuconazole has produced partial or complete response in patients with invasive fusariosis.

Mucormycosis

Primary cutaneous disease is associated with a favorable prognosis, and rarely disseminates. Prognosis is very poor in pulmonary or disseminated disease [92].

Table 17.28 First-line therapies for mucormycosis [126–130]

Medication	Dosing	Evidence level
Liposomal amphotericin B	5 mg/kg/day IV	D
Amphotericin B deoxycholate	1 mg/kg/day IV	D
	Duration of treatment: several weeks, or until favorable clinical response then transition to oral antifungal	
Posaconazole	Loading dose: IV twice daily for the first day	D/C*
	Maintenance: IV daily for several months	
Isavuconazole	Loading dose: po three times daily for the first 2 days	D
	Maintenance: po daily for several months	

The initial treatment of choice for mucormycosis is liposomal amphotericin B, based on retrospective data, historical experience, and in vitro data. The liposomal formulation of the drug is preferred if available. It is important to note that treatment should be initiated when this diagnosis is suspected, and not delayed until identification by culture or microscopy is available, given a twofold increase in mortality with delayed treatment. Additionally, when microscopy reveals an angioinvasive hyphal infection, amphotericin B should be selected for treatment until culture results are available, given that *Aspergillus* is sensitive to voriconazole while Mucorales are not. Surgical debridement should also be undertaken at the time of presumptive diagnosis.

Posaconazole and isavuconazole both have *in vitro* activity against Mucorales, and data supportive for their use as step-down therapy after induction or for salvage therapy in patients with disease refractory to treatment with amphotericin B. In a retrospective study of patients requiring salvage therapy, clinical response occurred in 60% of patients treated with posaconazole. Given issues with bioavailability of the oral solution formulation of posaconazole, only the IV formulation or extended-release oral tablets should be used. Isavuconazole demonstrated efficacy in a single-arm open study.

Table 17.29 Second-line therapies for mucormycosis [131–134]

Medication	Dosing	Evidence level
Caspofungin	(Not specified)	D/C*
Deferasirox	20 mg/kg/day for 14 days	C*

In a small retrospective study, patients with mucormycosis who received combination therapy with caspofungin and amphotericin B had better outcomes than those who received monotherapy alone. However, echinocandins do not have *in vitro* activity against Mucorales, and this data suggests utility as an adjunct treatment only.

Given that the iron chelator deferoxamine is a risk factor for mucormycosis, deferasirox has been used as adjunctive therapy to amphotericin B, but with mixed results. In a small open study, survival rate was high, but in a randomized, controlled trial, survival was poorer than with placebo.

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