Clinical Syndromes: Rare Fungi

8

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Besides the more prevalent deep fungal infections covered in individual chapters, additional fungi are regularly described as human pathogens. Typical attributes of human pathogenic fungi include the ability to grow at human body temperature and mechanisms to resist host defenses. Human pathogenic fungi are found in all major fungal lineages. Therefore, this chapter is predominantly organized by clinical syndromes covering important infections.

Fungal pathogens causing the so-called *endemic mycoses* can be cultivated from the environment, typically from soil in restricted geographic areas. After inhalation of spores, these fungi cause localized, in non-immunocompromised subjects mostly self-limiting infections. However, they may persist in the body or can disseminate leading to life-threatening infections mostly in immunocompromised hosts. These infections, including histoplasmosis, coccidioidomycosis blastomycosis, and paracoccidioidomycosis, can mimic several infectious and noninfectious medical conditions and may be lethal if not recognized early and treated. In endemic areas, these infections can be highly prevalent. Outside endemic areas, travel history is frequently a trigger for specific diagnostic tests establishing the diagnosis.

Implantation mycoses occur after traumatic inoculation by environmental fungi. Most of these infections have a subacute to chronic course and remain restricted to subcutaneous tissues. However, they can become recalcitrant to antifungal therapy and lead to physical disabilities. Although many of the causative fungi are found worldwide, infections are more prevalent in tropical climates.

Phaeohyphomycosis and *hyalohyphomycosis* are terms used to classify mold infections according to the appearance of fungal hyphae documented by histopathology as either melanized or non-melanized hyaline hyphae, irrespective of the mode of infection, the regional distribution, or the causative agent. These terms are used in an attempt to avoid the generation of separate names for infections by rare fungi. The clinical presentation is often not different from the more prevalent mold infections such as aspergillosis or mucormycosis.

Rare yeast and yeast-like infections include diseases caused by opportunistic yeasts and non-fungal agents with tissue forms resembling yeasts. Infections are typically diagnosed after cultivation from sterile sites such as blood or after biopsies demonstrate suggestive tissue forms. The clinical presentation is often not different from the more prevalent mycoses including candidiasis.

8.1 Endemic Systemic Fungal Infections

The term endemic mycosis is used for systemic fungal infections caused by obligate pathogenic environmental fungi with restricted areas of

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Table 8.1 Endemic, systemic fungal infections: causative agents, distribution, tissue forms, and clinical presentations

Disease	Fungus	Main endemic areas	Tissue forms	Typical presentation
Histoplasmosis	*Histoplasma capsulatum*	USA (Mississippi, Ohio River Valley) South-Central America Caribbean Africa Australia Asia	Small (2–5 μm) yeasts with narrow-based budding, intra- and extracellular	Flu-like illness Acute pneumonia Chronic pneumonia Disseminated infection
Coccidioidomycosis	*Coccidioides immitis* *Coccidioides posadasii*	USA (Southwest, Eastern Washington) Central-South Americas	Spherules (5–100 μm) and endospores (2–5 μm)	Flu-like illness Acute pneumonia Chronic pneumonia Disseminated infection Meningitis
Blastomycosis	*Blastomyces dermatitidis* *Blastomyces gilchristii* *Blastomyces percursus*	USA (Mississippi, Ohio River Valley) Canada Africa India Israel	Thick-walled yeast-like cells (3–30 μm) with broad-based budding	Acute pneumonia Chronic pneumonia Cutaneous infections Disseminated infection
Paracoccidioidomycosis	*Paracoccidioides brasiliensis* *Paracoccidioides lutzii*	From the south of Mexico to the north of Argentina	Yeast cells (3–30 μm) with multiple buds ("ship's wheel")	Juvenile form Adult form
Adiaspiromycosis	*Emmonsia crescens* *Emmonsia parva*	Worldwide	Adiaspores 200–400 μm	Pulmonary infections
Emergomycosis	*Emergomyces pasteurianus* *Emergomyces africanus* *Emergomyces orientalis*	South Africa China Other locations likely	Small (2–5 μm) yeasts with narrow-based budding, intra-, extracellular	Pulmonary infections disseminated infections with skin lesions
Talaromycosis (formerly known as penicilliosis)	*Talaromyces* (*Penicillium*) *marneffei*	India Southeast Asia Southern China Hong Kong Taiwan	Non-budding yeast cells (3–5 μm) with transverse septum, intra-, extracellular	Pulmonary infections Disseminated infection with skin lesions

endemicity. These fungi are thermally dimorphic; they grow as molds at environmental temperatures but develop specialized tissue forms including yeast cells (histoplasmosis, blastomycosis, and emergomycosis) or cysts (coccidioidomycosis, adiaspiromycosis) at mammalian body temperature.

After inhalation of infectious propagules from environmental sources, most encounters between non-immunocompromised humans and these fungi result in subclinical or self-limiting, localized infections, but these fungi may persist in the host and cause reactivation. They may also cause potentially life-threatening disseminated infections predominantly in immunocompromised hosts. As clinical symptoms of these infections are nonspecific, the diagnosis requires a high index of suspicion, especially in non-endemic areas where these infections are diagnosed mainly in immigrants or after travel to endemic regions. Except for rare transmission with transplanted organs, person-to-person spread has not been documented. Typical infections, their causative agents, endemic regions, and frequent clinical presentations of these infections are summarized in Table 8.1.

The diagnostic workup of these infections includes antibody and antigen testing, the detection of characteristic tissue forms by microscopy in secretions or tissue samples, and the cultivation of the fungi. As specific culture conditions and prolonged incubation periods are needed; microbiology laboratories need to be informed when these infections are suspected. Presumptive identification of these fungi may be achieved by macro- and micromorphology of the cultivated fungi and in some by demonstration of a switch from the mold phase that grows at 25–30 °C to the yeast phase after incubation at 37 °C. Many of these fungi need to be handled in biosafety level 3 laboratories to prevent laboratory infections. Sequencing of barcoding genes is necessary for an exact identification of these pathogens, as phylogenetic studies suggest they represent species complexes of separate species with differing environmental niches and potentially clinically relevant physiologic differences that cannot be distinguished by culture morphology alone.

Antifungal therapy is often not prescribed in otherwise healthy hosts with localized, self-limiting infections. However, patients with persistent symptoms, or at increased risk for dissemination, including immunocompromised subjects, are treated with systemic antifungal agents to prevent progressive infections potentially leading to lethal outcome.

8.2 Histoplasmosis

Histoplasmosis refers to infections caused by *Histoplasma capsulatum*. Following inhalation, these fungi cause a variety of clinical manifestations ranging from asymptomatic pulmonary infections, acute or chronic pneumonia, to disseminated infections. While most infections are asymptomatic, high inoculum exposure or host characteristics including immunodeficiencies may predispose to clinical disease.

Histoplasma capsulatum is found in the soils of river valleys especially when enriched with bird or bat droppings and in places such as bat caves. Traditionally, three varieties have been distinguished:

- *H. capsulatum* var. *capsulatum* is the most prevalent agent of histoplasmosis in most countries.
- *H. capsulatum* var. *duboisii,* the causative agent of so-called African histoplasmosis, is found in Central and in West Africa. This variety may be differentiated by larger, thicker-walled yeasts in tissue. Infections often manifest with disseminated skin and bone lesions not typically found in histoplasmosis in other regions.
- *H. capsulatum* var. *farciminosum* has been described as an agent of superficial infections of animals such as horses in North Africa.

More recently, the application of molecular typing data suggests that the differentiation of these varieties may not be accurate. Instead, seven and potentially more phylogenetic species can be differentiated with differing geographic distribution and potentially differences in clinical manifestations. After inhalation of spores present in the environment, *H. capsulatum* transforms into yeast cells. The infection may be asymptomatic in most cases or present as flu-like illness after an incubation period from 1 to 3 weeks and as acute to chronic pneumonia or disseminated infections with the involvement of the skin, mucous membranes, and bone marrow among other organs. Fungi may also persist in the body to cause disease subsequently.

Acute pulmonary histoplasmosis may present with high-grade fever, chills, myalgia, headache, cough, and pleuritic chest pain. Additional symptoms include arthralgia and erythema nodosum in a minority of patients. Chest X-rays may demonstrate nodular infiltrates and mediastinal lymphadenopathy. Most otherwise healthy people recover within 3 weeks, but constitutional symptoms can persist for months. Lung infiltrates heal as calcified lesions. In the absence of calcification, these nodules resemble neoplasm and may be diagnosed incidentally. In immunosuppressed patients or after massive exposure, the infection can present with diffuse infiltrates associated with respiratory distress syndrome. In some patients, massive enlargement of single or multiple lymph nodes occurs due to granulomatous inflammation

leading to caseating necrosis (granulomatous mediastinitis). Lymph node enlargement may lead to tracheal, bronchial, or esophageal compression or pericarditis. Resulting symptoms including cough and chest pain usually resolve spontaneously over months. Mediastinal fibrosis is an uncommon, late complication of pulmonary histoplasmosis that may lead to the occlusion of central blood vessels or bronchi.

Chronic pulmonary histoplasmosis typically occurs in patients with chronic lung conditions such as chronic obstructive lung disease. Here, pneumonic infiltrates may slowly progress to tissue destruction leading to cavitation and fibrosis resulting in progressive worsening of lung function if untreated. Clinical manifestations include productive cough, chest pain, hemoptysis, and potentially constitutional symptoms.

8.2.1 Disseminated Histoplasmosis

Hematogenous dissemination from pulmonary lesions occurs early in the course of most acute infections. However, after specific immunity develops, most lesions are not symptomatic, and radiography may demonstrate calcified lesions subsequently. Symptomatic disseminated infections occur in about 1 in 2000 exposed individuals, often subjects with impaired T-cell immunity such as HIV infection, in children or older patients. In elderly (>54 years) patients without immunosuppression, disseminated infection manifests as a progressive disease and may be fatal in weeks to months if untreated. Presenting symptoms include mucosal ulcers of the gastrointestinal tract (60%), mostly the mouth, the genitourinary tract, or other sites. Hepatosplenic enlargement and adrenal gland destruction are frequently found, while skin lesions are unusual. Often, chest X-rays are unremarkable. CNS involvement may present as chronic meningitis or brain abscess. In AIDS patients and infants, the course is often more acute and is even with specific treatment often fatal within several weeks. Unspecific symptoms including high fever, fatigue, weight loss, hepatosplenomegaly, anemia, leukocytopenia, and thrombocytopenia may be present with or without pulmonary infiltrates and mucocutaneous lesions. If the diagnosis of disseminated histoplasmosis is missed, the infection can progress to a sepsis-like syndrome and may be associated with a hemophagocytic syndrome and high mortality rate.

African histoplasmosis takes a more indolent course and rarely manifests with pulmonary lesions but with papular skin lesions, soft tissue, and bone involvement. Involvement of the liver, the spleen, and other organs is possible and manifests with a wasting syndrome. The infection is fatal within weeks to months if left untreated. Besides these infections caused by the variety *duboisii*, infections resembling histoplasmosis in other regions caused by classic *H. capsulatum* also occur in endemic African regions.

Differential diagnosis of acute pulmonary histoplasmosis includes atypical pneumonias, other endemic mycoses, and cryptococcosis. The presentation of chronic pulmonary histoplasmosis is similar to tuberculosis, sarcoidosis, blastomycosis, and coccidioidomycosis. The mucocutaneous lesions of the disseminated form are similar to the lesions of other infections including tuberculosis, emergomycoses, paracoccidioidomycosis, syphilis, viral infections, and noninfectious diseases.

Diagnosis of histoplasmosis requires a high index of suspicion and often involves a combination of different laboratory techniques. Microscopic examinations of respiratory secretions, pus, and even blood smears stained with fungal stains such as Grocott or calcofluor may show small yeast cells (<5 μm) with narrow-based buds typically clustering within phagocytes. These cells may not always be differentiated from other small yeasts such as *Candida glabrata*, *Talaromyces marneffei*, *Emergomyces*, or acapsular *Cryptococci*. Larger, thick-walled yeasts are suggestive for African histoplasmosis. Cultivation of *Histoplasma capsulatum* is required for definitive proof of the infection. Mold colonies can be cultivated on standard mycological media containing cycloheximide for inhibition of other fungi at 25–30 °C for 4–6 weeks. As colony morphology may be difficult to distinguish from other molds, the conversion to yeast form at 37 °C on rich media or sequencing of barcoding genes is needed for confirmation. Multiple samples from

the respiratory tract may be cultivated to increase sensitivity. In disseminated infections, fungi can be cultivated from bloodcultures and bone marrow aspirates. Cerebrospinal fluid is a valuable first sample to confirm CNS infection. Antibody testing is most useful for subacute and chronic pulmonary histoplasmosis, granulomatous mediastinitis, and pericarditis. Antibodies detected with the immunodiffusion (ID) test appear 4–8 weeks after exposure in up to 75% of patients with acute pulmonary histoplasmosis. The complement fixation (CF) test becomes positive after 2–6 weeks and is more sensitive but less specific than the ID test. Titers of 1:8 or greater are considered as presumptive evidence for histoplasmosis. Titers above 1:32 or a fourfold rise in paired samples offer strong evidence for active infection. Titers decrease with successful therapy and increase in chronic progressive disease. Cross-reactions may be observed with blastomycosis and coccidioidomycosis. Both tests may be applied to CSF if CNS disease is suspected. Antigen detection by ELISA is useful for the diagnosis of disseminated infections in immunocompromised patients that often do not produce antibodies. Sensitivity is greatest in urine where it is detected in over 90% of AIDS patients with disseminated disease. Antigen levels decline with successful antifungal therapy. Cross-reactions may be observed with blastomycosis, paracoccidioidomycosis, and coccidioidomycosis.

Antifungal treatment is indicated for moderately severe acute pulmonary histoplasmosis with symptoms such as fever, fatigue, or weight loss persisting for more than 3 weeks with itraconazole 2 × 200 mg for 6–12 weeks. In severe pulmonary infections with diffuse infiltrates, therapy is started with conventional (0.7–1 mg/kg per day) or liposomal amphotericin B (3–5 mg/kg/day). After patients show improvement, treatment may be continued with itraconazole (3 × 200 mg for 3 days, than 2 × 200 mg daily) to complete a 12-week course. In patients with hypoxemia, prednisone may be added. Chronic pulmonary infection is treated with itraconazole for at least 12 months with therapeutic drug monitoring to assure adequate drug exposure. Treatment of disseminated and CNS infections is started with amphotericin B for 1–2 weeks and later switched to itraconazole with a 3-day loading dose and control of serum levels for a total of 12 months or newer azoles with better CNS exposure such as voriconazole or posaconazole. AIDS patients may require suppressive therapy with itraconazole (1 × 200 mg) after completion of treatment until CD4 count is above 200/μl for at least 6 months. Mild disseminated infections may be treated with itraconazole alone. If itraconazole is not tolerated, it may be switched to posaconazole or voriconazole. If these are not available, fluconazole 400–800 mg may be used.

8.3 Coccidioidomycosis

The infection is caused by fungi of the genus *Coccidioides*. These fungi can be found in alkaline soils in regions with arid climate, hot summers, and mild winters. The endemic region of *Coccidioides immitis* includes the San Joaquin Valley of California, Utah, and as recently discovered the eastern part of Washington State in the USA. *Coccidioides posadasii* has a much larger and dispersed geographic distribution including Arizona, New Mexico, and Texas in the USA, Mexico, and Central and South America, where it occurs in isolated pockets. Infection is acquired after inhalation of aerosolized arthroconidia often in the context of natural or human-induced soil disruption. After inhalation, arthroconidia enlarge and transform into immature spherules in host tissue. Spherules undergo nuclear division to develop endospores. After 3–4 days, mature spherules rupture and release 100–300 endospores, which can each transform into a new spherule. In certain regions of Arizona, about a quarter of community-acquired pneumonias are caused by *Coccidioides*. Based on earlier coccidioidal skin test studies, it is thought that most infections are subclinical. In the general population, only 1% of exposed individuals will develop disseminated infections. However, that percentage may be higher in immunosuppressed patients (HIV patients with a CD4 count <250/μl, allogenic transplant recipients, patients treated by TNF-α inhibitors or high doses of corticosteroids), people of certain ethnicities (Afro-Americans and Filipino), and pregnant women.

Acute pulmonary coccidioidomycosis develops about 1–3 weeks after exposure. Symptoms are nonspecific and may include fever, weight loss, malaise, nonproductive cough, dyspnea and pleuritic chest pain, and peripheral blood eosinophilia. Chest X-ray shows hilar adenopathy and pneumonic infiltrates. A generalized maculopapular rash may be present. These symptoms can be accompanied in 5% of the cases by the classical "valley fever" or "desert rheumatism," consisting of fever, arthralgia, and erythema nodosum or erythema multiforme. Most of the affected adults will recover spontaneously over 6–8 weeks. In HIV-infected persons with a CD4 count <100 cells/μl, the disease can be much more fulminant with diffuse pneumonia, potentially resulting in respiratory failure.

Chronic pulmonary coccidioidomycosis develops in 5–10% of infected individuals, many of whom suffer from previous lung conditions including COPD over weeks to months. Patients present with cough and hemoptysis. Chest X-ray findings include nodules, cavities, abscesses, or infiltrates. Potential complications include bronchopleural fistula, empyema, and pulmonary hemorrhage.

Disseminated coccidioidomycosis usually manifests 3–12 months after the primary infection. The presentation can range from an acute illness which may be fatal within a few weeks if left untreated to an indolent chronic disease, which may progress during months and even years. The most common symptoms at presentation include fever, cough, night sweats, and chills. Hematogenous spread may affect the skin, the bones, and the central nervous system. Cutaneous and subcutaneous lesions are the most common manifestations of disseminated disease. They may appear as verrucous nodules, papules, or subcutaneous abscesses. Often, these lesions occur in the face of the patients. Bone and joint disease is a common complication. Asymmetric arthritis regularly involves the knees, the joints of the hands and wrists, the feet and ankles, and the pelvis. Although long bones may be infected, the most affected bones are the vertebrae. On radiographs, osteolytic or osteosclerotic lesions may be seen. MRI is often necessary to exclude instability of the spine or a potential compression by an epidural abscess. The patients remain asymptomatic for a long time and develop often only a dull pain. Hematogenous spread to the leptomeninges almost always occurs within weeks to months following an initial untreated lower respiratory infection. Every patient with symptoms of CNS involvement, such as persistent headache, altered mental status, unexplained nausea, or new focal neurologic deficits, should undergo cerebral imaging and lumbar puncture with the analysis of the cerebrospinal fluid. Typically, CSF analysis will show pleocytosis, often with a lymphocytic predominance, but also a neutrophilic or an eosinophilic predominance is possible. Proteins may be normal or moderately elevated. The glucose may be normal but is often depressed.

8.3.1 Differential Diagnosis

The infection needs to be differentiated from viral and bacterial pneumonias and other respiratory and disseminated fungal or mycobacterial infections. Skin and bone lesions may resemble neoplasia.

8.3.2 Diagnosis

Microscopy of respiratory secretions may be positive in up to 30–40% of patients with pneumonia. Histopathological samples can show the characteristic spherules. If only endospores, which are 2–5 μm in size, are visualized, the diagnosis might be more difficult, requiring differentiation from small yeasts including *Histoplasma capsulatum* and *Candida*. Sometimes, hyphal forms are seen, especially in lung cavities. *Coccidioides* species are fast-growing molds and can be isolated from lower respiratory tract samples, blood cultures, and pus and sometimes from the CSF. After 2–7 days, this fungus will grow as an unpigmented mold on a variety of culture media at 35 °C. After 7–10 days, the mold will present a large number of infective arthroconidia. Laboratory-associated infections have occurred and cultures must be handled in BSL-3 laboratories. Serologic tests include antibody detection using immunodiffusion (ID) and complement fixation (CF). The ID test has the advantage to be

more specific than the CF test and to be able to detect IgM response and to be useful in the diagnosis of recent infections. Generally IgM appears 1–3 weeks and IgG 2–6 weeks after onset of the first symptoms. The CF test is more sensitive and becomes positive 4–12 weeks after infection. The advantage of this serologic test is that it is semi-quantitative and that the testing of serial samples may give a clue about the evolution of the disease. Titers of 1:16 or above are indicative of a disseminated disease. A lateral flow device has recently introduced to detect antibodies. The test provides a bed side diagnosis with sensitivity and specificity comparable to the ID and CF tests.

8.3.3 Management

Medical follow-up should be assured for all patients, treated or not, for a minimum of 1–2 years. In previously healthy patients including nonpregnant woman without debilitating disease, acute pulmonary coccidioidomycosis doesn't require antifungal treatment. Treatment should be initiated in acute pulmonary coccidioidomycosis if the infection is severe, if the patient has comorbidities, or in pregnant woman. Severe primary infection is clinically defined as a disease in which the patient has lost >10% of his weight, has intense night sweats for >3 weeks, has symptoms that persist for >2 months, needs a hospital stay, or is unable to work. Radiological signs of severity include bilateral infiltrates or infiltrates which cover >50% of one lung. In addition, complement fixation (CF) titers of >1:16 are considered as a sign of severe, potentially disseminated disease. If treatment is required, current guidelines recommend for nonpregnant adults a treatment with azole antifungals, for example, itraconazole (400–800 mg/day), fluconazole (400–2000 mg/day), or voriconazole (4 mg/kg/12 h), for 3–6 months or longer depending on the clinical response. Reversal of underlying immunodeficiency should be considered if feasible. In pregnant women, treatment with intravenous amphotericin B (0.6–1 mg/kg/day) or liposomal amphotericin B (3–5 mg/kg/day) should be initiated. During the second or the third trimester, a treatment with azoles can be considered. No treatment is recommended in patients with asymptomatic pulmonary nodules and in immunocompetent patients with an asymptomatic coccidioidal cavity. Adults with symptomatic chronic cavitary coccidioidal pneumonia should be treated by fluconazole (at least 400 mg/day) or itraconazole (2 × 200 mg/day) for 1 year. Coccidioidal eradication may not be achieved and surgical treatment may be necessary in specific cases. The first-line therapy in soft-tissue involvement is itraconazole (2 × 200 mg/day) or fluconazole (400–800 mg/day). The minimum duration of treatment should be 6–12 months. Bone or joint infections are treated with itraconazole (2 × 200 mg/day) unless extensive or limb- threatening skeletal or vertebral disease is present. In this case a treatment by intravenous amphotericin B may be initiated, followed by oral azole therapy for a total of at least 3 years. Suspected vertebral disease should prompt spine imaging and surgical advice. The recommended treatment of coccidioidal meningitis is fluconazole 400–1200 mg/day or itraconazole 2–4 × 200 mg/day with a therapeutic drug monitoring. Sometimes high intracranial pressure will need repeated lumbar punctures or placement of a permanent shunt. The medical treatment should be continued for life. In pregnant patients during the first trimester, intrathecal amphotericin B may be used. During the rest of the pregnancy, a treatment by azoles can be considered. An alternative would be to treat the patient during all the pregnancy by intravenous amphotericin B.

8.4 Blastomycosis

Blastomycosis refers to infections caused by fungi of the genus *Blastomyces*. Following inhalation of fungi present in soil or traumatic inoculation, they can cause a wide spectrum of clinical manifestations including the respiratory tract, skin, bone, central nervous system, and urogenital infections. Most infections have been reported in regions surrounding the Mississippi and Ohio rivers, the midwestern states of the USA, and Canadian regions bordering the Great Lakes and the St. Lawrence River. Cases have also been documented in Africa, India, Israel, Central-, and

South America. Those at greatest risk include middle-aged men with outdoor occupations (construction or farming) or recreational activities (fishing, hunting). More aggressive diseases are seen in patients with AIDS, transplant recipients, and patients receiving corticosteroids.

8.4.1 Pulmonary Blastomycosis

After an incubation period of 4–6 weeks, patients manifest with a nonspecific, flu-like illness with nonproductive cough and pleuritic chest pain. Chest X-ray shows nonspecific infiltrates. Pleural effusions are uncommon. In contrast to histoplasmosis, hilar lymphadenopathy is uncommon. In the absence of recovery, chronic pulmonary infection resembling lung tuberculosis or cancer or disseminated infection may develop.

8.4.2 Cutaneous Blastomycosis

Skin lesions, starting as maculopapular lesions progressing to raised, crusted verrucous lesions or ulcers over subcutaneous abscesses, may develop on exposed sites such as the face (nose, mouth, oral and pharyngeal mucosa), neck, or scalp.

8.4.3 Disseminated Blastomycosis

Impaired T-cell immunity, such as advanced HIV infection, predisposes to hematogenous dissemination. Involved organs include the central nervous system with subacute meningitis or brain abscess manifesting as headache, confusion, or focal neurologic deficits. Additional affected organs include the skin, the adrenal glands, the liver, the spleen, the heart, the gastrointestinal tract, the genitourinary tract, and the eye. Osteomyelitis of the spine, the pelvis, the skull, the ribs, and the long bones manifests as osteolytic or osteoblastic lesions. They may remain clinically silent until adjacent joints become involved. AIDS patients may also present with a sepsis syndrome as in disseminated histoplasmosis.

Differential diagnosis of pulmonary blastomycosis includes bacterial pneumonia and fungal infections including histoplasmosis and cryptococcosis. Chronic pulmonary forms need to be differentiated from tuberculosis, histoplasmosis, and bronchogenic carcinoma. These infections are also indistinguishable from coccidioidomycosis and paracoccidioidomycosis, but their endemic regions have almost no overlap.

8.4.4 Diagnosis

The fungi may be visualized in wet mounts or stained specimens of pus, sputum, bronchial secretions, cerebrospinal fluid, urine, or tissue. Yeast cells vary in diameter from 3 to 30 μm, are oval to round with thick walls, and show characteristic broad-based single buds. Confirmation of blastomycosis depends on the cultivation of the fungi. Antibody testing is done by immunodiffusion (ID) using a purified surface antigen. This test is specific but remains negative in 10% of patients with disseminated infections and as much as 60% of patients with localized infections. Complement fixation tests lack specificity due to cross-reactions with *Histoplasma capsulatum* and *Coccidioides* sp.

8.4.5 Management

Patients with acute pulmonary infection are often treated to prevent dissemination. Mild to moderate pulmonary infections are treated with itraconazole (3 × 200 mg/day for 3 days, than 1–2 × 200 mg) for 6–12 months. Moderately severe to severe disease is treated with amphotericin B for 1–2 weeks until clinical improvement and then switched to itraconazole with control of serum levels. While fluconazole (400–800 mg) is less active, posaconazole and voriconazole may be effective. The treatment of disseminated infections depends on the presence of CNS lesions. In the presence of CNS infections, liposomal amphotericin B (5 mg/kg for 4–6 weeks) is followed by oral azoles such as fluconazole (800 mg/day) or voriconazole (2 × 200–400 mg) for at least 12 months until resolution of CSF abnormalities. In the absence of CNS lesions and mild-moderate disseminated disease, itraconazole is used, while more severe infections are treated with amphotericin B for 1–2 weeks, fol-

lowed by itraconazole until resolution of symptoms and signs. Patients with osteoarticular disease should receive an azole for at least 12 months to prevent relapse. Surgical management may be needed for drainage of large abscesses and brain and epidural abscesses causing neurologic deficits. Debridement of bone lesions is only needed when refractory to antifungals.

8.5 Paracoccidioidomycosis

Paracoccidioidomycosis is a deep systemic mycosis caused by *Paracoccidioides brasiliensis* and *Paracoccidioides lutzii*. The disease is geographically restricted to subtropical areas of Latin America from the south of Mexico to the north of Argentina with a high prevalence in Brazil, Colombia, Venezuela, and Argentina. *Paracoccidioides lutzii* is predominantly found in the Central-West and Amazon Regions of Brazil and Ecuador. In Latin America, it is the second most prevalent endemic mycosis after histoplasmosis. Involvement in agriculture is an important risk factor for infection that occurs via inhalation of aerosolized spores from the soil. Symptomatic disease is predominantly diagnosed in males over 30 years as a chronic progressive granulomatous infection involving the skin and lymph nodes. Immunocompromised subjects are not at increased risk for infection, as are travelers spending less than 6 months in an endemic area.

8.5.1 Acute or Subacute Disseminated Paracoccidioidomycosis (Juvenile Type)

It is responsible for 5–25% of the cases and is mostly seen in children and adolescents. This may be related to specific phylogenetic clusters, as it is seen more frequently in certain endemic regions. Disease history is characterized by a short period of evolution and a more severe course. The most prominent symptoms and signs are linked to localized or generalized lymphadenopathy and hepatomegaly. The lumps may form fistulas or coalesce and exert compression on various organs. Systemic symptoms, such as fever, weight loss, and anorexia, are often present. A pulmonary (10–20%) or a mucocutaneous involvement (25%) in this form is uncommon. Eosinophilia occurs in 30–50% of the cases.

8.5.2 Chronic Disseminated Paracoccidioidomycosis (Adult Type)

The most often encountered type, which progresses slowly and often persists during months to years before the diagnosis is established. Besides the lungs, ulcerative mucocutaneous lesions of the face are present. Chest X-rays show bilateral infiltrates. Mucosal lesions may first involve the gums, evolve over weeks or months, and can lead to malnourishment. They can also involve other parts of the gastrointestinal tract, predominantly the ileocecal region. Skin involvement manifests as papular or nodular lesions that evolve to plaques, verrucous lesions, or ulcers. About 15% of the affected adults will develop adrenal gland insufficiency. CNS involvement is seen in a minority of patients leading to meningitis or encephalitis.

8.5.3 Differential Diagnosis

The differential diagnosis of the mucocutaneous lesions includes histoplasmosis, sporotrichosis, cryptococcosis, chromoblastomycosis, syphilis, leishmaniosis, leprosy, and tuberculosis. Pulmonary infections may be difficult to differentiate from tuberculosis, histoplasmosis, coccidioidomycosis, lymphoma, cancer, and cryptococcosis. The gastrointestinal symptoms and lesions may be misdiagnosed as amebiasis, balantidiasis, tuberculosis, cancer, or inflammatory bowel disease. The other etiologies to consider in case of CNS involvement are tuberculosis, cryptococcosis, cysticercosis, and neoplasia.

8.5.4 Diagnosis

The microscopic examination of KOH preparations or histopathology sections may be diagnos-

tic. The typical findings include yeast cells at varying sizes (3–30 μm) with sometimes multiple budding. The definite diagnosis relies on the cultivation of the fungus which may take weeks to months. Serological tests can be helpful for the diagnosis of *P. brasiliensis* infection, but experience for the diagnosis *P. lutzii* infection is limited. The ID test is specific and has a good sensitivity. In contrast to the following antibody detection tests, cross-reactions with *Histoplasma capsulatum* antibody are uncommon with ID. The CF test has a comparable sensitivity but is less specific. A CF titer of 1:8 is considered as a presumptive evidence of the diagnosis.

8.5.5 Management

Patients with mild and moderate paracoccidioidomycosis are treated with itraconazole 200 mg/day for 9–18 months. Treatment with itraconazole is more advantageous than the treatment with cotrimoxazole (adults, TMP 160–240 mg/SMX 800–1200 mg 2×/day; children, TMP 8–10 mg/kg and SMX 40–50 mg/kg in two daily doses for 18–24 months), which is the second treatment option in endemic resource-limited regions. Although only a small number of patients have been treated with these drugs, voriconazole and posaconazole are potential alternatives. Amphotericin B deoxycholate (0.3–0.5 mg/kg/day, with a maximum of 50 mg/day) or lipid formulation (3–5 mg/kg/day) should be reserved for the induction period (for 2–4 weeks) of the treatment in severe cases, as well as for the treatment of pregnant women. Transition to oral medication should occur after clinical stabilization once the drug's oral absorption has been confirmed.

8.6 Talaromycosis (Penicilliosis)

Talaromycosis is an infection caused by *Talaromyces marneffei*, formerly known as *Penicillium marneffei*. The infection follows the inhalation of spores. Occupational exposure to plants and animals has been associated with human infection. The infection is diagnosed in India, Southeast Asia, Southern China, Hong Kong, and Taiwan. The disease affects primarily patients with impaired T-cell immunity such as AIDS patients. In addition, infections in organ or stem cell transplant recipients and patients with hematologic malignancy have been reported.

8.6.1 Clinical Manifestations

The infection is mostly diagnosed in HIV patients with a CD4 count below 100/μl. The lungs are the initial site of contact with the fungi but the infections may already be disseminated at the time of diagnosis. Presenting symptoms include fever and weight loss, nonproductive cough, generalized lymphadenopathy, and hepatosplenomegaly. Papulous skin lesions are among the most common symptoms of disseminated infections. They are often localized in the face, at the upper trunk, or the extremities. CNS involvement is uncommon and may present as altered mental state.

8.6.2 Differential Diagnosis

The skin lesions may be misdiagnosed as sporotrichosis, histoplasmosis, cryptococcosis, melioidosis, necrotic *Herpes zoster* infection, or *Molluscum contagiosum* or *Mycobacterium* sp. infection. The differential diagnosis of the lung lesions includes tuberculosis, histoplasmosis, bacterial pneumonia, and *Pneumocystis jirovecii* pneumonia.

8.6.3 Diagnosis

Microscopy from respiratory tract samples or tissue biopsies may reveal intra- or extracellulary located, non-budding yeast cells, with prominent transverse septum. *T. marneffei* cells can be confused with those of *Histoplasma capsulatum*, *Candida*, *Pneumocystis jirovecii*, *Toxoplasma gondii*, and *Leishmania* due to their size. Cultivation of *Talaromyces marneffei* mold colonies from bone marrow, blood, cutaneous, or respiratory tract specimens may be diagnostic.

Colonies produce a red pigment that diffuses into the agar. However, other nonpathogenic species of *Penicillium* may also produce red pigments. Therefore molecular tests are necessary to identify this organism. Antibody detection tests are not widely available. They are specific but less sensitive than culture in immunocompromised patients. Of note, the galactomannan antigen detection test for aspergillosis has been found to give false-positive results in HIV-infected patients with talaromycosis.

8.6.4 Management

In AIDS patients, deoxycholate amphotericin B (0.6–1 mg/kg/day) for 2 weeks, followed by itraconazole (400 mg/day) for 10 weeks, followed by low-dose itraconazole (200 mg/day) continued until CD4 counts >100/μl for 6 months minimum, is recommended. Induction therapy with itraconazole has been studied and is linked to higher mortality.

8.7 Other Infections Caused by Thermally Dimorphic Fungi and Close Relatives

Emergomycosis has been recently described as an emerging disseminated fungal infection in South African patients mostly with advanced HIV infection. Additional cases have been described in organ transplant recipients and non-immunocompromised hosts. Patients present with pulmonary involvement and disseminated skin lesions. The causative agent has been named *Emergomyces africanus*. The fungus is closely related to *Emmonsia* and *Histoplasma*, being thermally dimorphic. Closely related fungi have been isolated mostly from immunocompromised subjects in Canada, China, Italy, and Germany, suggesting a wide distribution of these fungal pathogens. Differential diagnosis includes other disseminated fungal infections such as histoplasmosis, tuberculosis, and other infections causing disseminated skin lesions. The diagnosis may be suggested by histopathology of skin lesions showing small budding yeast cells clustering in phagocytic cells resembling *Histoplasma capsulatum*. Therefore, cultivation of the fungi is necessary to establish the diagnosis. Fungi may be cultivated from skin and respiratory tract samples, from blood, or from bone marrow. Cross-reactivity with the *Histoplasma* urinary antigen detection test has been described. Good in vitro activity has been described for azoles and amphotericin B, while echinocandins and flucytosine are not active. Amphotericin B appears to be the most active agent clinically, while fluconazole therapy seems to be associated with worse outcome. Start of antiretroviral therapy has been linked to new and progressive skin lesions suggesting immune reconstitution inflammatory syndrome (IRIS) as described in cryptococcosis and other infections. Mortality of disseminated infections is up to 48% in case series from South Africa with half of the patients being diagnosed postmortem.

Adiaspiromycosis is a pulmonary fungal infection caused by *Emmonsia parva* and *Emmonsia crescens* present in soil. After inhalation, the fungi enlarge to form 40–500 μm large, non-replicating, not disseminating structures called adiaspores. They may induce a granulomatous tissue reaction associated with respiratory decline. Disease ranges from subclinical infections to diffuse pneumonia. The infection is common in small terrestrial mammals globally but has only rarely been diagnosed in humans. Diagnosis relies on the demonstration of characteristic adiaspores by histopathology. The fungi are not usually cultivated from human specimens. Steroids have been given as tissue destruction is mediated by the inflammatory response. The role of antifungals is not well defined.

8.8 Implantation Mycoses

Implantation mycoses are a diverse group of fungal infections that develop at the site of transcutaneous trauma with implantation of fungi present in environmental sources such as soil or on plant materials. These infections are also referred to as subcutaneous mycoses, but in some cases they

Table 8.2 Common implantation mycoses of the skin: etiologic agents, distribution, histopathological characteristics, and clinical presentation

Disease	Fungus	Distribution	Tissue form	Presentation
Sporotrichosis	*Sporothrix schenckii* *Sporothrix brasiliensis* *Sporothrix globosa* *Sporothrix luriei*	Worldwide	Cigar-shaped yeasts that may be surrounded by an asteroid body. Culture (3–5 days) is superior to histopathology	Papulonodular, ulcerating skin lesion with ipsilateral lesions following lymphatic vessels Pulmonary infection Disseminated infection
Chromoblastomycosis	*Fonsecaea pedrosoi* *Fonsecaea compacta* *Cladophialophora carrionii* *Phialophora verrucosa* *Rhinocladiella aquaspersa* *Exophiala jeanselmei* *Exophiala spinifera* *Fonsecaea monophora*	Worldwide (especially Brazil, Madagascar, and Costa Rica)	Muriform cells	Chronic skin infection with verrucous lesions
Eumycetoma	*Madurella mycetomatis* *Scedosporium apiospermum* *Diverse others*	Africa (worldwide)	Grains with fungal hyphae	Chronic painless soft-tissue swelling with draining sinuses

also involve adjacent structures such as the lymphatics, cartilage, fascia, joints, and bones.

Most affected individuals are otherwise healthy non-immunocompromised subjects with exposition to the fungi during outdoor activities including agriculture, hunting, and lumbering. These infections mostly occur in tropical or subtropical regions caused by fungi of diverse taxa. They represent subacute to chronic, slowly progressive infections that usually do not disseminate to distant organs. Typical disease entities are summarized in Table 8.2.

The diagnosis of particular entities within the implantation mycoses includes the clinical presentation, cultivation of the causative fungi, and demonstration of pathognomonic fungal elements such as muriform cells in chromoblastomycosis or grains in eumycetoma by microscopy or histopathology.

Although these infections may be cured with surgical resection of early, localized lesions, extensive infections may be difficult to control, requiring long-term antifungal therapy to prevent relapses. Surgical interventions may be needed in cases unresponsive to medical treatment.

8.9 Sporotrichosis

Sporotrichosis refers to subacute or chronic infections caused by thermally dimorphic fungi of the genus *Sporothrix*. The fungi are found in soil, on decomposing vegetation, and on plant materials. Infections occur worldwide after traumatic inoculation of the fungus, often by minor trauma afflicted by thorns or wood splinters. Sporotrichosis is the most prevalent implantation mycosis worldwide, mostly in tropical countries, especially in South America. Pulmonary infections may occur after inhalation of spores.

8.9.1 Lymphocutaneous Infections

This infection mostly occurs sporadically after outdoor work such as gardening or recreational activities. The disease may also be acquired as a zoonosis by scratches or bites from infected or colonized animals. Sporotrichosis should be suspected in patients with ulcerative skin lesions especially with ipsilateral ascending lymphatic nodules unresponsive to antibacterial treatment. Arthritis and bone infections occur after local spread from lymphocutaneous infections or rarely after hematogenous spread in immunocompromised subjects such as AIDS patients.

Extra-cutaneous infections are usually limited to a single site. Pulmonary infections occur after inhalation of spores by patients with underlying illnesses including COPD and alcoholism. The subacute to chronic infections may resemble reactivated tuberculosis.

8.9.2 Disseminated Disease

Hematogenous spread has been described in individuals with AIDS or hematologic malignancy. It may represent as widespread ulcerative cutaneous lesions with or without involvement of bones, joints, and the CNS. Ocular infections including chorioretinitis and endophthalmitis are rare manifestations presenting as visual disturbances.

8.9.3 Diagnosis and Differential Diagnosis

The fungi may be visualized in pus or tissue with GMS or PAS staining as small, round-, oval- to cigar-shaped cells. The definitive diagnosis is based on the cultivation of the fungus on fungal media at 25–30° for 3–5 days where *Sporothrix* grows as a mold. Identification relies on the micromorphology and demonstration of thermal dimorphism after incubation on blood or BHI agar at 37 °C which may not be possible for all isolates. Sporotrichosis needs to be differentiated from bacterial infections including nocardiosis, atypical mycobacterial infections, and fungal infections including blastomycosis, paracoccidioidomycosis, and cryptococcosis.

8.9.4 Management

Lymphocutaneous infections are not life-threatening but do not usually resolve without antifungal therapy. Potential complications

include deep infections, scarring, and bacterial superinfections. Oral itraconazole is the treatment of choice (200 mg/day) for 3–6 months. Recalcitrant infections may be treated with higher dosage (2 × 200 mg/day), terbinafine (2 × 500 mg), or combinations. Fluconazole and voriconazole are less active. Experience with posaconazole is limited. Extra-cutaneous infections are treated with itraconazole (2 × 200 mg for 12 months) with therapeutic drug monitoring. Acutely ill patients with respiratory or CNS infections may need therapy with conventional (0.7 mg/kg/day) or liposomal amphotericin B (3–5 mg/kg/day).

8.10 Chromoblastomycosis

Chromoblastomycosis is a chronic fungal infection of the skin and subcutaneous tissues. The initial lesion is a small painless subcutaneous papule that occurs mostly on the lower extremities after minor trauma. A diagnostic hallmark of the infection is the microscopic detection of small, round, thick-walled brown cells (termed muriform cells) that differentiate chromoblastomycosis from subcutaneous phaeohyphomycosis and other infections. The fungi are associated with a granulomatous, purulent fibrotic inflammation. If left untreated, the lesions will enlarge to form multiple verrucous lesions. The lesions usually are painless except in the case of bacterial superinfection but may be pruritic. Scratching can result in satellite lesions by autoinoculation. In rare cases, metastatic lesions develop in the lymph nodes, brain, liver, bones, or elsewhere. Carcinomatous transformation may occur in long-standing skin lesions. A specific group of dematiaceous fungi present in the environment in soil, rotting wood, and decomposing plants is responsible for these slowly progressive infections that mostly occur in tropical countries including Brazil, Costa Rica, Southern Africa, Asia, and Australia but rarely also elsewhere.

8.10.1 Diagnosis

When verrucous lesions suggest the diagnosis, microscopic presentation of the typical muriform cells is needed to establish the diagnosis. They may be visualized in skin scrapings or histologic sections together with a granulomatous tissue reaction, microabscesses, and hyperkeratosis. In addition, cultures should be performed to isolate the causative agents. Cultivation should be performed for 4–6 weeks at 25–30 °C. Typically dark brown to tan molds will often grow within 1–2 weeks.

Differential diagnosis includes other fungal infections including blastomycosis, paracoccidioidomycosis, eumycetoma, phaeohyphomycosis, lobomycosis, or sporotrichosis, leishmaniosis, tuberculosis, leprosy, and syphilis.

8.10.2 Management

Chromoblastomycosis is difficult to treat with low cure rates and high risk of relapse. Scarring and bacterial superinfections are common complications. Complete surgical resection is indicated for small lesions. Alternatives may include local physical therapies including cryotherapy. Antifungal therapy should be prescribed before and after surgery to prevent local spread. In those with extensive lesions, antifungal therapy with itraconazole (200–400 mg/day) or terbinafine (500–1000 mg/day) for 6–12 months is used. Therapy should be continued for several months after clinical cure to prevent relapse. Posaconazole or amphotericin B in association with 5-flucytosine and the combination of itraconazole and terbinafine are alternative treatment options.

8.11 Eumycetoma

Eumycetoma is defined as a slowly progressive infection of the skin characterized by indurated swelling and the production of so-called grains, compact masses of fungal filaments, which are discharged through sinus tracts. The infection occurs after traumatic inoculation of diverse fungi into subcutaneous tissues mostly of the feet and hands. Local progression to underlying tissues including bones is possible, but spread through lymphatics or the blood is rare. Mycetomas are most common in arid tropical and subtropical regions, particularly in Senegal,

Sudan, Somalia, India, and South and Central America. Sporadic cases occur in many other parts of the world affecting mostly middle-aged men walking barefoot or having outdoor occupations. Besides *Madurella mycetomatis* and *Scedosporium apiospermum*, diverse melanized and non-melanized molds have been implicated as causative agents.

8.11.1 Diagnosis

Initial lesions (small subcutaneous nodules) appear several months after minor trauma afflicted by thorns or wood splinters. The infections evolve slowly to form abscesses with multiple sinuses containing characteristic grains. The lesions are mostly painless. Pain heralds the impeding rupture of a sinus onto the skin surface. Radiologic examination is useful in determining the extent of bone involvement. Bacterial superinfections may aggravate symptoms. The mycological diagnosis of mycetoma depends on the demonstration of grains. If possible, they should be obtained from an unruptured pustule (sinus) with a sterile needle by puncturing the lesion and squeezing its content onto a glass slide. If this is not possible, deep surgical biopsies are necessary. Superficial biopsies are seldom helpful. Cultivation of fungi or amplification of fungal DNA may identify causative agents.

8.11.2 Differential Diagnosis

Actinomycetoma is suggested by grains with small filaments, cultivation of aerobic actinomycetes, and response to antibacterial agents. Actinomycotic grains contain fine filaments (1 μm in diameter), while fungal etiology is suggested by grains containing masses of short fungal hyphae (2–4 μm in diameter). Histology shows the same picture including granulomatous inflammation. Cultures are incubated to grow actinomycetes and fungi at 25–30 and 37 °C for up to 6 weeks. Differentiation from chromoblastomycosis or cutaneous tuberculosis is usually possible by the clinical appearance with documentation of grains.

8.11.3 Management

Medical management is possible in patients without bone lesions and when supervision of the treatment over a number of months is possible. The most effective drugs include itraconazole (200–400 mg/day) and terbinafine (500–1000 mg/day) for up to 24 months. Posaconazole (2 × 400 mg/day) and voriconazole (2 × 200 mg) are alternatives. Surgical management is indicated for limited disease that can be completely removed and for patients with advanced disease for debulking during medical treatment.

8.12 Other Implantation Mycoses

Entomophthoramycosis is caused by molds belonging to the order Entomophthorales previously assigned to the Zygomycota. These fungi are characterized by broad, irregular-shaped, pauciseptate hyphae. In contrast to the Mucorales, these fungi are not angioinvasive. The fungi are found in soil, decaying wood, and decomposing vegetation in tropical regions. Two clinical forms are distinguished, basidiobolomycosis and conidiobolomycosis. *Basidiobolomycosis* manifests as a slowly progressive subcutaneous infection occurring after traumatic implantation of plant debris in tropical environments. The disease is caused by fungi of the genus *Basidiobolus*. Underlying bones are usually not affected. Lymphatic obstruction may occur and result in elephantiasis. Gastrointestinal infection may be caused by oral ingestion of soil, animal feces, or contaminated food. It presents with abdominal pain of subacute onset and fever, constipation, or diarrhea. Disseminated infections resemble mucormycosis. The diagnosis may be established by microscopy, histopathology, or culture from endoscopic biopsy specimens showing typical hyphae. Cultures may grow the organism in less than a week at 25–37 °C. The treatment of choice appears to be itraconazole which must be given for several months. Patients with gastrointestinal infection may need resection of the affected bowel followed by itraconazole for 3 months or more. *Conidiobolomycosis* is a chronic subcutaneous fungal infection, caused by *Conidiobolus corona-*

tus, originating in the nasal mucosa that invades adjacent facial tissue with the potential to cause severe disfigurement. Dissemination is uncommon. The disease has been reported in West Africa (Nigeria, Cameroon) and other tropical regions (Madagascar, India, China, South and Central America). The infection may present with nasal obstruction and later painless facial swelling and nasal discharge. Underlying bones are not affected. Disseminated infections resemble those of mucormycosis. The diagnosis may be established by smears or histopathological samples of nasal mucosa demonstrating typical hyphae. *Conidiobolus* grows rapidly, but cultivation frequently fails to grow the fungus. Antifungal therapy with itraconazole for at least 4 weeks after lesions have been cleared seems to be an acceptable treatment strategy. Surgery is usually not successful due to local spread.

8.12.1 Lacaziosis (Lobomycosis)

Lacaziosis refers to a rare, localized granulomatous skin and soft-tissue infection caused by *Lacazia loboi*. Infections are reported in Central and northern South America. The fungus has not been cultivated. Molecular tests suggest it to be a close relative of *Paracoccidioides*. The habitat is unknown. Besides humans, the infection has been diagnosed in dolphins suggesting an aqueous habitat. The disease presents as slowly progressing cutaneous lesions starting as a papule, evolving to a keloidal, verrucous, or ulcerating lesion. Autoinoculation may lead to additional lesions that may involve an entire limb. While regional lymph nodes may be affected, hematogenous spread is unusual. Long-standing lesions may undergo carcinomatous transformation. Diagnosis is established by histopathology. Grocott or PAS stains will reveal round to oval, thick-walled cells of *L. loboi* (>10 μm) in long unbranched chains joined by small tubules. Multiple buds may be present as in paracoccidioidomycosis. Differential diagnosis includes chromoblastomycosis, paracoccidioidomycosis, leishmaniosis, mycobacterial infections, keloids, and neoplasia. Effective medical treatment has not been evaluated. Promising results have been described in some patients receiving oral clofazimine (300 mg/kg). Localized lesions may be treated by surgery or cryotherapy.

8.13 Phaeohyphomycosis

The term phaeohyphomycosis refers to infections defined by the presence of melanized dark-colored fungal elements, consisting of hyphae, but also yeast-like cells or a combination of both in tissue samples. Phaeohyphomycosis is caused by melanized, dematiaceous fungi. This diverse group of fungi consists of more than 100 species that have been reported as rare human fungal pathogens. While dematiaceous fungi are found worldwide in soil in association with plants and in polluted water, individual fungal species may have a restricted distribution. While most encounters between humans and these fungi do not cause symptomatic illness, a broad spectrum of diseases, ranging from allergic disorders of the lungs and sinuses to localized cutaneous, subcutaneous, or deep infections, has been described. Localized subcutaneous infections are mostly seen in tropical and subtropical regions. Chronic sinusitis occurs worldwide. Both are mostly diagnosed in otherwise healthy persons. Life-threatening disseminated infections have been diagnosed in both immunocompromised and otherwise healthy subjects. The diagnostic workup relies on the pathologic examination of clinical specimens demonstrating melanized hyphae in tissue. The identification of cultivated fungi may require a reference laboratory as these agents may produce different culture morphologies under different culture conditions making identification without molecular tests sometimes difficult.

Localized phaeohyphomycosis may be cured by surgical resection. Published experience with antifungal therapy of these infections is limited to case reports and case series without evidence of randomized treatment trials.

Subcutaneous infections are the most frequently reported form of phaeohyphomycosis. Infections occur after inoculation by minor

trauma and manifest as a nodule at the site of inoculation, often on the feet, hands, or head. In immunocompromised subjects the infection may present with pustules, ulcers, or eschars of the limbs. Rarely, subcutaneous lesions occur in immunocompromised hosts as part of a hematogenous disseminated infection. Typical agents include *Bipolaris*, *Exophiala*, and *Phialophora*, but many others have been described. Differential diagnosis includes other implantation mycoses and the endemic fungal infections. Resection of small lesions is curative. Itraconazole and terbinafine alone or in combination given for several months may be successful in some cases.

Keratitis, infections of the cornea, can cause severe visual impairment and blindness. Fungal keratitis is mainly caused by yeasts, hyaline molds, but also dematiaceous fungi including *Curvularia* and *Bipolaris*. Human infections follow traumatic inoculation of spores or by surgical procedures. The inoculation may involve plant material harboring fungal spores. The onset of infections is often insidious and a particular trauma may not be recognized by the patients. Symptoms include ocular pain, redness, diminished vision, and ocular discharge. Infections caused by dematiaceous molds progress more slowly than infections caused by bacteria, yeasts, *Aspergillus*, or *Fusarium*. The fungal elements may be seen by confocal microscopy. Identification of the causative agents requires cultivation or molecular tests such as PCR.

Rhinosinusitis caused by dematiaceous molds occurs in different clinical forms, mostly allergic fungal rhinosinusitis or chronic invasive rhinosinusitis. Allergic fungal rhinosinusitis is a noninvasive disease that may develop after inhalation of spores of fungi including *Alternaria*, *Bipolaris*, and *Curvularia*. Patients present with nasal polyposis and thick nasal or sinus mucus. The polyposis may form an expansive mass leading to a thinning of sinus walls. The diagnosis is favored by the presence of noninvasive fungi, eosinophilic mucin at the time of surgical debridement, eosinophilia, elevated serum IgE, and specific IgE against cultivated fungal pathogens. Chronic invasive rhinosinusitis is a slowly progressive destructive condition that may remain confined to the sinuses or spread to the orbit and the brain. This condition affects non-immunocompromised subjects presenting with long-lasting nasal discharge and obstruction, nasal polyposis, and headache.

Pulmonary infection is usually diagnosed in immunocompromised patients where it resembles invasive pulmonary aspergillosis with cough, fever, and presentation of nodular lung lesions with or without halo that may evolve to cavitation. In patients with asthma, colonization with fungi including *Bipolaris* and *Curvularia* may cause a clinical syndrome similar to allergic bronchopulmonary aspergillosis.

Cerebral phaeohyphomycosis is a rare but often fatal disease caused by neurotropic molds including *Cladophialophora bantiana*, *Ramichloridium mackenziei*, and agents of the genera *Bipolaris* and *Exophiala*. It occurs after inhalation of fungal spores and hematogenous dissemination. These infections have been diagnosed even in young healthy adults without obvious predisposition and are associated with case fatality rates exceeding 70%. Individuals manifest with headache, fever, and neurologic deficits due to brain abscess. The CSF is often unremarkable but may show signs of inflammation. Elevated opening pressure is a possible complication. As CSF cultures are often sterile, etiologic diagnosis is often possible after surgical resection only. Meningitis, encephalitis, and myelitis are other potential manifestations. The differential diagnosis includes bacterial CNS infections, toxoplasmosis, cryptococcosis, and the endemic fungal infections. Long-term survival is being reported when surgical resection of solitary nodules was performed. Antifungal treatment with agents showing good CNS levels such as voriconazole, posaconazole, or liposomal amphotericin B is frequently used.

Disseminated phaeohyphomycosis is an uncommon form of phaeohyphomycosis occurring in immunocompromised patients with hematological malignancies often during antifungal prophylaxis and is caused by the multidrug-resistant *Lomentospora* (*Scedosporium) prolificans* as a frequent pathogen. Patients may present with fever, lung-, and

cutaneous lesions. These infections may be associated with a sepsis syndrome and the fungi are often cultivated from blood cultures late in the course of infection. As *L. prolificans* is usually resistant against many antifungals including amphotericin B, combinations of voriconazole with terbinafine and echinocandins may provide the most active antifungal approach. New antifungals with in vitro activity are entering clinical trials.

8.13.1 Diagnosis

As melanized fungi are widespread in the environment, they may be cultivated from the respiratory tract without clinical infection. Therefore, the diagnosis of phaeohyphomycosis often relies on the demonstration of hyphae in tissue. Microscopy reveals pleomorphic fungal elements consisting of yeast-like cells, pseudohyphae, and short, thin, and septate hyphal fragments. These elements can show pigmentation in wet mounts or HE-stained slides. The pigmentation may be easier to detect by the Fontana-Masson stain, and is not usually identified with Grocott's stain. Identification of the causative agents is necessary for correct management and can be established by cultivation on standard mycological culture media that will grow brown to black mold colonies. The identification of cultivated dematiaceous fungi by morphology is difficult due to variable morphology and may need to involve a reference laboratory.

8.13.2 Management

Evidence for the usefulness of antifungal agents is limited to case reports and small case series. Amphotericin B is active against most etiologic agents except for *S. prolificans*, some *Exophiala*, and *Rhinocladiella mackenziei* isolates. Itraconazole and terbinafine are options for subcutaneous infections. Eye infections may respond to topical natamycin and voriconazole. Respiratory tract infections may be treated with voriconazole or amphotericin B. Disseminated and central nervous system infections may respond to combination therapies including liposomal amphotericin B with voriconazole and echinocandins, but the best approach has not been validated.

8.14 Hyalohyphomycosis

Hyalohyphomycosis refers to mold infections characterized by non-melanized septated hyphae documented in tissue specimens. Etiologic agents include predominantly ascomycetous molds including *Fusarium* and *Scedosporium*. However, a growing list of other fungi is being reported as agents of hyalohyphomycosis. As the etiologic fungi often cannot be differentiated by tissue morphology but may differ in susceptibility against antifungals, identification of the causative agents by culture or molecular techniques guides treatment decisions. If the identification of the causative agents was established, specific names such as fusariosis or scedosporiosis are used. In immunocompetent patients, hyalohyphomycosis often presents as a localized infection after penetrating trauma. Inhalation of spores may lead to respiratory tract infections including pneumonia or sinusitis. Disseminated infections are possible and usually occur in immunocompromised patients. Predisposing conditions include hematologic malignancy and especially prolonged and profound neutropenia in leukemia. As these infections are rare, optimal antifungal therapies have not been defined. Treatment decisions are based on the in vitro susceptibility of the causative agents and may include surgery, as many agents show in vitro resistance against antifungals. In patients with underlying conditions, their reversal might be needed for successful outcomes.

8.15 Fusariosis

Fusarium is a diverse, globally distributed fungal genus encompassing plant and human pathogens. They also produce toxic metabolites which may contaminate food. The fungi can be cultivated

from soil, water, fruits, and decomposing organic materials. Most of the human pathogenic species belong to the *Fusarium solani, Fusarium oxysporum*, and *Fusarium fujikuroi* species complexes. As identification at the species level by conventional morphology is unreliable, molecular approaches are needed for correct identification of these fungi. Clinical presentations of fusariosis may include nail, superficial, and deep skin infections or organ infections such as sinusitis, pneumonia, endophthalmitis, osteomyelitis, arthritis, and brain abscess that cannot be differentiated from other mold infections including aspergillosis and mucormycosis. *Fusarium* has a predilection for vascular invasion resulting in thrombosis, infarction, and necrosis. Dissemination occurs mostly in immunocompromised patients predominantly neutropenic patients and may present with sepsis syndrome and skin lesions. The diagnosis of fusariosis depends on the cultivation of the fungi from sterile specimens including blood cultures. In tissue samples, fusariosis is characterized by thin, septated mold hyphae with acute angle branching. However, differentiation from other agents of hyalohyphomycosis and even aspergillosis may be difficult. As *Fusarium* frequently shows in vitro resistance against many antifungals, these infections may manifest as breakthrough infections in patients receiving prophylactic or empiric antifungals.

8.15.1 Eye Infections

Keratitis is the most common infection caused by *Fusarium* and among the most common implantation mycosis of the eye. It has been mostly described in contact lens users, after eye surgery, or ocular trauma. Patients manifest with blurred vision, pain, photophobia, and local inflammation. Infections may progress to endophthalmitis with potential for loss of vision.

8.15.2 Skin and Nail Infections

Fusarium is a rare cause of onychomycosis. In addition to infected nails, cellulitis of adjacent tissues may represent as intertrigo, tinea pedis, and hyperkeratotic plantar lesions. Soft-tissue infections occur after penetrating trauma and may present with necrotic skin lesions.

Respiratory tract infections occur after inhalation of spores. They can present as sinusitis or pneumonia. Clinical differentiation from other mold infections is not usually possible. However dissemination with skin lesions is more prevalent in fusariosis.

Disseminated infection is frequent in immunocompromised patients, who present with fever unresponsive to antibacterial and antifungal therapy as *Fusarium* may be in vitro resistant to several antifungals. Ports of entry, including onychomycosis, may be visible as well as metastatic skin lesions. There are classically three different types of cutaneous lesions which are described: necrotic lesions, target lesions, and subcutaneous lesions. *Fusarium* may be cultivated from blood cultures in disseminated infections.

8.15.3 Diagnosis and Differential Diagnosis

A clinical differentiation from *Aspergillus* and other agents of hyalohyphomycosis is not possible in most cases. Therefore cultivation of *Fusarium* from skin, nail, and corneal scrapings, respiratory tract specimens, or blood cultures is needed to establish the diagnosis. Reference laboratories may be needed for correct identification to the species level and for in vitro resistance testing to guide therapeutic decisions. Specific PCR assays may provide a sensitive identification of *Fusarium* from clinical samples. There are no specific serologic tests available for *Fusarium*, but patients may have a positive beta-D-glucan or *Aspergillus* galactomannan antigen test.

8.15.4 Management

The treatment of keratitis includes the use of topical antifungals such as natamycin 5% (50 mg/ml eye drops) or voriconazole 1% (10 mg/ml eye

drops). Voriconazole has been used in regimes combining topical and oral (400 mg/day) administration when deeper tissues are involved. Posaconazole (oral: 200 mg 4×/day) has been rarely used as salvage therapy, but results are encouraging. Liposomal amphotericin B has been used as systemic (5 mg/kg/day) or intravitreal therapy in the treatment of endophthalmitis often together with surgery. Onychomycosis may be treated with terbinafine (250–500 mg/day) or oral azoles including voriconazole and itraconazole (200–400 mg/day). The optimal treatment strategy of patients with severe *Fusarium* infection remains unclear. Localized disease may be cured by surgical debridement. Voriconazole (6 mg/kg/12 h as loading dose, 24 h, followed by 4 mg/kg/12 h) is the most active antifungal. Lipid-based amphotericin B formulations are often used at the highest tolerable dosage (>5 mg/kg/day). Combination therapies are frequently used for immunocompromised patients with disseminated, life-threatening infections. Most drug combinations of amphotericin, voriconazole, echinocandins, and terbinafine do not show antagonism in in vitro testing. Reversal of underlying conditions and surgical interventions are important for successful treatment strategies.

8.16 Scedosporiosis

Scedosporiosis refers to infections caused by the fungi of the genus *Scedosporium*. This mold can be isolated from soils, polluted waters, and decaying plants worldwide. Human infections are mainly caused by *Scedosporium apiospermum, Scedosporium boydii* (*previously Pseudallescheria boydii*), and *Scedosporium aurantiacum.* Infections caused by *Lomentospora prolificans* (previously *Scedosporium prolificans*) are described under disseminated phaeohyphomycosis. Spores of *Scedosporium* may be inhaled potentially leading to temporary or chronic colonization of the respiratory tract of patients with cystic fibrosis and rarely other chronic lung diseases. In addition, soft-tissue infections may follow traumatic implantation. *Scedosporium* can be cultivated from clinical specimens including respiratory and soft-tissue samples. The use of selective media containing benomyl improves their detection in the presence of bacteria or faster-growing fungi such as *Candida* and *Aspergillus*. There are no commercial-specific serologic assays available for scedosporiosis. In tissue samples, *Scedosporium* cannot be differentiated from other agents of hyalohyphomycosis, although detection of conidia in tissue may point to *Scedosporium*. *Scedosporium* is intrinsically resistant to antifungals including amphotericin B. Voriconazole is the most active antifungal. The optimal treatment approach has not been validated in clinical trials. Surgical interventions are an important part of the management of localized infections.

8.16.1 Soft-Tissue Infections

Subcutaneous infections have been described after penetrating trauma in previously healthy individuals. *Scedosporium* is a common cause of fungal mycetoma. Local dissemination to joints and bones and hematogenous spread to distant organs including bones and the central nervous system have been described even in non-immunocompromised hosts. *Scedosporium* is also found in ocular infections including keratitis and endophthalmitis and otitis externa.

Pulmonary infection may follow colonization of the respiratory tract in patients with chronic lung disease such as cystic fibrosis. Invasive infection is difficult to diagnose in the absence of a tissue biopsy. Manifestations may include fungus ball formation, pneumonia resembling invasive aspergillosis, and allergic bronchopulmonary aspergillosis. Pneumonia has also been described in immunocompromised hosts without preexisting lung conditions. A typical presentation is pneumonia and brain abscess after near drowning in waters containing the fungi.

Disseminated infections are predominantly diagnosed in immunocompromised patients including neutropenic cancer patients and allogeneic bone marrow and solid organ transplant recipients. However, dissemination to distant sites such as bones, joints, and the CNS is also diagnosed in previously healthy subjects.

Brain abscess may result from local spread in patients with sinusitis, after penetrating trauma or near drowning in polluted water after hematogenous dissemination from respiratory tract infections.

Clinical presentation and radiographic findings of *Scedosporium* infections are nonspecific. Therefore, the diagnosis relies on the cultivation of these slow-growing molds. Identification of *Scedosporium* as a causative agent offers important therapeutic clues as these fungi are resistant to amphotericin B and other antifungals. Identification to the species level and in vitro resistance testing is necessary for optimal patient management. When tissue biopsies show hyphae suggestive for hyalohyphomycosis in the absence of positive cultures, PCR may reveal the fungal etiology.

8.16.2 Management

Optimal treatment strategies have not been evaluated in clinical trials. In localized infections, surgical debridement should be considered. Voriconazole is the most active antifungal, while amphotericin B is intrinsically resistant. Combinations with antifungals including echinocandins and terbinafine are usually not antagonistic in vitro. Combination therapy has often been used in successfully treated patients with disseminated infections published in case reports. The reversal of underlying conditions is an integral part of the management of these infections.

8.17 Rare Yeast Infections

A number of yeasts that had been previously thought to represent harmless colonizers of the skin or to cause superficial skin disorders only are now recognized as significant pathogens causing systemic infections mostly in immunocompromised patients. Clinical presentation of these infections usually is fever unresponsive to antibacterials as in deep candidiasis due to bloodstream or pulmonary infections. Diagnosis relies on the cultivation from sterile sites such as blood cultures. Identification of these fungi can be accurately done by DNA sequencing or MALDI-TOF-MS with the use of high-quality databases. Some have been renamed repeatedly impairing the retrieval of information from the literature. Several of these yeasts show reduced in vitro susceptibility against antifungal agents used to prevent or treat candidemia including fluconazole and the echinocandins. Therefore, they may present as breakthrough infections in patients receiving prophylactic or empiric antifungal therapy. Management of these infections is based on antifungal treatment guided by in vitro resistance testing and reversal of underlying conditions such as removal of infected catheters. Due to the small numbers of infections reported, published experience is restricted to case reports and small case series, and the best management strategies are unknown.

Geotrichum candidum are filamentous ascomycetous yeasts. They have been described as agents of bloodstream infections mostly in cancer patients. As fluconazole and echinocandins are not active, as suggested by high MICs and breakthrough infections, newer azoles such as voriconazole or amphotericin B with or without flucytosine are therapeutic options.

Magnusiomyces capitatus previously named *Saprochaete capitata*, *Geotrichum capitatum*, *Trichosporum capitatum*, and *Blastoschizomyces capitatus* are ascomycetous yeasts found in environmental sources including soil, in dishwashers, and as part of the normal microbiota of humans. These fungi have been described as agents of bloodstream infections in neutropenic cancer patients. Infections are mostly diagnosed by cultivation from blood culture bottles. In vitro resistance testing suggests that fluconazole and echinocandins are not active. Voriconazole and posaconazole show good activity as flucytosine that may be used as a combination partner with amphotericin B.

Saprochaete clavata previously known as *Geotrichum clavatum* are ascomycetous yeasts causing infections typically diagnosed in patients with hematologic malignancy and neutropenia. Infections may present as fever of unknown origin, but deep organ involvement of the lung, spleen, liver, or kidneys is frequently identified.

Diagnosis is established by cultivation from blood cultures. Isolates may show in vitro resistance for echinocandins and reduced susceptibility for fluconazole, but newer triazoles are usually susceptible.

Malassezia are basidiomycetous yeasts and part of the normal skin flora. They can cause various skin conditions including pityriasis versicolor, seborrheic dermatitis, dandruff, or onychomycosis. Invasive infections have been described in patients receiving lipid containing parenteral nutrition, in cancer patients, and in the presence of central venous catheters. *Malassezia* infections may be difficult to diagnose as they may not be cultivated using standard laboratory methods. Amphotericin B and azoles including fluconazole and voriconazole have been suggested as therapeutic options, while the echinocandins and flucytosine appear to be in vitro resistant.

Rhodotorula are basidiomycetous yeasts commonly found in environments and as colonizers of the skin and the respiratory and gastrointestinal tract. Invasive infections have been reported in the presence of intravenous catheters and underlying hematologic malignancy. They are usually diagnosed by cultivation of these yeasts in blood culture bottles. *Rhodotorula* are regarded as intrinsically resistant to azoles and echinocandins but susceptible to amphotericin B and flucytosine.

Trichosporon are basidiomycetous yeasts widely distributed in the environment and regularly found as part of the human microbiota. The genus has undergone major taxonomic revisions. Therefore the existing literature may not provide correct species identification precluding the extraction of evidence for species-specific information. Most cases have been ascribed to *Trichosporon asahii* and *T. dermatis*. Invasive infections including fungemia, endocarditis, meningitis, and peritonitis have been described. In addition *Trichosporon mycotoxinivorans* may be an emerging pulmonary pathogen in the context of cystic fibrosis. Voriconazole seems to be the most active antifungal, while amphotericin B, echinocandins, and flucytosine are not active in vitro.

8.18 Yeast-Like Infections

Protothecosis refers to infections caused by achlorophyllic algae of the genus *Prototheca*. These algae are widespread in the environment in soils and water. They are thought to be less virulent than typical fungal pathogens. Human infections are reported rarely. They predominantly cause superficial infections in immunocompromised patients. Vesiculobullous skin lesions may progress to ulcerative lesions with purulent discharge and crusts after minor trauma with an incubation time of weeks to months. Deep systemic infections have been described with and without association with contaminated catheters. Diagnosis can be established when the algae are cultivated after 72 h on fungal media at 25–37 °C from sterile sites. They resemble yeast colonies. Microscopy demonstrates non-budding spherical unicellular organisms ranging from 3 to 30 μm with endospores. Therapy includes surgical intervention, drainage and excision, removal of contaminated catheters, and systemic antifungals especially in deep infections. Amphotericin B appears to be the most active antifungal in vitro. Azoles such as fluconazole, itraconazole, and voriconazole also show in vitro activity as do some antibacterials including gentamicin and polymyxin B.

Pythiosis is a term used for infections caused by *Pythium insidiosum*, which belongs to the order Oomycota of the kingdom Stramenopila. In contrast to true fungi, cell wall of these microbes contains cellulose instead of glucan, chitin, and mannan. They are found in aquatic environments where they form biflagellate, motile zoospores. Infections in the absence of water suggest additional niches. Infections occur in tropical as well as tempered regions. After traumatic implantation, clinical manifestations begin with a small itching papule that rapidly progresses to large, painful, ulcerating lesions and spreads to subcutaneous tissues. Ocular infections may manifest as keratitis or periorbital cellulitis. The vascular (arterial) form is characterized by invasion of blood vessels with thrombosis, infarction, and necrosis manifesting as claudication and later necrosis and hemorrhage. Diagnosis of pythiosis

is based on the demonstration of broad, irregular septate hyphae with nonparallel walls resembling mucormycosis. They are very hard to detect in HE stains. They grow rapidly on Sabouraud dextrose agar at 37 °C as white submerged colonies. Despite lacking ergosterol in the cell wall, infections have been responded to antifungals such as amphotericin B, itraconazole, and terbinafine. Corneal infection may need surgical intervention. The vascular form requires prompt start of antifungals and surgical debridement.

Rhinosporidiosis is an infection of the nasal and other mucosal surfaces and the ocular conjunctiva by the protozoon *Rhinosporidium seeberi*. The pathogen has not been cultivated. It may have aquatic as well as terrestrial niches. The diagnosis relies on the demonstration of large, thick-walled structures of oval to spherical sporangiospores, containing endospores. Endospores are released from mature sporangiospores that develop into new sporangiospores. The disease occurs in tropical and subtropical regions worldwide, except for Australia, but is most often reported from India and Sri Lanka in rural areas among persons bathing in public ponds or working in stagnant water such as rice fields. The infection presents as nasal infections with nasal obstruction by large painless sessile or pedunculated papillomatous lesions containing the sporangiospores. In some cases, lesions develop on the conjunctiva or the ears. Diagnosis relies on microscopic examination of biopsy specimens demonstrating sporangia of different stages and sizes. Mature sporangia resemble spherules of *Coccidioides* and can be differentiated from those of *Emmonsia* by the zonation of the internal sporangiospores. The treatment of choice is surgical resection.