2 Opportunistic Mold Infections

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CONTENTS

I. Introduction

This chapter provides an overview of opportunistic mold infections, including aspergillosis, mucormycosis, infections caused by *Fusarium* spp. and *Pseudallescheria boydii*, and infections caused by the dematiaceous molds (Table 2.1). Although each of these agents is also capable of causing disease in normal individuals, special emphasis has been placed on infections in compromised hosts.

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II. Aspergillosis

Species of *Aspergillus* are responsible for a wide variety of different clinical syndromes, including saprophytic colonization of the pulmonary airspaces in patients with chronic lung disease, chronic noninvasive mycelial masses of the lungs or paranasal sinuses, and rapidly-progressive life-threatening invasive infections of the lungs or paranasal sinuses in neutropenic hosts. In addition, *Aspergillus* spp. produce a number of different allergic syndromes, including extrinsic allergic alveolitis, bronchopulmonary aspergillosis, and allergic *Aspergillus* sinusitis.

A. Mycology

Aspergillus spp. are ascomycetes that are ubiquitous in nature, and most species can be recovered from soil. One hundred and thirty-two species are listed by Raper and Fennell (1965); the species most commonly responsible for human disease are *A. fumigatus*, *A. flavus* (Miloshev et al. 1967; Green et al. 1969; Young et al. 1972), and *A. niger*, with fewer cases caused by relatively nonpathogenic species such as *A. avenaceus* (Washburn et al. 1988), *A. nidulans* (Redmond et al. 1965; Bujak et al. 1974; White et al. 1988), *A. oryzae* (Ziskind et al. 1958), and *A. terreus* (Moore et al. 1988; Hara et al. 1989). The organism grows at temperatures ranging over 4–55 °C, with most abundant growth at 30–37 °C.

Aspergillus grows in air conditioning conduits, fire-proofing material, and decaying vegetation; since it is thermophilic, the organism grows in almost pure culture in compost heaps. *Aspergillus*

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Table 2.1. Clinical syndromes caused by opportunistic molds

Aspergillus spp.	
Invasive disease	Invasive pulmonary aspergillosis ± disseminated infection
	Invasive *Aspergillus* sinusitis
	Skin and wound invasive aspergillosis
	Keratomycosis
Noninvasive disease	Noninvasive mycelial mass of lung or paranasal sinus
	Bronchopulmonary aspergillosis
	Extrinsic allergic alveolitis
	Allergic *Aspergillus* sinusitis
Agents of mucormycosis	
	Rhinocerebral mucormycosis
	Invasive pulmonary mucormycosis ± disseminated infection
	Gastrointestinal mucormycosis
	Skin and wound mucormycosis
Fusarium spp.	
	Disseminated infection
	Keratomycosis
	Mycetoma
	Onychomycosis
Pseudallescheria boydii	
	Pneumonia
	Brain abscess
	Invasive sinusitis
	Noninvasive mycelial mass of lung or paranasal sinus
	Mycetoma
Dematiaceous molds	
Invasive disease	Brain abscess
	Localized subcutaneous infection
	Disseminated infection
	Invasive sinusitis
Noninvasive disease	Allergic bronchopulmonary disease
	Allergic sinusitis

spp. possess a wide array of different degradative and biosynthetic enzymes, and therefore the organisms are able to grow on many different substrates, including not only rich media (e.g. Sabouraud's agar), but also chemically defined media comprised solely of low molecular weight components (e.g. Czapek–Dox agar).

The infectious particles are airborne conidia (2–5 µm diameter) produced by phialides that are borne on conidiophores. When these tiny spheres are inhaled, they are capable of reaching the pulmonary alveoli. In normal hosts, the organisms are effectively cleared by mucociliary mechanisms and phagocytic killing (Waldorf et al. 1984a; Levitz and Diamond 1985; Washburn et al. 1987); however, in susceptible hosts, severe invasive pneumonia may ensue (discussed below). The elongated hyphae that invade tissue are narrow (2–5 µm), regular, septate, and dichotomously branching (ca. 45-degree angles). In invasive disease, hyphae invade blood vessels, producing distal tissue infarction.

B. Epidemiology

Conidia are continuously inhaled, but typically cause infection only in immunocompromised individuals; e.g. those with prolonged neutropenia (Young et al. 1970), supraphysiologic glucocorticoid therapy, chronic granulomatous disease (Bujak et al. 1974), or AIDS (Pursell et al. 1990; Woods and Goldsmith 1990; Denning et al. 1991). Concentrations of airborne conidia increase during construction and there is some evidence to support a link between hospital construction and nosocomial outbreaks of invasive pulmonary aspergillosis. Thus, the recommendation has been made that susceptible hosts (e.g. bone marrow transplant recipients) should be housed in rooms with high-efficiency particulate air (HEPA) filters (Sherertz et al. 1987).

Less commonly, infection can result from direct percutaneous inoculation in susceptible hosts; e.g. by intravenous catheters or contaminated tape

(Prystowsky et al. 1976; Carlile et al. 1978; McCarty et al. 1986; Googe et al. 1989). Invasive disease of the eye (Cameron et al. 1991) or deep structures (e.g. vertebrae or endocardium) can follow surgical procedures even in previously normal individuals, presumably due to direct inoculation (Corrall et al. 1982; Mawk et al. 1983; Weber and Washburn 1990). Rarely, *Aspergillus* endocarditis may be encountered in intravenous drug abusers. There is no documented human-to-human transmission.

C. Clinical Manifestations

1. Invasive Pulmonary Aspergillosis and Disseminated Infection

The most lethal form of aspergillosis is invasive disease in the neutropenic host with leukemia or lymphoma. The disease is characterized by fever, dyspnea, pleuritic chest pain, cough, and rapidly progressive pulmonary infiltrates after ca. 2–4 weeks of neutropenia. Invasive pulmonary aspergillosis usually progresses rapidly during several weeks. Even in the face of appropriate antifungal therapy the infection is almost uniformly fatal unless bone marrow function returns. Vascular invasion and pulmonary infarction may lead to hemoptysis. In approximately one-third of cases the infection disseminates to distant organs; e.g. brain (Boon et al. 1990), kidneys, liver, and spleen. Gastrointestinal (GI) lesions may produce bleeding and perforation (Meyer et al. 1973b).

In patients with abnormal phagocyte function (e.g. those with chronic granulomatous disease; CGD) or those taking daily high-dose glucocorticoids (e.g. bone marrow transplant patients with graft versus host disease) the infection is more slowly progressive than that seen in patients with prolonged neutropenia. In CGD, invasive pulmonary aspergillosis typically presents with multiple nodules and the infection often invades contiguous structures such as mediastinum, ribs, vertebrae, or clavicle (Altman 1977). Hyphae are scarce, but the granulomatous inflammation is exuberant.

Several cases of invasive pulmonary aspergillosis have been reported in small children following inhalation of large inoculae of conidia or in alcoholics with chronic liver disease (Zellner et al. 1969; Blum et al. 1978; Brown et al. 1980). Spontaneous resolution is the rule in the childhood form of the disease, whereas invasive aspergillosis in alcoholics carries a poor prognosis.

2. Invasive *Aspergillus* Sinusitis

Invasive sinusitis can be either acute (e.g. in the neutropenic host) (Young et al. 1970; Swerdlow and Deresinski 1984) or chronic (e.g. in immunologically normal individuals) (Washburn et al. 1988; Washburn 1998). In general, the acute form of the disease resembles rhinocerebral mucormycosis (McGill et al. 1980), but acute *Aspergillus* sinusitis is most commonly encountered in the setting of prolonged neutropenia, and rhinocerebral mucormycosis usually occurs in poorly controlled diabetics.

Acute *Aspergillus* spp. sinusitis typically begins in the maxillary or ethmoid sinuses and rapidly invades blood vessels, producing tissue necrosis and violating anatomic barriers (Peterson and Schimpff 1989; Dyken et al. 1990; Talbot et al. 1991). Thus, the disease may be recognized because of a black eschar on the hard palate due to inferior extension through the floor of the maxillary sinus. Unilateral proptosis and chemosis may occur because of superior erosion through the roof of the maxillary sinus or lateral extension through the ethmoid sinus into the lamina papyracea. Focal neurological findings and altered mental status are signs that the disease has already extended into the brain and such involvement in neutopenic individuals usually predicts a fatal outcome. However, patients with chronic granulomatous disease have more indolent brain involvement that may respond to antifungal therapy.

Aspergillus may produce a more chronic form of invasive sinusitis in apparently normal hosts (Washburn 1998). Patients typically present with painless unilateral proptosis, and they are not systemically ill. The infection is endemic in the arid portion of the Sudan where *A. flavus* is the predominant causative organism presumably because of high ambient concentrations of airborne *A. flavus* conidia. It has been postulated that chronic upper respiratory mucosal fissuring due to the arid climate facilitates passage of the organism into submucosal tissue. In this disease erosion through anatomic barriers requires months or years and produces granulomatous inflammation.

3. Noninvasive Mycelial Mass of the Lung

Aspergillus spp. may grow as noninvasive mycelial masses in preexisting lung cavities caused by emphysema, tuberculosis, cancer, or sarcoidosis (Varkey and Rose 1976; Jewkes et al. 1983).

The fungus ball is usually mobile and not attached to the wall of the cavity. Radiographically, a crescent of air can often be seen above the mass. *Aspergillus* spp. may be recovered repeatedly from expectorated sputum, and when *Aspergillus niger* is the causative organism calcium oxalate crystals may be observed (Wilson and Wilson 1961). Patients with noninvasive pulmonary mycelial masses may develop life-threatening hemoptysis (Jewkes et al. 1983). Repeated severe hemoptysis is an indication for surgery (discussed below).

4. Noninvasive Mycelial Mass of the Paranasal Sinuses

Patients with chronic bacterial sinusitis and impaired sinus drainage (e.g. due to polypoid obstruction) may accumulate inspissated mucus that supports noninvasive mycelial growth. Intermittent unilateral maxillary sinus pain, vertex headaches due to sphenoid sinus pressure, and cacosmia are common complaints (Washburn 1998). In this disease the mucosa and submucosa may be chronically thickened and infiltrated by lymphocytes and plasmacytes but hyphae do not invade tissue.

5. Bronchopulmonary Aspergillosis

Bronchopulmonary aspergillosis represents an allergic response that is usually seen in patients with preexisting asthma. The syndrome is characterized by bronchospasm, fleeting pulmonary infiltrates, bronchiectasis, mucus plugging, repeated recovery of *Aspergillus* spp. from sputum, and eosinophils and Charcot–Leyden crystals in sputum (Washburn 1996). Additional features include immediate cutaneous hypersensitivity to *Aspergillus* antigens, peripheral eosinophilia, elevations of total IgE, and specific anti-*Aspergillus* precipitins, including IgE and IgG.

6. Allergic *Aspergillus* Sinusitis

Allergic *Aspergillus* sinusitis shares many features with bronchopulmonary aspergillosis, except that the inflammation is located in the paranasal sinuses instead of the lungs (Katzenstein et al. 1983; Waxman et al. 1987). These individuals have chronic sinusitis with positive cultures and visible hyphae in direct smears of mucus. The characteristic mucus is termed "allergic mucin" because it contains eosinophils and Charcot–Leyden crystals. There may be mucosal and submucosal thickening, with eosinophilic inflammation. Eventually, patients may have bony rearrangement, probably due to sustained increases in intrasinus pressure. By definition, the infection does not cross anatomic barriers and thus, for example, extension into the brain has not been described in carefully defined cases of allergic *Aspergillus* sinusitis. Similar to patients with bronchopulmonary aspergillosis, those with allergic *Aspergillus* sinusitis exhibit peripheral eosinophilia, immediate-type hypersensitivity to *Aspergillus* antigens, elevated total IgE, and specific anti-*Aspergillus* precipitins, including IgE and IgG.

D. Diagnosis

Diagnosis of invasive pulmonary aspergillosis is usually made at autopsy. To firmly establish the diagnosis antemortem, biopsies must demonstrate invasive hyphae; cultures are confirmatory. Diagnostic yield of transbronchial biopsy is low, so open-lung biopsy is the gold standard. Unfortunately, thrombocytopenia or coagulopathy often render biopsy inadvisable. In that setting a low attenuation halo surrounding a nodule visualized by computerized tomography (CT) is suggestive of invasive fungal disease. In nonsmokers a presumptive diagnosis can be established by repeated recovery of *Aspergillus* from expectorated sputum, bronchoalveolar lavage fluid, or nasopharyngeal cultures. In contrast, smokers are so frequently colonized that recovery of *Aspergillus* spp. from these same sources carries less diagnostic weight (Yu et al. 1986).

New cerebral mass lesions in the setting of neutropenia and progressive pulmonary infiltrates raise the specter of central nervous system dissemination; and GI hemorrhage raises suspicions for GI dissemination. Unfortunately, blood cultures are virtually always negative, but galactomannan detection by enzyme immunoassay is now gaining practical diagnostic value.

Invasive *Aspergillus* spp. sinusitis is diagnosed by visualizing characteristic hyphae in mucosa and deeper structures, and cultures are confirmatory. In the neutropenic host with thrombocytopenia, the ability to safely obtain deep biopsy specimens may be limited. However, in immunologically intact hosts biopsies are helpful for defining the invasive nature of the infection and delineating the associated inflammatory response.

Noninvasive mycelial mass of the lung is diagnosed by the appearance of a fungus ball on chest roentgenograms, combined with repeated recovery of *Aspergillus* spp. from expectorated sputum and/or bronchoalveolar lavage specimens; more invasive procedures would rarely be warranted. Many patients have circulating anti-*Aspergillus* precipitins, usually IgG (Kurup and Fink 1978).

Noninvasive mycelial mass of the paranasal sinus is diagnosed by sinoscopic visualization of a greasy or friable mass that shows entangled hyphae limited to the airspace, and thickened submucosa that may contain lymphocytic inflammation. Occasionally, conidiophores may be seen within the mycelial mass, providing a clue about the causative species; cultures are confirmatory.

Diagnostic criteria for bronchopulmonary aspergillosis and allergic *Aspergillus* sinusitis are outlined in the respective sections concerning clinical manifestations (discussed above).

E. Treatment

Therapy for invasive pulmonary aspergillosis with or without dissemination is vorizonazole 4 mg/kg every 12 h (Steinbach and Stevens 2003) or amphotericin B deoxycholate to a total dose of at least 1–2 g. Liposomal amphotericin B is approved as salvage therapy and has the advantage of being less nephrotoxic than amphotericin B deoxycholate. There is some evidence to support adjunctive use of 5-fluorocytosine or rifampin with amphotericin B-based regimens in especially difficult cases (Kitahara et al. 1976; Arroyo et al. 1977; Hughes et al. 1984). Additionally, caspofungin is approved for invasive aspergillosis in patients who are refractory or intolerant of other therapy (Patterson 2005). Some authorities advocate surgical resection of infected lung tissue for patients in whom hemostasis can be achieved (Weiland et al. 1983). Unfortunately the disease remains highly lethal unless bone marrow function returns and immunosuppression is reduced. For those patients in whom the infection comes under control, a course of oral voriconazole or itraconazole 400 mg/day could be considered for follow-up therapy (Denning et al 1994; Patterson 2005). Posaconazole also has useful clinical activity against invasive aspergillosis (Walsh et al. 2007).

The same antifungal options are available for invasive *Aspergillus* sinusitis. Aggressive surgical extirpation of necrotic tissue is recommended when hemostasis can be achieved, and follow-up therapy with oral voriconazole, itraconazole, or posaconazole would be an option for patients who can be discharged from the hospital.

Noninvasive mycelial masses of the lung do not require therapy except when severe hemoptysis ensues, and in those cases surgical excision can be life-saving (Jewkes et al. 1983). Noninvasive mycelial masses of the paranasal sinuses can be cured with complete surgical removal of the fungus ball (Washburn et al. 1988). No antifungal chemotherapy is required for noninvasive masses of lung or sinuses.

For patients with bronchopulmonary aspergillosis, bronchodilation with cromolyn sodium facilitates clearance of infected secretions. Oral steroid therapy may also be required for control of acute exacerbations; dosage recommendations are reviewed elsewhere (Washburn 1996). A few patients become steroid dependent. There is now some evidence to support the use of itraconazole to prevent recurrent episodes of bronchopulmonary aspergillosis.

There is no controlled data to guide therapy of allergic *Aspergillus* sinusitis. However, accumulating evidence suggests that a reasonable approach would be surgical removal of inspissated mucus and inflamed mucosa, combined with postoperative topical steroids, e.g. beclomethasone (Washburn 1998). The roles of systemic antifungal agents and systemic glucocorticoids remain controversial.

III. Mucormycosis

Mucormycosis is caused by zygomycetous fungi of the order Mucorales. There are several different clinical forms of mucormycosis, including acute rhinocerebral disease, invasive pulmonary disease (often accompanied by disseminated infection), GI infection, and locally invasive cutaneous disease arising from direct inoculation. Patients at risk include poorly controlled diabetics and individuals with prolonged neutropenia (e.g. leukemia or lymphoma), chronic renal insufficiency, kidney transplantation, deferoxamine chelation therapy for iron- or aluminum-overload, metabolic acidosis, burns, malnutrition, and intravenous drug abuse.

A. Mycology

Three different genera account for the majority of mucormycosis cases: *Rhizopus* (*R. oryzae* and *R. microsporus* var. *rhizopodiformis*; Bottone et al. 1979), *Cunninghamella bertholletiae* (Boyce et al. 1981; Sands et al. 1985; Rex et al. 1988; Mostaza and Barbado 1989; Zeilender et al. 1990), and *Saksenaea vasiformis* (Pierce et al. 1987; Kaufmann et al. 1988; Goldschmied-Reouven et al. 1989). The infectious particles, tiny sporangiospores measuring 2–3 µm in diameter, are produced within sporangia borne on sporangiophores. Alveolar macrophages bind to the spores and inhibit germination (Waldorf et al. 1984a, b). Coenocytic hyphae are the tissue-invasive form of the organism. Those structures are morphologically distinct from *Aspergillus* hyphae, because they are aseptate or only sparsley septate, broad and irregular (up to 15 µm wide), and they exhibit right-angle branching. The broad hyphae of mucormycosis invade blood vessels and produce extensive tissue infarction similar to invasive aspergillosis. Neutrophils kill *Rhizopus* hyphae (Schaffner et al. 1986). Deferoxamine enhances growth of the fungus (Boelaert et al. 1993, 1994).

B. Epidemiology

The airborne spores are ubiquitious; for example, the mold grows on decaying vegetation, stale bread, and fruit. Infection is acquired by inhalation, or rarely by direct inoculation into skin e.g. by Elastoplast bandages (Gartenberg et al. 1978; Hammond and Winkelmann 1979; Sheldon and Johnson 1979), or by intravenous and peritoneal dialysis catheters (Baker et al. 1962; Branton et al. 1991), or into the eye, e.g. by lens insertion (Orgel and Cohen 1989). In severely malnourished children GI infection is believed to be acquired by oral ingestion (Watson 1957; Isaacson and Levin 1961; Washburn and Bennett 1995). There is no documented human-to-human transmission.

C. Clinical Manifestations

1. Rhinocerebral Mucormycosis

Rhinocerebral mucormycosis is a catastrophic illness, usually seen in patients with poorly controlled diabetes mellitus; it may also be encountered in renal allograft recipients and patients with other forms of severe immunocompromise. The infection represents a true medical and surgical emergency because it can progress rapidly to death. Patients typically present with unilateral nasal discharge, headache, and fever. As the disease progresses, an eschar may form over the hard palate due to erosion through the floor of the maxillary sinus. Unilateral proptosis and chemosis are indicators of superior extension through the roof of the maxillary sinus or lateral extension through the ethmoid. Contiguous areas of involved skin progress rapidly from erythematous to violaceous, and ultimately become necrotic.

Lateral extension from the sphenoid sinus can lead to cavernous sinus thrombosis and cranial nerve palsies (cranial nerves III–VI). Brain invasion presents with focal neurological deficits and altered mental status progressing to coma and death. Central nervous system lesions may be visualized by CT scan or magnetic resonance imaging, but cerebrospinal fluid (CSF) cultures are almost uniformly negative and other CSF parameters may be normal. Intravenous drug abusers may present with brain abscesses, presumably due to infected emboli (Pierce et al. 1982; Smith et al. 1989; Stave et al. 1989; Fong et al. 1990).

2. Invasive Pulmonary Mucormycosis and Disseminated Infection

Invasive pulmonary mucormycosis is a life-threatening infection usually found in patients with prolonged neutropenia (Meyer et al. 1972), diabetes mellitus, or deferoxamine therapy. Clinical presentations of the disease are similar to those of invasive pulmonary aspergillosis; the infection may extend locally into the mediastinum (Connor et al. 1979) or across the diaphragm, and hemoptysis may result from vascular invasion and pulmonary infarction (Murray 1975). Disseminated disease most commonly affects the brain and GI tract.

3. Gastrointestinal Mucormycosis

GI mucormycosis is principally a disease of neutropenic and kidney transplant patients and is usually a manifestation of disseminated infection (Lyon et al. 1979; Washburn and Bennett 1995). The disease typically produces localized tissue infarction and thus presents with abdominal pain and GI bleeding. The stomach is most commonly involved, but infection of the colon (Agha et al.

1985) and esophagus have also been described. Small children with protein-calorie malnutrition may develop gastric mucormycosis (Ismail et al. 1990; Thomson et al. 1991).

4. Skin and Wound Mucormycosis

In susceptible patients (e.g. those with diabetes mellitus or immunosuppression), skin and underlying structures may become infected by inoculation with tape (e.g. Elastoplast), intravenous or intraperitoneal catheters, or minor trauma (e.g. spider bite), leading to extensive localized tissue destruction. Even in previously normal hosts, tissue that becomes devitalized through crush injury or burns can become locally infected by agents of mucormycosis (Pierce et al. 1987; Vainrub et al. 1988). Rarely, disseminated mucormycosis produces skin lesions that resemble echthyma gangrenosa (Meyer et al. 1973a).

D. Diagnosis

Blood and urine cultures are almost uniformly negative and there is no readily available serologic test for invasive mucormycosis, so diagnosis relies on documentation of tissue-invasive hyphae with characteristic morphologic features. Positive tissue cultures are confirmatory but the yield is extremely low. Unfortunately, thrombocytopenia and coagulopathy often render biopsy procedures inadvisable, so most cases of invasive pulmonary mucormycosis evade diagnosis until autopsy. Patients with rhinocerebral or skin disease have more accessible lesions, so biopsy is safer.

E. Treatment

Therapy for all forms of mucormycosis includes amphotericin B deoxycholate or lipid formulations of amphotericin B to reduce nephrotoxicity. Reduction of immunosuppression and control of diabetic ketoacidosis contribute to likelihood of successful outcome. The recommended daily dosage of amphotericin B deoxycholate is at least 1 mg/kg for life-threatening disease until the infection has been brought under control; the daily dose may then be reduced to 0.5 mg/kg during completion of an 8-week course of therapy. Lipid formulations of amphotericin B reduce nephrotoxicity. Posaconazole has clinical activity against mucormycosis, but at present there is less experience to support its use compared with amphotericin B-based regimens (Sugar 2005).

Surgical extirpation of necrotic tissue is helpful when hemostasis can be achieved, and is strongly advised for diabetic patients with acute sinusitis if intracranial extension has not yet occurred. Mortality for all forms of invasive mucormycosis is significant, with the exception of localized skin, wound, and eye disease. With appropriate therapy, mortality from rhinocerebral mucormycosis can be limited to 15–24% (Meyers et al. 1979; Lehrer et al. 1980).

IV. Infections Caused by *Fusarium* spp.

Fusarium spp. are soil saprophytes that are responsible for a number of different clinical syndromes, including disseminated infection in neutropenic hosts or patients with burns (Anaissie et al. 1988; Merz et al. 1988; Richardson et al. 1988; Venditti et al. 1988; Gamis et al. 1991; Robertson et al. 1991) and localized disease in normal hosts; e.g. mycetoma, onychomycosis (DiSalvo and Fickling 1980), and keratomycosis (Zapater and Arrechea 1975). The species most commonly responsible for human disease are *F. solani*, *F. oxysporum*, and *F. moniliforme*.

Hyphae of *Fusarium* spp. appear similar to those of *Aspergillus* spp. in tissue. However, three key features help to distinguish disseminated fusariosis from invasive aspergillosis: (1) unlike aspergillosis, a majority of patients with disseminated fusariosis have painful skin lesions resembling echthyma gangrenosa that can provide diagnostic tissue (60–70%), (2) the majority of patients with fusariosis have positive blood cultures (~60%), and (3) fusariosis is even more refractory to antifungal chemotherapy than is aspergillosis. Because of the highly lethal nature of fusariosis (Anaissie et al. 1988), it is recommended that patients should be treated with high daily doses of amphotericin B (1.0–1.5 mg/kg daily; Merz et al. 1988). Voriconazole is approved as second-line therapy (Hospenthal 2005).

V. Infections Caused by *Pseudallescheria boydii*

Pseudallescheria boydii, a fungus found in soil and water, gives rise to a number of clinical entities,

including pneumonia following near-drowning (often complicated by brain abscess; Fisher et al. 1982; Dubeau et al. 1984; Hachimi-Idrissi et al. 1990), invasive sinusitis in normal or immunocompromised hosts (Bryan et al. 1980; Winn et al. 1983; Schiess et al. 1984; Salitan et al. 1990), noninvasive pulmonary mass (Louria et al. 1966; Arnett and Hatch 1975; Rippon and Carmichael 1976), paranasal sinus mass (Washburn et al. 1988), and mycetoma (Green and Adams 1964). The course of *Pseudallescheria* infections in compromised hosts is usually more rapidly progressive than in previously normal individuals (Winston et al. 1977; Gumbart 1983; Shih and Lee 1984; Smith et al. 1985).

In tissue, hyphae of *P. boydii* appear similar to those of *Aspergillus* spp., and cultures are required to make a positive identification. However, in noninvasive mycelial masses *P. boydii* can sometimes be presumptively identified even without culture confirmation, on the basis of fascicle-like structures called coremia (Gluckman et al. 1977), and teardrop-shaped conidia.

Since *P. boydii* is resistant to amphotericin B but susceptible to imidazoles in vitro, and since clinical successes also support the use of imidazoles, most authorities agree that intravenous miconazole is preferable to amphotericin B for treatment of *Pseudallerscheria* infections in patients that require intravenous therapy (Lutwick et al. 1979; Anderson et al. 1984; Collignon et al. 1985; Berenguer et al. 1989). Oral itraconazole (Piper et al. 1990) or ketoconazole (Schiess et al. 1984) have been used successfully to complete therapy. More recently voriconazole (Nesky et al. 2000) and posaconazole have been shown to possess clinical activity and voriconazole has been approved for treatment of patients who are refractory to or intolerant of other antifungal therapy. Surgical debridement of infected tissue improves the chances for a permanent cure.

VI. Dematiaceous Molds

Dematiaceous molds are soil- and plant-fungi that produce brown pigments in vitro and sometimes in vivo. Human infection caused by these organisms is termed phaeohyphomycosis. Genera producing human infections include species of *Alternaria*, *Bipolaris*, *Cladosporium*, *Curvularia*, *Drechslera*, *Exophiala*, *Exserohilum*, and *Phialophora* (Adam et al. 1986; Washburn et al. 1988). Clinical syndromes that affect compromised hosts include brain abscess (Seaworth et al. 1983; Anandi et al. 1989; Aldape et al. 1991), localized subcutaneous inoculation disease (Fincher et al. 1988), and disseminated disease. Syndromes found principally in previously normal hosts include chronic invasive fungal sinusitis (Washburn 1998), allergic fungal sinusitis with clinical features paralleling those of allergic *Aspergillus* sinusitis (Brummund et al. 1986; MacMillan et al 1987; Bartynski et al. 1990; Gourley et al. 1990; Friedman et al. 1991), and allergic bronchopulmonary disease (Dolan et al. 1970; Halwig et al. 1985). In tissue, the septate branching hyphae of dematiaceous fungi are irregular in diameter, and may contain globose swellings. Therapy for chronic invasive fungal sinusitis includes surgical extirpation of infected tissue combined with a prolonged course of antifungal chemotherapy, usually amphotericin B to a total dose of ca. 2 gm. Therapy for allergic fungal sinusitis includes surgical removal of inspissated mucus and inflamed mucosa, combined with topical steroids; in contrast, roles of systemic steroids and antifungal chemotherapy remain to be defined. Anecdotal literature concerning allergic bronchopulmonary disease suggests that combined therapy with bronchodilators and systemic steroids is effective. Disseminated disease in normal hosts or immunocompromised patients is treated with a prolonged course of amphotericin B.

Itraconazole has been used successfully in nonlife-threatening disease and there is anecdotal evidence for posaconazole as salvage therapy after amphotericin B failure (Hospenthal 2005). The in vitro activity of voriconazole against dematiaceous molds is more potent than that of itraconazole.

VII. Rare Agents

The following molds only rarely cause infection in humans: *Acremonium*, *Paecilomyces*, *Penicillium*, *Schizophyllum*, and *Scopulariopsis*. For a full discussion of those organisms, the reader is referred to Kwon-Chung and Bennett (1992).

VIII. Conclusions

The molds discussed in this chapter are those that take opportunistic advantage of an immunocompromised host.

Aspergillosis is an infection caused by one or another species in the genus *Aspergillus*. These molds produce pigmented colonies in culture. The conidia produced are phialoconidia arranged in a characteristic fashion on the conidiophore (Raper and Fennell 1965). *Aspergillus* spp. appear in the tissues of an infected host as septate hyphae with branches occurring at acute angles. Mycelial fungi such as *Fusarium* spp. and *Pseudallescheria boydii*, among others, resemble *Aspergillus* spp. in tissue.

The disease mucormycosis is caused by zygomycetes of the order Mucorales. Both deep-seated, systemic diseases and inoculation mycoses may be produced. These zygomycetes produce asexual spores called sporangiospores. The mycelium is composed of nonseptate hyphae, and this morphologic form is observed in tissues of an infected host.

There are a large number of fungi other than species of *Aspergillus* and mucoraceous zygomycetes that can cause infections in an immunosuppressed host.

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