Management of Fungal Infections

Management of fungal infections was discussed at the New York meeting by William G. Powderly, MD, from Washington University School of Medicine, St. Louis, Missouri.

Candidiasis

As related by Dr Powderly, candidiasis is ubiquitous in patients with advanced HIV disease, with oral infection being nearly universal, vaginal infection extremely common, and esophageal involvement occurring in some 10% to 20% of patients. Local (clotrimazole troches, nystatin) or systemic (fluconazole, ketoconazole) treatment of acute oral candidiasis and systemic treatment of acute esophageal infection are effective, with systemic treatment probably being associated with some increase in time to relapse. Relapse is quite common; virtually all HIV disease patients with a CD4+ cell count of 100/μL harbor oral *Candida* and it has become clear that neither acute antifungal therapy nor chronic suppressive therapy succeeds in eradicating the organism from the mouth, with chronic suppression being associated with changes in flora rather than eradication. Dr Powderly and colleagues have found that infection with a new strain of *C albicans* or a new species occurs in approximately 50% of patients with recurrence, with the frequency of novel isolates being associated with advanced immunosuppression, low CD4+ cell count, and use of azoles.

Such observations provide an explanation for the emerging problem of clinical resistance to fluconazole, which, according to Dr Powderly, is most likely to be seen in patients with CD4+ cell counts <50/μL who have had significant prior intermittent or continuous exposure to the agent. In one study cited by Dr Powderly, increased fluconazole minimal inhibitory concentrations (MICs) of colonizing organisms were found in patients on chronic azole prophylaxis, with approximately 10% having fluconazole-resistant strains and fluconazole resistance being observed in patients receiving other azoles (Figure 4). Although clinical resistance is being encountered sporadically, it is unclear what the frequency of the problem is in this country. According to Dr Powderly, some European investigators have cited resistance rates of 40% to 50%, although such rates could be associated with differences in treatment practices. Currently, it is unknown whether resistance is more likely to result from chronic drug exposure or multiple acute treatments; this issue currently is being examined in an ACTG study.

As related by Dr Powderly, although there are a number of options for treating fluconazole-resistant candidiasis, none has emerged as more effective than another. Typically, different approaches are attempted until the patient responds; in some, IV amphotericin B is required, with some of these patients subsequently failing therapy due to resistance to this agent. Higher-dose fluconazol—eg, up to 800 mg/d—may be used; Dr Powderly noted that doses of up to 2 g/d have been used in unsuccessful attempts to treat aspergillosis. Treatment with other azoles may be attempted, since not all fluconazole-resistant organisms are resistant to other agents. There are some data to indicate that 20% to 30% of resistant strains retain in vitro susceptibility to itraconazole. Oral suspension of nystatin constitutes another option. Oral amphotericin B is not available in this country. Flucytosine treatment may also be attempted. Dr Powderly related that he has observed some success with the combined use of flucytosine and fluconazole.

Cryptococcosis

Cryptococcosis is observed in 7% to 10% of patients with advanced HIV disease. There is continued debate over whether optimal initial treatment of cryptococcosis consists of amphotericin B or an azole, with there being an apparent trend toward use of the former. In two small comparative trials in cryptococcal meningitis, amphotericin B treatment with or without flucytosine was associated with a 100% response rate, whereas fluconazole and itraconazole were associated with response rates of 40% to 50%. However, in a larger ACTG trial in 194 patients, the response rate with amphotericin B treatment was 40% versus 34% with fluconazole (P = 0.39). According to Dr Powderly, the lower response rate with amphotericin B in this study may have been associated with suboptimal dosing or a lower frequency of concomitant use of flucytosine. Although there was little difference in response rate, it was found that cerebrospinal fluid (CSF) cultures tended to clear more rapidly in amphotericin B recipients (Figure 5) and that early mortality was decreased, albeit nonsignificantly, in these patients. According to Dr Powderly, these findings may have contributed to concern over the use of fluconazole in patients with adverse prognostic signs.

Factors associated with greater risk of mortality in the study were a decreased level of consciousness at diagnosis, which was the single most important factor; high CSF cryptococcal antigen titer (>1:1024); low CSF white cell count (<20); and younger age (<35 years). As related by Dr Powderly, in at least those patients with such signs, initial treatment currently is optimally begun with amphotericin B at relatively high doses (eg, 0.7 mg/kg/d) for 2 to 3 weeks, with the addition of flucytosine remaining a subject of study, followed by 10 weeks of fluconazole 400 mg/d, and maintenance therapy with fluconazole 200 mg/d. Although Dr Powderly maintained that his bias is to implement amphotericin B treatment in all patients, he suggested that it may be reasonable to consider initial treatment with fluconazole in patients without adverse prognostic signs. The approach of initial amphotericin B treatment followed by fluconazole currently is being evaluated in a large scale ACTG trial, results of which may be available later in the year.

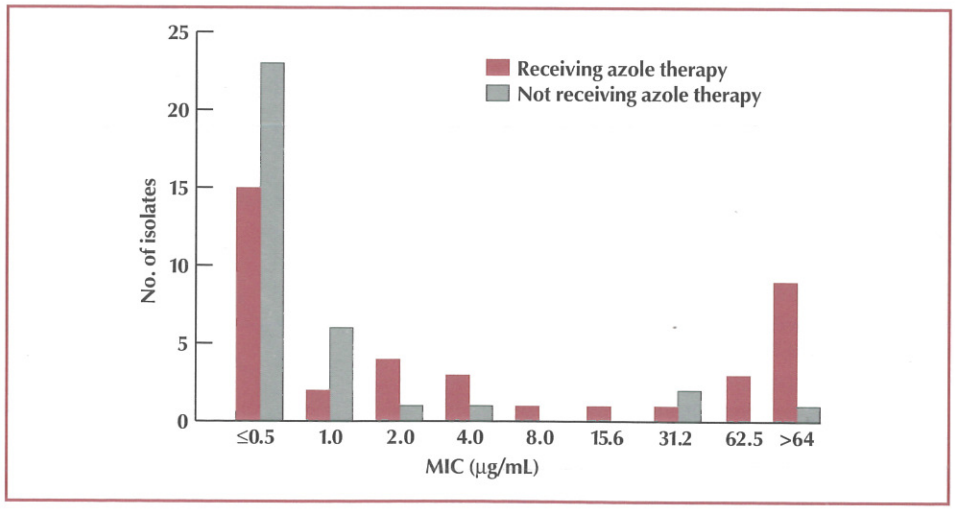

Figure 4. Correlation of* Candida *in vitro susceptibility to fluconazole with prior azole use. MIC = minimal inhibitory concentration. Data are adapted from Cameron et al. Antimicrob Agents Chemother. 1993;37:2449.

With regard to alternatives, one promising approach may be the combination of oral fluconazole and flucytosine in initial treatment. According to Dr Powderly, available data from an ongoing study of fluconazole 400 mg/d and flucytosine 150 mg/kg/d conducted by the California Collaborative Treatment Group indicate a mycologic response of 75% and a complete clinical response of 63% in 32 patients. The early findings suggest that dose-limiting flucytosine toxicity did not occur in the majority of patients over 2 to 3 weeks, with discontinuation being required in 28%. Other potential alternatives include itraconazole. Data from acute and maintenance treatment studies of the agent may be available by year end. In addition, liposomal formulations of amphotericin B are currently being investigated.

Dr Powderly stressed that mechanical management of intracranial pressure in patients with cryptococcal meningitis is an important adjunct of therapy, with much of the associated acute mortality being related to intracranial pressure rather than infection per se. According to Dr Powderly, removal of fluid can be accomplished as effectively with daily lumbar puncture as with placement of an intraventricular shunt. The role of steroids in this setting, which remains controversial, is being evaluated in an ongoing ACTG study.

Histoplasmosis

Histoplasmosis may be observed in 20% of patients in endemic areas, including the Mississippi River basin and regions of Latin America. The considerable number of cases of disseminated disease found in New York City represent reactivation infections, primarily occurring in hispanic patients harboring strains endemic to Puerto Rico or Latin America. Although no formal prospective studies of amphotericin B use in disseminated histoplasmosis have been performed, experience indicates a response rate of approximately 80%, with weekly or twice weekly maintenance therapy with this agent also being effective in preventing relapse. The relapse rate in the absence of maintenance therapy has been found to be 80% over 2 years. Recent findings suggest that itraconazole may be a viable alternative in maintenance or acute treatment. In ACTG 084, itraconazole suppression in patients who had received at least 500 mg of amphotericin B in acute treatment was successful in preventing relapse in 39 (93%) of 42 patients over median follow-up of 109 weeks; there were two cases of relapse, both in noncompliant patients, and one patient stopped treatment due to toxicity. Subsequently, acute itraconazole treatment was evaluated in patients with non-life-threatening disease (eg, excluding patients with meningitis or shock) in ACTG 120; treatment was associated with response in 83% of patients (43/52) with proven disseminated disease and each of seven with other disease. As related by Dr Powderly, a study of initial fluconazole treatment motivated by these findings showed that, whereas a dosage of 600 mg/d was not associated with substantial efficacy, treatment with 800 mg/d produced response in approximately 80% of patients. However, approximately one third of patients relapsed by 6 months, leading to termination of the study. Dr Powderly maintained that although the inferiority of fluconazole cannot be established on the basis of these noncomparative studies, the discrepant relapse findings in what were similar patient populations lead him to prefer itraconazole use.

Fluconazole prophylaxis study

Dr Powderly also presented available data from a large-scale ACTG study of primary antifungal prophylaxis. In ACTG 981, approximately 440 patients, a subpopulation of patients enrolled in *Pneumocystis carinii* pneumonia (PCP) primary prophylaxis study ACTG 081, were randomized to receive fluconazole 200 mg/d or clotrimazole troches 10 mg five times daily, with the active control being used to decrease what would be expected to be a high incidence of oral candidiasis in a placebo control group. The median duration of follow-up was 35 months. Invasive fungal infection was observed in 9 fluconazole patients and 23 clotrimazole patients (P=0.0063), with the CD4+ cell count-adjusted relative risk of invasive infection in clotrimazole patients being 3.25 times that in fluconazole patients. The significant difference was attributable to a highly significant difference in invasive cryptococcal disease, which was observed in 2 fluconazole recipients and 15 clotrimazole recipients (P=0.00095). Fluconazole was also associated with a significant effect in preventing esophageal candidiasis (3 vs 17 cases) and in preventing thrush or other superficial infections (P<0.0001; 10 vs 36 confirmed cases and 23 vs 64 presumed cases). The preventive benefit of fluconazole was greatest among patients with a baseline CD4+ cell count <50/μL, who accounted for nearly all invasive fungal infections observed. However, no significant difference between the two groups was observed with regard to mortality or the combined measure of time to first invasive fungal infection or death.

As stated by Dr Powderly, given the absence of mortality benefit despite the significant preventive effect of fluconazole prophylaxis, it is unclear how the findings of this study are to be translated into clinical practice. Although such prophylaxis could be expected to decrease morbidity and hospitalization due to cryptococcal disease and morbidity due to candidiasis, it may also be associated with increased cost and potential for drug interactions and would likely result in an increase in *Candida* resistance. Dr Powderly noted that resistance may have been operative in the breakthroughs of thrush on fluconazole treatment in the study. However, since clinical specimens were not preserved, no definitive information on development of resistance in the study patients will be forthcoming. ■

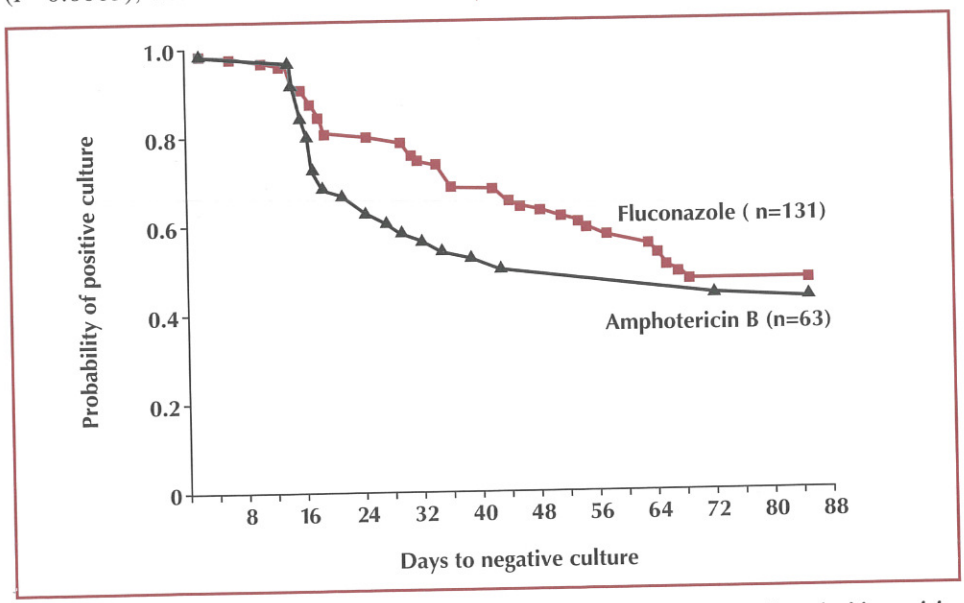

Figure 5. Time to conversion to negative culture among patients with cryptococcal meningitis receiving fluconazole or amphotericin B in ACTG-Mycoses Study Group. Data are from Saag et al. N Engl J Med. 1992;326:83-89.