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Emerging Fungal Pathogens

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Fungi such as *Fusarium* spp., *Curvularia* spp., *Alternaria* spp. or *Trichosporon beigelii*, had been thought to represent contamination or harmless colonization when isolated from humans. More recently, the role of these and other newly recognized fungi as serious pathogens has been clearly established. Three diverse groups of fungi are responsible for these infections: the agents of phaeohyphomycosis and hyalohyphomycosis and certain yeasts. These infections, which have been encountered in both presumably healthy and immunocompromised individuals, tend to be localized in the former, and disseminated and frequently fatal in the latter group of patients. A major concern is that these organisms are not uniformly susceptible to amphotericin B. Standardization of antifungal susceptibility testing may, therefore, be helpful in determining the antifungal drug of choice for each infection. It is also hoped that the advent of newer antifungals and biologic response modifiers will have a significant impact on the morbidity and mortality of these emerging infections.

Invasive fungal infections are occurring with increasing frequency in immunocompromised patients, particularly among those with malignancies and the acquired immunodeficiency syndrome (AIDS) (1–4). Broad spectrum antibacterial agents, adrenal corticosteroids, cytotoxic chemotherapy, organ transplantation and prolonged use of indwelling catheters have all contributed to this phenomenon. While most invasive fungal infections were previously thought to be due to *Candida* spp., *Aspergillus* spp., *Cryptococcus neoformans*, the *Zygomycetes*, *Coccidoides immitis*, *Histoplasma capsulatum* variety *capsulatum*, and *Blastomyces dermatitids*, reports from multiple institutions are now emphasizing the importance of several newly recognized fungal pathogens (3, 5–10). This paper will review the role of some specific agents responsible for these opportunistic infections.

Phaeohyphomycosis

Phaeohyphomycoses are fungal infections incited by a group of darkly pigmented (dematiaceous) fungi whose etiologic agents form in tissue, either yeast-like cells that are solitary or in short chains, or hyphae that are septate, often irregularly swollen to toruloid, branched or unbranched, or any combination of the above mentioned forms (11). These fungi are dematiaceous due to the presence of melanin in their cell walls. It is not unusual that these fungi are confused in tissue with the more common *Aspergillus* spp. At many institutions, the preliminary histopathologic diagnosis of infections caused by some of these dematiaceous fungi is aspergillosis. However, on staining with the Fontana-Masson technique (a melanin specific stain), the dematiaceous elements are seen and the correct diagnosis is made. The often-used Gomori methenamine silver stain stains all fungi black irrespective of their natural pigmentation and in some instances the hematoxylin and eosin and/or periodic acid Schiff stains will not allow visualization of the dematiaceous nature of fungi in tissue. Hence, the Fontana-Masson technique becomes useful. This staining method can also be particularly helpful when the fungal cultures are negative.

There are considerable differences in the clinical spectrum of infection and response to therapy among various agents of phaeohyphomycosis (3). Because of these differences and the similarity in histopathology, correct identification of the infecting organism is essential for appropriate therapy. While antifungal chemotherapy may play a role in some cases of phaeohyphomycosis, surgery is important for both diagnosis and treatment, especially when the paranasal sinuses or the central nervous system are involved (12). Phaeohyphomycosis represent a significant and increasingly prevalent group of oppourtunistic fungal diseases. Approximately 71 species classified in 39 genera have been documented to cause human and animal infection thus far (13). Table 1 lists all the

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Table 1: Agents of phacohyphomycosis.

Alternaria	*Phaeonnellomyces*
Anthopis	*Phaeosclera*
Bipolaris	*Phialemonium*
Botryodiplodia	*Phoma*
Botryomyces	*Phyllosticta*
Chaetomium	*Phyllostictina*
Cladosporium	*Pseudomicrodochium*
Collectotrichum	*Pyrenochaeta*
Curvularia	*Ramichloridium*
Dactylaria	*Sarcinomyces*
Exophiala	*Scolecobasidium*
Exserohilum	*Scytalidium*
Hendersonula	*Stenella*
Hormonema	*Taeniolella*
Lecythophora	*Tetraploa*
Moniliella	*Trichomaris*
Mycocentrospora	*Ulocladium*
Oidiodendron	*Wangiella*
Peyronellaea	*Xylohypha*

currently known agents of phaeohyphomycosis in humans and animals. Four genera have been most frequently encountered in humans and are: *Curvularia, Bipolaris, Exserohilum,* and *Alternaria.*

Curvularia spp. are common soil inhabitants. Despite their ubiquity in the environment, human infections caused by *Curvularia* spp. have been uncommon and have recently been reviewed (14). Three species have been associated with human infection. These are: *Curvularia lunata* (20 cases), *Curvularia geniculata* (2 cases), and *Curvularia pallescens* (1 case). Only four patients had disseminated infection. Sites of involvement included paranasal sinuses (6 cases), cornea (6 cases), lower respiratory tract (5 cases), skin and subcutaneous tissues (2 cases), bone, endocardium and nasal septum (1 case each). One case of peritoneal catheter obstruction has also been reported (15). The pathogenesis of the infection is unknown, although skin inoculation has been incriminated in four instances. A case of endocarditis occurred four months after implantation of an aortic valve (16). Only two patients were systemically immunosuppressed. The patient with endocarditis was being treated with adrenal corticosteroids while a second patient was receiving chemotherapy for acute leukemia (16, 17). The latter patient had a dual infection of the nasal septum with *Curvularia* and *Alternaria.* Infection occurred during neutropenia and responded to surgical excision of the involved tissue and resolution of myelosuppression.

At the M. D. Anderson Cancer Center (MDCC) we recently cared for a patient with *Curvularia* sinusitis. The patient was a 25-year-old male with Hodgkin's disease who was receiving high dose chemotherapy and allogenic bone marrow transplantation. While profoundly neutropenic, he developed fever and clinical and radiologic evidence of sinusitis. Biopsy of the nasal septum revealed acute branching septate hyphae and the presumptive histopathologic diagnosis was aspergillosis. Nasal septum cultures yielded *Curvularia* and the Fontana-Masson stain showed dematiaceous fungal elements. The patient recovered uneventfully following extensive surgical debridement, amphotericin B and resolution of his myelosuppression. The majority of reported patients with localized disease had improvement or resolution of their infection. Patients with disseminated disease however tended to do poorly (14). Because of the paucity of cases, there is no established therapy for *Curvularia* infections. At present, antifungal therapy, together with surgical debridement, would represent a rational approach to therapy. The antifungal agent of choice remains to be determined. In vitro susceptibility studies suggest that amphotericin B, miconazole and ketoconazole could be used. All strains tested have shown resistance to 5-fluorocytosine (14).

The genera *Bipolaris* and *Exserohilum* are fungi that were erroneously classified as *Helminthosporium* spp. or *Drechslera* spp. They are fungi with wide geographic distribution. According to McGinnis et al. (18), it appears that only *Bipolaris australiensis, Bipolaris hawaiiensis, Bipolaris spicifera, Exserohilum longirostratum, Exserohilum mcginnisii* and *Exserohilum rostratum* are confirmed agents of phaeohyphomycosis. Infections caused by these agents share many clinical and pathological similarities with those due to *Aspergillus* spp., such as dissemination in the immunocompromised host, vascular invasion, tissue necrosis, involvement of the central nervous system and sinuses, and association with allergic bronchopulmonary disease (5). The most common form of disease caused by species of *Bipolaris* and *Exserohilum* is sinusitis occurring in otherwise healthy patients with nasal polyposis and allergic rhinitis (19, 20). The treatment of choice for this condition appears to be amphotericin B and surgical excision of infected tissues (5). The role of ketoconazole and the newly synthesized azole derivatives needs to be studied in this setting.

Alternaria spp. are ubiquitous fungi known to be soil saprobes and plant pathogens. Inhalation of conidia has been associated with bronchial asthma and hypersensitivity pneumonitis (21–23). Human infections caused by *Alternaria* spp. have occurred in presumably healthy and immunocompromised patients, and included cutaneous infections, keratitis, paranasal sinusitis with osteomyelitis, peritonitis in a patient undergoing peritoneal dialysis and a granulomatous pulmonary nodule (12, 24). The most common species involved in human infections is *Alternaria alternata* although infection by other species has also been reported. Therapy consists of surgical debridement and amphotericin B. In vitro and clinical resistance of *Alternaria* spp. to ketoconazole have been demonstrated (24).

Other dematiaceous fungi have been reported to cause human disease. Their role has been recently reviewed by Rippon (12).

Hyalohyphomycosis

An important group of emerging fungal infections have been termed hyalohyphomycosis. This umbrella term encompasses all opportunistic fungal infections caused by non-dematiaceous moulds whose basic tissue form is in the nature of hyaline, light colored, hyphal elements that are branched or unbranched and occasionally toruloid (13). Table 2 lists some documented species causing hyalohyphomycosis. Important human pathogens included in this group are the genera *Fusarium, Scopulariopsis, Pseudallescheria* and *Scedosporium.*

Fusarium derives its name from its fusiform conidia (25). *Fusarium* spp. are important plant pathogens and common soil fungi (6). Systemic illness following the ingestion of cereals contaminated with *Fusarium* spp. was first reported in 1913 in Russia (26). At the end of the World War II as many as one million people may have been poisoned by infected grain. Contamination with *Fusarium* spp. occurs in grains that remain under the snow in winter and are harvested in the spring (27). In Russia the resulting disease is known as alimentary toxic aleukia. It begins with gastrointestinal symptoms and weakness and culminates in aplastic anemia and death if ingestion of contaminated grain persists. Clinical disease is attributed to ingestion of a mycotoxin rather than to systemic infection.

Fusarium spp. have long been recognized as etiologic agents of localized infections of the skin, nails and cornea (28, 29). Reports of deep tissue infections have been rare. Endophthalmitis has been reported usually following trauma or ocular surgery (30, 31). Skin and subcutaneous infection occurred in four cases, one after renal transplantation (32), one during the course of chronic granulomatous disease (33), and two in otherwise healthy hosts (34, 35). Three patients were reported to have developed osteomyelitis, following a puncture wound in one case (36), prolonged antibiotic treatment in another (37), and severe bilateral lower leg fractures and extensive soft tissue damage in the third (38). Trauma was the only predisposing factor in the patient with arthritis (39), and peritoneal dialysis was implicated in the pathogenesis of peritonitis associated with *Fusarium* spp. (40). One patient with brain abscess had an underlying chronic mononucleosis-like syndrome (41). Also, one case of invasive intranasal *Fusarium oxysporum* infection was reported in a diabetic patient (42).

Patients with hematologic malignancies receiving cytotoxic chemotherapy and patients with extensive burns are at an increased risk of dissemination. Including our own cases, a total of 29 cases have already been reported (6, 43–45). The majority of the patients had a hematological malignancy while two patients had extensive burns. At the MDCC, *Fusarium* spp. produced a variety of infections, including skin and soft tissue infection, fungemia, major organ infection, and most commonly disseminated disease. Eleven patients have been documented to have disseminated or major organ infection. *Fusarium* spp. involved in human infection include *solani, oxysporum* and *moniliforme.* One case each of *Fusarium antophylum, Fusarium proliferatum* and *Fusarium chlamydosporum* have also been reported. At the MDCC, we recently cared for an additional patient with disseminated *Fusarium proliferatum* infection. Some investigators consider *Fusarium moniliforme* to be the same as *Fusarium proliferatum* (46).

The clinical characterstics of patients with disseminated *Fusarium* infection are similar in many respects to those with disseminated aspergillosis. They share in common the occurrence of nodular erythematous skin lesions with central necrosis. The portal of entry for both infections include the paranasal sinuses, lung and skin (6). However, infection with *Fusarium* spp. is associated with a significantly higher incidence of skin and subcutaneous lesions and a much higher yield of the organism in blood culture specimens than infection with *Aspergillus* spp. (6, 43).

Because the clinical features of *Fusarium* infections are not characteristic, and because of the histopathologic similarities between aspergilli and fusaria, fungal cultures are essential for establishing the diagnosis. Microscopically, *Fusarium* colonies begin as a white patch which quickly develops a pink, purple or yellow center with a lighter periphery. Microsocpically, the characteristic microconidia and/or macroconidia may be seen. Species differentiation may be difficult because of the propensity of fusaria to undergo rapid morphologic changes. Recently, immunohistologic staining has been used successfully for tissue diagnosis (47) and represents a most encouraging trend in diagnostic mycology.

Table 2: Agents of hyalohyphomycosis.

Acremonium	*Myriodontium*
Anxiopsis	*Paecilomyes*
Beauvaria	*Penicillium*
Chrysosporium	*Pseudallescheria*
Coprinus	*Scedosporium*
Fusarium	*Schizophyllum*
Geotrichum	*Scopulariopsis*
Gibberella	*Scytalidium*
Gymnascella	*Trirachium*
Microascus	*Volutella*

Probably the most important factor predicting the outcome of *Fusarium* infection is the immune status of the host. All patients with an underlying malignancy and disseminated *Fusarium* infection had severe neutropenia at the onset of their infection (6). Except for three patients reported by Merz et al. (43), no patient with disseminated multiple organ infection survived even when adequate doses of amphotericin B were given (6). Prophylactic amphotericin B in three patients failed to prevent the infection (48). In the above mentioned report, three of four patients with disseminated *Fusarium* infection responded. Of note, two of these three patients had resolution of myelosuppression (43).

The susceptibility of *Fusarium* isolates to antifungal agents seems to suggest resistance to amphotericin B, miconazole, ketoconazole and 5-fluorocytosine. In view of the favorable results obtained by Merz et al. (43), these authors have recommended the use of amphotericin B at a dose of 1.5 mg/kg/day plus 5-fluorocytosine 25 mg/kg every 6 hours adjusted to achieve maximal serum levels of $\leqslant$ 60 mcg/ml.

Scopulariopsis spp. are common soil saprobes with wide geographical distribution. The fungus has not been associated with invasive human infection until recently, when it was noted to cause pneumonia and disseminated infection in a patient with acute leukemia (49). Two additional patients with disseminated *Scopulariopsis* infection have been reported (50). One patient had chronic myelogenous leukemia and had undergone allogeneic bone marrow transplantation after treatment with cyclophosphomide and total body irradiation. While neutropenic, the patient developed disseminated infection and the fungus was isolated from the nasal septum, blood, lungs and brain. The organism was highly resistant to amphotericin B in vitro. The mould was identified as *Scopulariopsis candida*, a new agent of human hyalohyphomycosis. The second patient had acute leukemia and developed a very persistent local case of hyalohyphomycotic ear invasion which remained until the time of death, despite multiple debridements and antifungal therapy with several antimycotics for 9 1/2 months. Yet another case of locally invasive disease caused by *Scopulariopsis brevicaulis* has been followed up by one of the authors. This patient was a 40-year-old white male with aplastic anemia. Following a stormy course due to his disease and therapy thereof, the patient developed invasive halohyphomycosis of the greater right toe caused by *Scopulariopsis brevicaulis* (histopathologically and culturally confirmed) which eventually required amputation. It is of interest that the patient developed invasive disease adjacent to the great toe nail, the site of the most frequent form of non-invasive disease due to *Scopulariopsis brevicaulis*.

Pseudallescheria boydii, a fungus frequently isolated from soil, is well known as a causative agent of eumycotic mycetoma of the lower extremity. Recently, it became apparent that this fungal species may cause a wide range of fungal diseases. These include corneal ulcers, endophthalmitis, otitis, sinusitis, pneumonia, endocarditis, meningitis, arthritis, osteomyelitis, and abcesses of skin, lung, thyroid and brain (51). Like other agents of hyalohyphomycosis, the fungus has histologic similarity to *Aspergillus* spp. and cannot be distinguished from them on the basis of histopathology alone. This distinction is not only of academic interest since *Pseudallescheria boydii* is resistant in vitro and in vivo to amphotericin B and is susceptible to miconazole (51). Therefore, cultural documentation of the fungus is essential for optimal therapy. In addition to antifungal therapy, surgical intervention may be necessary.

Scedosporium inflatum is characterized by its inflated flask-shaped conidiogenous cells (52). Most reported infections have been cases of osteomyelitis occurring in normal patients and resulting from trauma. Additionally, one case each of keratitis, endocarditis, pulmonary infection and peritonitis have been noted (53). Since the original description of this fungus, one of the authors has tested the in vitro susceptibility of 17 isolates (14 from humans and animals and 3 from the soil of potted plants in hospital rooms). The isolates were found to be resistant to amphotericin B, ketoconazole, fluconazole and itraconazole. The poor in vitro susceptibility of *Scedosporium inflatum* to antifungal agents parallels the poor in vivo activity of these drugs. Surgical debridement of infected tissue appears to be the major means to halt progression of the infection. Other agents have been associated with serious human hyalohyphomycotic infections. These infections were the subject of a recent review by Rippon (53).

Yeasts of Emerging Importance

While *Candida albicans, Candida tropicalis, Candida parapsilosis* and *Torulopsis glabrata* remain the most commonly encountered pathogenic yeast fungi, other species have been demonstrated to cause human disease, particularly in the immunocompromised host. At the MDCC we have recently encountered ten cases of systemic candidiasis caused by *Candida krusei*, and isolated cases caused by *Candida guillermondii, Candida pseudotropicalis, Candida zeylanoides, Candida lusitaniae, Candida lipolytica* and *Candida rugosa*. Other yeasts have recently emerged as significant human pathogens and will be discussed here.

Trichosporon beigelii (previously called *Trichosporon cutaneum*), a known agent of white piedra, has been associated with systematic and invasive fungal infections in patients with profound persistent neutro-

penia and manifests itself by fever and multiple necrotic skin lesions (3, 8–10). Cultures from blood and urine are frequently positive. Over the last ten years we have encountered 26 patients at the MDCC with serious infections due to *Trichosporon beigelii*. The extent of the infection was as follows: systemic infection (18 patients), pulmonary infection (6 patients) and fungemia alone (2 patients). Sites of infection in 18 patients with multiorgan involvement included lungs (10 patients), liver, spleen and skin (6 patients each). Other sites of involvement (bone, bone marrow and gastrointestinal tract) were also noted. Resolution of myelosuppression is the most important factor for survival from serious infection with *Trichosporon beigelii*. Of 14 patients treated with amphotericin B, only those four whose neutrophil counts returned to normal survived. Data on the susceptibility of *Trichosporon beigelii* isolates to various antifungals are scarce. We tested the in vitro susceptibility of 20 isolates from patients with cancer to various antifungals. Results of the study showed that 5-fluorocytosine was not significantly active against *Trichosporon beigelii* isolates. Amphotericin B had moderate activity with 60 % of isolates being susceptible, while the azoles, particularly miconazole and ketoconazole, were very active. On the basis of these in vitro data and on limited clinical experience, we believe that miconazole may be an effective treatment for disseminated *Trichosporon beigelii* infection. Additional data on the vivo activity of miconazole and the combination of amphotericin B and 5-fluorocytosine are needed to confirm our in vitro findings.

Rhodotorula spp. are airborne contaminants found in the skin, lungs, urine and feces. *Rhodotorula rubra* has been implicated in systemic infections, endocarditis, meningitis and peritonitis in patients on peritoneal dialysis (54). Fungemia related to colonization of catheters and hospital supplies and equipment has been associated with a clinical picture of endotoxic shock. At the MDCC, we have recently encountered two patients with cancer and *Rhodotorula rubra* fungemia. Both had an adequate neutrophil count at the onset of their infection and were clinically and hemodynamically stable. Cure of the infection was achieved with removal of the offending central venous catheter in one patient, and removal of the central venous catheter and a short course of amphotericin B in the other.

Malassezia furfur, known as the cause of the dermatologic disease pityriasis (tinea) versicolor, has been recently recognized as causing systemic infections in humans (55–58). *Malassezia furfur* is a small, unipolar budding yeast, which is found as normal skin flora in humans. This organism lacks the ability to synthesize medium and long chain fatty acids, and needs an exogenous source of lipid for growth. Individuals at risk of systemic infection with this fungus are debilitated or immunosuppressed patients and premature infants who have a long duration of hospitalization, and are receiving hyperalimentation with intravenous lipid through central venous catheter (55). Some patients remain asymptomatic while others develop fever (particularly adults) and/or thrombocytopenia (particularly neonates). Dissemination to organ systems has not been demonstrated except in one case where yeast forms consistent with *Malassezia furfur* were seen in sections of the pulmonary arteries of a neonate receiving intravenous lipid (58). The diagnosis can be made by examination of blood smears in which ovoid to ellipsoidal yeastlike cells often can be identified intracellularly. *Malassezia furfur* grows best at 35–37 °C, in an aerobic environment on Sabouraud agar overlaid with a few drops of olive oil. Recently, a new medium has been developed which allows successful primary isolation and identification of *Malassezia furfur* (59).

Most patients will respond to removal of the offending central venous catheter and discontinuation of the lipid infusions. The addition of antifungals may be necessary if infection persists after removal of the infected central venous catheter and if patients have severe thrombocytopenia. Available information on the in vitro susceptiiblity of *Malassezia furfur* to various antifungals suggests that the organism is susceptible to amphotericin B and the azoles. Susceptibility to 5-fluorocytosine is variable.

Another *Malassezia* species, *Malassezia pachydermitis*, has been associated with systemic infections in humans (60). In contrast to *Malassezia furfur*, this lipophylic fungus is able to grow on complex media without fatty acid supplementation. The predisposing factors for and symptoms of infection with *Malassezia pachydermatis* appear to be similar to those described for *Malassezia furfur* sepsis.

Saccharomyces spp. are ascosporogenous yeasts usually employed as bakers and brewers yeasts. Human infections associated with *Saccharomyces cerevisiae* have included fungemia, peritonitis, endocarditis and pneumonia (61–63). In two patients, it was felt that the infection was related to a central venous catheter. Most patients had some form of underlying disease, but the organism has not been shown to cause death in any patient. In one instance, massive ingestion of viable microorganisms was presumed to be the source of the infection in a manner similar to that which has been described with *Candida albicans* (64). Removal of the offending central venous catheter and antifungal therapy with amphotericin B would represent the treatment of choice of this infection. At the MDCC, we have recently cared for two leukemia patients with *Saccharomyces cerevisiae* fungemia. In one patient who had an adequate neutrophil count, removal of the central venous catheter was the only maneuver required to control the infection. In the second

patient, who was profoundly neutropenic, intravenous amphotericin B resulted in eradication of the infection.

Other ascoporogenous yeasts which have been involved in human infections are *Pichia farinosa* and *Hansenula* spp. At the MDCC, a 12-year-old female with abdominal teratoma had persistent fever and fungemia with *Pichia farinosa* which required removal of the central venous catheter. *Hansenula* spp., particularly *Hansenula anomala,* have been associated with infections in immunocompromised patients who had manipulations of their central venous catheter (65). Patients tended to respond rapidly to catheter removal and amphotericin B. Most isolates were susceptible to amphotericin B. At the MDCC, a 34-year-old leukemia patient developed high-grade fever on broad-spectrum antibiotics and *Hansenula anomala* was isolated from several blood cultures. Administration of amphotericin B and removal of the central venous catheter were necessary for control of his infection (66). In another patient with fever and pleural effusion, *Torulopsis pintolopesii* was the only organism cultured from pleural tissue and lungs. Results of histopathologic examination of pleura and lung tissue were compatible with infection by this organism.

Disseminated infection caused by urease-negative *Cryptococcus neoformans,* variety *neoformans,* has been recently reported in a patient with AIDS. Mycologists should be aware of the occurrence of atypical strains of *Cryptococcus neoformans,* particularly those recovered from patients with AIDS (67). Other yeasts have been occasionally implicated in human disease. Their role has been recently reviewed by Rippon (54).

Lessons from the Past and Challenges for the Future

The emergence of these previously harmless fungi as significant human pathogens clearly demonstrates the dynamic nature of medicine. We have learned that early diagnosis is difficult, and that results of in vitro susceptibility testing for fungi cannot, at the present time, be relied upon for initiation of and/or modification of antifungal chemotherapy. We have also learned that amphotericin B should not always be considered the "all-around" antifungal drug because of the emergence of amphotericin B resistant *Candida* strains (68), and the inherent resistance of several other fungi to this drug (3). In addition, the poor response of fungal infections to adequate antifungal chemotherapy in persistently immunosuppressed individuals has emphasized the critical role of the immune system in the fight against mycoses (1, 2).

With the growing number of patients with AIDS and cancer, we should expect an increase in opportunistic mycoses. More rapid and sensitive techniques are needed for early diagnosis of these infections. Standardization of in vitro susceptibility testing should be possible and could contribute to the management of infected patients. Better antifungal agents are clearly needed (3, 69, 70). These agents should ideally have the following characteristics: a) fungicidal activity against a broad spectrum of fungi, b) good penetration into tissue including the central nervous system, c) potential for oral or parenteral administration, d) low toxicity, and e) affordable price. In addition, shortening the duration of post-cytotoxic neutropenia by the use of colony-stimulating factors may become the best means of preventing the development of these serious mycoses (71).

Conclusion

There is little doubt that newer fungi previously considered as contaminants or harmless colonizers have now emerged as significant human pathogens, particularly in the immunocompromised host. Only through collaboration between clinicians, pathologists and microbiologists can these fungal infections be recognized and treated early. It is hoped that the advent of newer antifungal agents and biologic response modifiers will result in a significant improvement in the prevention and treatment of these life threatening opportunistic infections.

References

1. **Bodey, G. P.:** The emergence of fungi as major hospital pathogens. Journal of Hospital Infection 1988, 11: 411–426.
2. **Bodey, G. P.:** Topical and systemic antifungal agents. Medical Clinics of North America 1988, 72: 637–659.
3. **Walsh, T. J., Pizzo, A.:** Treatment of systemic fungal infections: recent progress and current problems. European Journal of Clinical Microbiology 1988, 460–475.
4. **Horn, R., Wong, B., Kiehn, T. E., Armstrong, D.:** Fungemia in a cancer hospital: changing frequency, earlier onset, and results of therapy. Reviews of Infectious Diseases 1985, 7: 646–654.
5. **Adam, R. D., Paquin, M. L., Petersen, E. A., Saubolle, M. A., Rinaldi, M. G., Corcoran, J. G., Galgiani, J. N., Sobonya, R. E.:** Phaeohyphomycosis caused by the fungal genera *Bipolaris* and *Exserohilum:* a report of 9 cases and review of the literature. Medicine 1986, 65: 203–217.
6. **Anaissie, E., Kantarjian, H., Ro, J., Rolston, K., Fainstein, V., Bodey, G. P.:** The emerging role of *Fusarium* infections in patients with cancer. Medicine 1988, 67: 77–83.
7. **June, C. H., Beatty, P. G., Shulman, H. M., Rinaldi, M. G.:** Disseminated *Fusarium moniliforme* infection after allogeneic marrow transplantation. Southern Medical Journal 1986, 79: 513–515.
8. **Walling, D. M., McGraw, D. J., Merz, W. G., Karp, J. E., Hutchings, G. M.:** Disseminated infection with *Tricho-*

sporon beigelii. Reviews of Infectious Diseases 1987, 9: 1013–1019.
9. **Walsh, T. J., Newman, K. R., Moody, M., Wharton, R. C., Wade, J. C.:** Trichosporonosis in patients with neoplastic disease. Medicine 1986, 65: 268–279.
10. **Hoy, J., Kuo-Ching, S., Rolston, K., Hopfer, R. L., Luna, M., Bodey, G. P.:** *Trichosporon beigelii* infection: A review. Reviews of Infectious Diseases 1986, 8: 959–967.
11. **Ajello, L.:** Phaeohyphomycosis: definition and etiology. In: Mycoses. Scientific Publication No. 304. Pan American Health Organization, Washington, DC, 1975, p. 126–133.
12. **Rippon, J. W.:** Phaeohyphomycosis. In: Rippon, J. W. (ed.): Medical mycology. Saunders, Philadelphia, 1988, p. 297–324.
13. **Ajello, L.:** Hyalohyphomycosis and phaeohyphomycosis: two global disease entities of public health importance. European Journal of Epidemiology 1986, 2: 243–251.
14. **Rinaldi, M. G., Phillips, P., Schwarts, J. G., Winn, R. E., Holt, G. R., Shagets, F. W., Elrold, J., Nishioka, E. G., Aufdemorte, T. B.:** Human *Curvularia* infections: report of five cases and review of the literature. Diagnostic Microbiology and Infectious Disease 1987, 6: 27–39.
15. **DeVault, G. A., Brown, S. T., King, J. W., Fowler, M., Oberle, A.:** Tenckhoff catheter obstruction resulting from invasion by *Curvularia lunata* in the absence of peritonitis. American Journal of Kidney Diseases 1985, 2: 124–126.
16. **Kaufman, S. M.:** *Curvularia* endocarditis following cardiac surgery. Journal of Clinical Pathology 1971, 56: 466–470.
17. **Loveless, M. O., Winn, R. E., Campbell, M., Jones, S. R.:** Mixed invasive infection with *Alternaria* spp. and *Curvularia* spp. American Journal of Clinical Pathology 1981, 76: 491–494.
18. **McGinnis, M. R., Rinaldi, M. G., Winn, R. E.:** Emerging agents of phaeohyphomycosis: pathogenic species of *Bipolaris* and *Exserohilum.* Journal of Clinical Microbiology 1986, 24: 250–259.
19. **Rolston, K. V. I., Hopfer, R. L., Larson, D. L.:** Infections caused by *Drechslera* spp.: Case report and review of the literature. Reviews of Infectious Diseases 1985, 7: 525–529.
20. **Sobol, S. M., Love, R. G., Stutman, H. R., Pysher, T. J.:** Phaeohyphomycosis of the maxilloethmoid sinus caused by *Drechslera spicifera:* a new fungal pathogen. Laryngoscope 1984, 94: 620–627.
21. **Pedersen, N. B., Mardh, P. A., Hallberg, T., Jonsson, N.:** Cutaneous alternariosis. British Journal of Dermatology 1976, 94: 201–209.
22. **Wyse, D. M., Malloch, D.:** Christmas tree allergy: mould and pollen studies. Canadian Medical Association Journal 1970, 103: 1272–1276.
23. **Schlueter, D. P., Fink, J. N., Hensley, G. T.:** Wood-pulp workers' disease: a hypersensitivity pneumonitis caused by *Alternaria.* Annals of Internal Medicine 1972, 77: 907–714.
24. **Wiest, P. M., Wiese, K., Jacobs, M. R., Morrissey, A. B., Abelson, T. I., Witt, W., Lederman, M. M.:** *Alternaria* infection in a patient with acquired immunodeficiency syndrome: case report and review of invasive *Alternaria* infections. Reviews of Infectious Diseases 1987, 9: 799–803.
25. **Young, N. A., Kwon-Chung, K. J., Kubota, T. T., Jennings, A. E., Fisher, R. I.:** Disseminated infection by *Fusarium moniliforme* during treatment of malignant lymphoma. Journal of Clinical Microbiology 1978, 7: 589–594.
26. **Mayer, C. F.:** Endemic panmyelotoxicosis in the Russian grain belt. Part I: The clinical aspects of alimentary toxic aleukia: a comprehensive review. Military Surgeon 1953, 113: 173–189.
27. **Marshall, E.:** The soviet elephant grass theory. Science 1982, 217: 32.
28. **Zaias, N.:** Superficial white onychomycosis. Sabouraudia 1966, 5: 99–103.
29. **Zapater, R. C., Arrechea, A.:** Mycotic keratitits by *Fusarium.* A review and report of two cases. Ophthalmologica 1975, 170: 1–12.
30. **Forster, R. K., Zachary, I. G., Cottingham, A. J., Norton, E. W. D.:** Further observations on the diagnosis, cause, and treatment of endophthalmitis. American Journal of Ophthalmology 1976, 81: 52–56.
31. **Guss, R. B., Koenig, S., De La Pena, W., Marx, M., Kaufman, H. E.:** Endophthalmitis after penetrating keratoplasty. American Journal of Ophthalmology 1983, 95: 651–658.
32. **Young, C. N., Meyers, A. M.:** Opportunistic fungal infection by *Fusarium oxysporum* in a renal transplant patient. Sabouradia 1979, 17: 219–223.
33 **Benjamin, R. P., Callaway, J. L., Conant, N. F.:** Facial granuloma associated with *Fusarium* infection. Archives of Dermatology 1970, 101: 598–600.
34. **Chandrani, A. M., Anandakrishnam, C.:** Extensive subcutaneous hyphomycosis caused by *Fusarium oxysporum.* Journal of Medical and Veterinary Mycology 1986, 24: 105–111.
35. **Collins, M. S., Rinaldi, M. G.:** Cutaneous infection in man caused by *Fusarium monoliforme.* Sabouraudi 1977, 15: 151–160.
36. **Page, J. C., Friedlander, G., Dockery, G. L.:** Postoperative *Fusarium* osteomyelitis. Journal of Foot Surgery 1982, 21: 174–176.
37. **Bourguignon, R. L., Wash, A. F., Flynn, J. C., Baro, C., Spinos, E.:** *Fusarium* species osteomyelitis. Case report. Journal of Bone and Joint Surgery 1976, 58: 722–723.
38. **Nuovo, M. A., Simmonds, J. E., Chacho, M. S., McKitrick, J. C.:** *Fusarium solani* osteomyelitis with probable nosocomial spread. American Journal of Clinical Pathology 1988, 90: 738–741.
39. **Jakle, C., Leek, J. C., Olson, D. A., Robbisn, D. L.:** Septic arthritis due to *Fusarium solani.* Journal of Rheumatology 1983, 10: 151–153.
40. **Young, J. B., Ahmed-Jushuf, I. H., Brownjohn, A. M., Parsons, F. M., Foulkes, S. J., Evans, E. G.:** Opportunistic peritonitis in continuous ambulatory peritoneal dialysis. Clinics of Nephrology 1984, 22: 268–269.
41. **Steinberg, G. K., Britt, R. H., Enzmann, D. R., Finlay, J. L., Arvin, A. M.:** *Fusarium* brain abscess: case report. Journal of Neurosurgery 1983, 56: 598–601.
42. **Valenstein, P., Schell, W. A.:** Primary intranasal *Fusarium* infection: potential for confusion with rhinocerebral zygomycosis. Archives of Pathology and Laboratory Medicine 1986, 110: 751–754.
43. **Merz, W. G., Karp, J. E., Hoagland, M., Jett-Goheen, M., Junkins, J. M., Hood, A. F.:** Diagnosis and successful treatment of fusariosis in the compromised host. Journal of Infectious Diseases 1988, 158: 1046–1055.
44. **Richardson, S. E., Bannatyne, R. M., Summberbell, R. C., Milliken, J., Gold, R., Weitzman, S. S.:** Disseminated fusarial infection in the immunocompromised host. Reviews of Infectious Diseases 1988, 10: 1171–1181.
45. **Venditi, M., Micozzi, A., Gentile, G., Polonelli, L., Morace, G., Bianco, P., Avvisati, G., Papa, G., Martino, P.:** Invasive *Fusarium solani* infections in patients with acute leukemia. Reviews of Infectious Disease 1988, 10: 653–659.
46. **Ellis, J. J.:** Lesser known species in section *Liseola* of *Fusarium* and near relatives in the *Fusarium oxysporum* group. Mycologia 1988, 80: 734–738.
47. **Okuda, C., Sato, M. Y., Oka, K., Hotchi, M.:** Disseminated cutaneous *Fusarium* infection with vascular in-

vasion in a leukemic patient. Journal of Medical and Veterinary Mycology 1987, 25: 177–186.
48. **Blazar, B. R., Hurd, D. D., Snover, D. C., Alexander, J. W., McGlane, P. B.:** Invasive *Fusarium* infections in bone marrow transplant recipients. American Journal of Medicine 1984, 77: 645–651.
49. **Wheat, L. J., Bartlett, M., Cicarelli, M., Smith, J. W.:** Opportunistic *Scopulariopsis* pneumonia in an immunocompromised host. Southern Medical Journal 1984, 77: 1608–1609.
50. **Neglia, J. P., Hurd, D. D., Ferrieri, P., Snover, D. C.:** Invasive *Scopulariopsis* in the immunocompromised host. American Journal of Medicine 1987, 83: 1163–1166.
51. **Rippon, J. W.:** Pseudallescheriasis. In: Rippon, J. W. (ed.): Medical mycology. Saunders, Philadelphia, 1988, 651–680.
52. **Salkin, I. F., McGinnis, M. R., Dykstra, M. J., Rinaldi, M. G.:** *Scedosporium inflatum,* an emerging pathogen. Journal of Clinical Microbiology 1988, 26: 498–503.
53. **Rippon, J. W.:** Hyalohyphomycosis, pythiosis, miscellaneous and rare mycoses, and algoses. In: Rippon, J. W. (ed.): Medical mycology. Saunders, Philadelphia, 1988, 714–745.
54. **Rippon, J. W.:** Miscellaneous yeast infections. In: Rippon, J. W. (ed.): Medical Mycology. Saunders, Philadelphia, 1988, 610–617.
55. **Dankner, W. M., Spector, S. A., Fierer, J., Davis, C. E.:** *Malassezia* fungemia in neonates and adults: complication of hyperalimentation. Reviews of Infectious Diseases 1987, 9: 743–753.
56. **Aschner, J. L., Punsalang, A., Maniscalco, W. M., Menegus, M. A.:** Percutaneous central venous catheter colonization with *Malassezia furfur:* incidence and clinical significance. Pediatrics 1987, 80: 535–539.
57. **Middleton, C., Lowenthal, R. M.:** *Malassezia furfur* fungemia as a treatable cause of obscure fever in a leukemia patient receiving parenteral nutrition. Australian and New Zealand Journal of Medicine 1987, 17: 603–604.
58. **Redline, R. W., Dahmrs, B. B.:** *Malassezia* pulmonary vasculitis in an infant on long-term intralipid therapy. New England Journal of Medicine 1981, 305: 1395–1398.
59. **Leeming, J. P., Notman, F. H.:** Improved methods for isolation and enumeration of *Malassezia furfur* from human skin. Journal of Clinical Microbiology 1987, 25: 2017–2019.
60. **Mickelsen, P. A., Viano-Paulson, M. C., Stevens, D. A., Diaz, P. S.:** Clinical and microbiological features of infection with *Malassezia pachydermatis* in high-risk infants. Journal of Infectious Diseases 1988, 157: 1163–1168.
61. **Cimolai, N., Gill, M. J., Church, D.:** *Saacharomyces cerevisiae* fungemia: case report and review of the literature. Diagnostic Microbiology and Infectious Disease 1987, 8: 113–117.
62. **Dougherty, S. H., Simmons, R. L.:** Postoperative peritonitis caused by *Saccharomyces cerevisiae.* Archives of Surgery 1982, 117: 248–249.
63. **Eschete, L., West, B. C.:** *Saccharomyces cerevisiae* septicemia. Archives of Internal Medicine 1980, 140: 1539.
64. **Krause, W., Matheis, H., Wulf, K.:** Fungemia and funguria after oral administration of *Candida albicans.* Lancet 1969, 598–599.
65. **Klein, A. S., Tortora, G. T., Malowitz, R., Greene, W. H.:** *Hansenula anomala:* a new fungal pathogen. Two case reports and a review of the literature. Archives of Internal Medicine 1988, 148: 1210–1213.
66. **Haron, E., Anaissie, E., Dumphy, F., McCredie, K., Fainstein, V.:** *Hansenula anomala* fungemia. Reviews of Infectious Diseases 1988 10: 1182–1186.
67. **Ruane, P. J., Walker, L. J., George, W. L.:** Disseminated infection caused by urease-negative *Cryptococcus neoformans.* Journal of Clinical Microbiology 1988, 26: 2224–2225.
68. **Powderly, W. G., Kobayashi, G. S., Herzig, G. P., Medoff, G.:** Amphotericin B-resistant yeast infection in severely immunocompromised patients. American Journal of Medicine 1988, 84: 826–832.
69. **Drouhet, E., Dupont, B.:** Evolution of antifungal agents: past, present, and future. Reviews of Infectious Diseases 1987, 9, Supplement: 4–14.
70. **Dismukes, W. E.:** Azole antifungal drugs: old and new. Annals of Internal Medicine 1988, 109: 177–179.
71. **Clark, S. C.:** The human hematopoietic colony-stimulating factors. Science 1987, 236: 1229–1237.