Dark Fungi Emerging as Cause of Lethal Infections

BY NANCY WALSH
New York Bureau

LAS VEGAS — Dematiaceous, or darkly pigmented, fungi are emerging as an important cause of disease, and certain types of infections with these pathogens are associated with high rates of mortality, even among the immunocompetent, Dr. Sanjay G. Revankar said at a meeting on fungal infections sponsored by Imedex.

This is a heterogeneous group of fungi that includes more than 60 genera and 100 species found worldwide in soil and air. Melanin, present in the cell wall, provides the coloration of these pathogens and appears to be a virulence factor, providing protection from free radicals, hydrolytic enzymes, and ultraviolet damage.

One of the clinical syndromes associated with various species of dematiaceous fungi increasingly being seen is phaeohyphomycosis. Most of the species implicated are opportunists, but some may be true pathogens, said Dr. Revankar of the University of Texas Southwestern Medical Center, Dallas.

The diagnosis of phaeohyphomycosis requires expert interpretation of colony and microscopic morphology. The typical histologic findings include irregularly swollen hyphae and yeastlike forms. In contrast to many other fungi, there are no adequate serologic or antigen tests for the species that cause phaeohyphomycosis, he said.

The range of clinical syndromes comprising phaeohyphomycosis includes the following:

► **Superficial infections.** These typically manifest as subcutaneous nodules appearing after minor trauma to the skin and inoculation with species of *Exophiala, Alternaria*, or *Phialophora*. Successful treatment often requires only excision, although an azole is sometimes also given.

► **Allergic disease.** Most cases of sinusitis and bronchopulmonary mycosis are caused by species of *Curvularia* or *Bipolaris*. Sinusitis is characterized by the presence of allergic mucin and elevated IgE; treatment includes surgery plus corticosteroids. Bronchopulmonary mycosis is associated with elevated IgE or eosinophilia, and treatment relies on corticosteroids. Antifungal therapy is not routinely used for these infections, Dr. Revankar said.

► **Pneumonia.** This has been seen most in immunocompromised patients, and may be characterized by hemoptysis. Among the pathogens implicated are species of *Exophiala* and *Chaetomium*. Lipid amphotericin B is the preferred treatment for these seriously ill patients, followed by an azole if the patient stabilizes, but mortality is high, he said.

► **CNS phaeohyphomycosis.** This infection shows a 3:1 male predominance and has been reported worldwide. "What is really unusual is that more than half of patients seem to have no risk factors—no chemotherapy, HIV, or other immunodeficiency," Dr. Revankar said. In a series of 101 patients with CNS infection, the classic triad seen with bacterial brain abscess—fever, headache, and neurologic deficits—was present in fewer than 5% of patients (Clin. Infect. Dis. 2004;38:206-16). Overall mortality was 72%.

Many species have been isolated in CNS infections, but in nearly half of cases *Cladophialophora bantiana* was implicated.

There was little evidence of efficacy for any particular antifungal regimen in these patients with CNS disease. A combination of amphotericin B, 5-fluorocytosine, and itraconazole was associated with improved survival, but only six patients in the series received this combination. Voriconazole and posaconazole have shown in vitro activity, but there is very little clinical experience with these agents for this indication, he said.

► **Disseminated phaeohyphomycosis.** "This has been seen increasingly during the past 10-15 years, probably reflecting the type of patients we are seeing, such as those who are immunocompromised from treatment for other diseases," Dr. Revankar said. Prior cardiac surgery, particularly involving bioprosthetic valve replacements, also has been identified as a risk factor.

In a series of 72 patients, fever was present in only 76%. Skin lesions were seen in 33%, sepsis in 11%, and eosinophilia in 11% (Clin. Infect. Dis. 2002;34:467-76). Blood cultures were positive, most commonly revealing *Scedosporium prolificans* in more than half of patients. Most of the cases were in Spain and Australia.

Overall mortality was 79%. In the immunocompromised it was 84%, and in the immunocompetent it was 65%. *S. prolificans* is resistant to all available agents, and no single drug or combination of drugs was associated with improved outcome in this series. In two cases, however, the combination of an azole plus terbinafine was successful. "I wouldn't recommend this routinely, but if you have no other options it might be something to consider. Terbinafine is not considered a particularly useful systemic drug because of its pharmacokinetics, but in these cases there really is not much else left," he said. ■

New Azole Found to Prevent Invasive Fungal Infections

BY NANCY WALSH
New York Bureau

LAS VEGAS — Results of two large studies have shown that prophylaxis with oral posaconazole can prevent invasive fungal infections in bone marrow transplant recipients and patients with hematologic malignancies, Dr. Catherine J. Hardalo reported.

Invasive fungal infections have emerged as a potentially lethal complication for immunosuppressed patients, and some of the pathogens involved are resistant to standard antifungal therapy. Posaconazole is a broad-spectrum agent with activity against *Aspergillus, Fusarium, Coccidioides, Candida,* pigmented and hyaline molds, and the Zygomycetes, she said at a meeting on fungal infections sponsored by Imedex.

Previously, the drug had been used primarily as salvage therapy for patients with invasive aspergillosis, with about 40% of patients responding, said Dr. Hardalo, senior director of anti-infectives clinical research, Schering-Plough Research Institute, Kenilworth, N.J.

Current prophylaxis options include fluconazole and micafungin for patients undergoing hematopoietic stem cell transplantation, and itraconazole (in Europe only) for the prevention of fungal infections during prolonged neutropenia.

Posaconazole now has been evaluated in a multicenter, double-blind study that included 600 patients who had undergone allogeneic stem cell transplantation and had graft-versus-host disease. They were randomized to receive either posaconazole 200 mg three times daily, or fluconazole 400 mg/day, for 16 weeks. The incidence of invasive fungal infections and invasive aspergillosis was 2% and 1%, respectively, in the posaconazole group vs. 8% and 6% in the fluconazole group.

A total of 76 patients in the posaconazole group died, as did 84 in the fluconazole group. This difference was not significant. However, only 4 patients on posaconazole died from fungal causes, which was significantly fewer than the 12 patients with fungal-related deaths in the fluconazole group.

In a second study, 600 patients with acute myelogenous leukemia or myelodysplastic syndrome received the same dose of posaconazole or fluconazole, 400 mg once a day, or itraconazole, 200 mg twice a day. The number of cases of invasive fungal infection and invasive aspergillosis were "virtually the same" as in the other study: 2% and 1% for posaconazole, and 8% and 7% for the other azoles, Dr. Hardalo said.

There were 49 deaths among patients receiving posaconazole and 67 among patients receiving the other azoles. Five deaths in the posaconazole group were fungal related, as were 16 in the other-azole groups. These differences were statistically significant.

Moreover, for the first time, a survival benefit was seen among neutropenic patients, she said. ■

One Hospital's Experience: Number Of MRSA Patients Doubled in 1 Year

BY KERRI WACHTER
Senior Writer

WASHINGTON — The number of methicillin-resistant *Staphylococcus aureus* infections has dramatically risen in recent years, and more and more cases are community acquired, at least in one emergency department, Dr. Mary-Claire Roghmann said at the annual Interscience Conference on Antimicrobial Agents and Chemotherapy.

"We had more than a doubling [in new cases of methicillin-resistant *S. aureus*] from 2003 to 2004," said Dr. Roghmann, the hospital epidemiologist for Veterans Affairs Maryland Health Care System. The ED at Baltimore VA Medical Center sees about 85 patients per day.

Tipped off by ED physicians that more MRSA cases seemed to be coming in, Dr. Roghmann and her colleagues identified patients with MRSA isolated for the first time for that patient from a culture taken in the ED. They discovered an increase in new cases of MRSA in the ED, starting with 0.2 new MRSA cases per 1,000 ED visits in 2001 and more than doubling from 1.1 to 2.6 new MRSA cases per 1,000 ED visits from 2003 to 2004.

To learn more about these cases, the researchers accessed data from the VA's patient records system. They excluded any patients with a history of MRSA prior to the ED visit. Specifically, they looked at type of infection, antibiotic susceptibility, and risk factors for hospital-acquired MRSA, said Dr. Roghmann, also of the University of Maryland in Baltimore.

They defined type of infection as a positive culture from the site and also signs and symptoms of infection at the site. Risk factors for hospital-acquired MRSA infection included history of hospitalization, surgery, dialysis, or residence in a long-term care facility in the last year. Patients were excluded if they had a percutaneous medical device or indwelling catheter at the time of the culture. Patients without any of these risk factors were determined to have community-acquired MRSA.

In 2004, there were 90 patients who met the criteria for newly acquired MRSA based on cultures from the ED. "Of these, 58% had community-acquired MRSA. The vast majority of patients had skin and soft tissue infections," Dr. Roghmann said at the meeting, which was sponsored by the American Society for Microbiology.

In terms of antibiotic susceptibility, community-acquired MRSA cultures were more likely than were health care–acquired MRSA cultures to be susceptible to clindamycin and tetracycline.

The emergency physicians had also indicated that there seemed to be more skin and soft tissue infections. To determine whether there was also an increase in skin and soft tissue infections during the same time period, the researchers looked at visits to the ED with ICD-9 codes specific to those infections.

"There has been almost a doubling of the incidence rate of skin and soft tissue–related visits to our ED during this period," said Dr. Roghmann. The number of these visits per 1,000 ED visits rose from 26 in 2001 to 54 in 2003. ■