TRAVEL MEDICINE ADVISOR

This Month's Compendium of Articles from Other Thomson American Health Consultants Publications

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INSIDE

- *Histoplasma capsulatum*
- Zygomycetes
- *Aspergillus*
- *Candida*
- Miscellaneous Mycoses
- Antifungal Agents

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ICAAC/IDSA/ASTMH 2003

CONFERENCE COVERAGE

The following is a summary of selected abstracts on fungal diseases from 3 meetings. The 43rd Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC) met in Chicago September 14-17, 2003. The Infectious Disease Society of America (IDSA) met in San Diego October 9-12, 2003. The American Society of Tropical Medicine and Hygiene met in Philadelphia December 3-7, 2003. — ***Stan Deresinski, MD, FACP***

Mycoses

Coccidioides immitis

The incidence of coccidioidomycosis increased from 15 to 43 per 100,000 people from 1995 to 2001 in Arizona, with the highest incidence in individuals older than 65. Peaks in activity occurred from November through February and were associated with areas of high construction activities. Rainfall, recent temperatures, and dust concentrations were predictive of seasonal outbreaks (*IDSA 354*).

Caspofungin, amphotericin B deoxycholate, and liposomal amphotericin B were each effective in reducing fungal load and prolonging survival in mice experimentally infected with *C immitis*. The combination of caspofungin with each of the amphotericin preparations had enhanced activity; spleen and liver sterility were achieved with caspofungin plus liposomal amphotericin B (*ICAAC M-475*).

Itraconazole was superior to fluconazole in a murine model of coccidioidal meningitis (*ICAAC M-355*).

All 6 patients with coccidioidomycosis who failed or were intolerant to other therapies who received posaconazole exhibited substantial clinical improvement (*IDSA 143*).

Cryptococcus neoformans

The polysaccharide capsule of *C neoformans* is an important virulence factor. Nonetheless, 6 of 15 patients with pulmonary cryptococcosis were infected with capsule-deficient organisms. The clinical presentation and course did not appear to differ from infection with encapsulated *C neoformans,* and only 1 patient in each group had a serum cryptococcal antigen titer > 1:8 (*IDSA 352*).

Chimeric human IgG2 directed against the major capsular polysaccharide, glucuronoxylomannan, protects mice against experimental cryptococcal infection, while IgG1 enhances infection. In addition, a monoclonal antibody derived from human immunoglobulin transgenic mice immunized with glucuronoxylomannan protected mice from challenge with *C neoformans* (*IDSA 186, M-374*).

Histoplasma capsulatum

Seven solid organ transplant recipients in Omaha developed histoplasmosis over an 8-month period. Five had a diffuse military pattern on chest x-ray. Urinary *Histoplasma* antigen was positive in all 5 patients. All were successfully treated and were alive 3 months to 1 year after diagnosis (*IDSA 393*).

Posaconazole therapy was associated with clinical improvement in 6 of 7 patients with histoplasmosis after failure or intolerance to other antifungal therapy (*ICAAC M-973*).

Zygomycetes

Four allogeneic hematopoietic stem cell recipients developed zygomycosis while receiving voriconazole as prophylaxis or empiric antifungal therapy (*ICAAC M-985*).

Posaconazole is emerging as a potentially effective agent in the treatment of the zygomycoses. Sixteen of 23 (70%) patients with zygomycosis (including 9 *Rhizopus*, 5 *Cunninghamella*, 3 *Mucor*, and 2 *Rhizomucor*) had successful outcomes after treatment with posaconazole (*ICAAC M-1757*).

Zygomycetes have been reported to be resistant to caspofungin in vitro. However, administration of caspofungin prolonged survival in mice experimentally infected with *Rhizopus oryzae*. Crude *R oryzae* cell membranes contain caspofungin-sensitive glucan synthase activity (*ICAAC M-371*).

Aspergillus

The Platelia Aspergillus Galactomannan™ assay recently received US FDA approval for use in the diagnosis of invasive aspergillosis. Its accuracy, however, has been variously reported, and its precise value remains to be fully determined. With a cut-off value of 0.66, the Platelia Aspergillus Galactomannan™ assay had a sensitivity of 30% and specificity of 95% for the diagnosis of invasive aspergillosis in lung transplant recipients. Furthermore, a very important and potentially frequent cause of error has been identified by 2 groups who found that false-positive results for circulating *Aspergillus galactomannan* using the Platelia Aspergillus kit were observed in patients receiving either piperacillin/tazobactam or tazocillin. Another

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assay (Glucatell™) designed to detect circulating (1fi3) ß-glucan had reasonable diagnostic sensitivity and specificity in patients with a variety of invasive fungal infections (*ICAAC M-1020, M-2062a, 2062b, M-1034a*).

An underlying pulmonary disease, most often COPD, was present in 17 of 18 patients with chronic, necrotizing pulmonary aspergillosis. The diagnosis was delayed for a median of 13 months from the onset of symptoms. *A fumigatus* was the etiologic agent in 89% of cases. Ten patients died (*IDSA 351*).

Information concerning treatment of invasive aspergillosis at specific sites other than the lungs is limited. Because of its rarity, this is especially true concerning antifungal therapy of bone and joint infections. However, voriconazole was successful in the treatment of 10 of 19 patients with *Aspergillus* infection (14 due to *A fumigatus*) of bone who had failed prior therapy. Central nervous system aspergillosis has been associated with high mortality. Nonetheless, a complete or partial response was achieved in 34% of 86 patients with definite or probable CNS aspergillosis who received voriconazole (13 as primary treatment) (*ICAACM-979, M-1755*).

The toxin-producing species *A versicolor* has been identified as a cause of onychomycosis but rarely identified as the cause of invasive infection. However, 11 of 15 (73%) cancer patients with invasive pulmonary infection due to *A versicolor* died (*IDSA 389*).

A terreus causes serious invasive infections and is commonly more resistant to antifungals than is, for example, *A fumigatus*. A retrospective analysis of 87 cases of *A terreus* infection (47% proven, 53% probable) found that the attributable mortality was 66%. In a multivariate analysis, receipt of voriconazole within 1 week of diagnosis of the infection was associated with reduced mortality compared to amphotericin B (OR, 0.28; 95% CI, 0.01-0.83; $P = .02$) (*ICAAC M-1753*).

An investigative azole, posaconazole, when combined with caspofungin, was synergistic or additive against 96.5% of *Aspergillus* spp. isolates; antagonism was not detected. Because many patients with invasive aspergillosis continue to fail therapy, there is much interest in the use of antifungals in combination. Five patients with invasive aspergillosis were successfully treated with a combination of caspofungin and voriconazole. In each case, an additive effect of the combination was achieved in vitro with the combination when tested against the patient's isolate (*ICAAC M-990, M-1759*).

Mutation of a mitochondrial enzyme, an NADH-ubiquinone oxireductase subunit in *A fumigatus*, is associated with itraconazole resistance (*ICAAC M-391*).

Candida

Fluconazole is being administered with increasing frequency as prophylaxis against *Candida* infection in critical care patients in the absence of strong supporting evidence for this approach. A meta-analysis of randomized, controlled trials led to the conclusion that fluconazole prophylaxis prevents invasive fungal infections in critically ill ICU or surgical patients but does not reduce mortality (*ICAAC K-452i*).

The SCOPE study involving 42 US hospitals found that 9.1% of nosocomial bloodstream infections (BSI) were due to *Candida* spp. Candidemia occurred at a rate of 4.6 per 10,000 admissions, making it the fourth most common cause of BSI. Separately, severe sepsis was observed in 8% and septic shock in 27% of 60 patients with candidemia. The overall crude mortality was 42%, while the 7-day mortality was 27% (*ICAAC K-452e, K-770*).

Candida dubliniensis has been identified as a cause of oropharyngeal candidiasis in HIV-infected patients, but it is often misidentified as *C albicans* because it forms both chlamydospores and germ tubes. While a previous study suggested that it may be less virulent than *C albicans* (*Med Mycol*. 2002;46:2829), it was reported that *C dubliniensis* was at least as virulent in experimentally infected mice as was *C albicans* (*IDSA 730*).

Echinocandins are nonenzymatically metabolized and do not appear intact in urine in significant concentrations. Nonetheless, candiduria resolved in 11 of 12 patients given the echinocandin caspofungin. Anidulafungin is 1 of 2 echinocandins in the late stages of clinical development. In a randomized, dose-ranging trial, anidulafungin and fluconazole were equally effective in the treatment of esophageal candidiasis when assessed at the end of treatment. The proportion of sustained successes at 2 weeks post-treatment was greater with fluconazole treatment (*IDSA 135, ICAAC M-1760*).

While there appears to be a reasonable degree of correlation between in vitro susceptibility testing of yeasts vis-á-vis azole agents and clinical therapeutic outcomes, the interpretation of susceptibility testing with amphotericin B remains more problematic. In fact, an evaluation of 100 patients with bloodstream infection due to *C albicans* failed to detect a correlation of amphotericin B MICs to clinical outcome in patients treated with this polyene (*IDSA 134*).

Miscellaneous Mycoses

An outbreak of penile infections due to the dematiaceous fungus *Phialemonium curvatum* was associated with contaminated intracavernous penile injections. *P*

curvatum has previously been reported to cause a variety of invasive infections (*J Clin Microbiol*. 2002;40:2207) (*ICAAC K-1431*).

Blastoschizomyces capitatus is an uncommon cause of invasive infection in severely immunocompromised patients (*Leuk Lymphoma*. 2000;39:209-212). The source of *B capitatus* infection in 4 neutropenic patients in Barcelona was identified as a contaminated thermos flask used for breakfast milk distribution (*ICAAC K-1435*).

Five of 6 patients with chromoblastomycosis due to *Fonsecaea pedrosi* were successfully treated with posaconazole (*ICAAC M-976*).

Pentamidine had in vitro antifungal activity against 10 *Fusarium* isolates at clinically relevant concentrations, being fungistatic against 5 *F solani* isolates and fungicidal against 5 isolates of species other than *F solani* (*ICAAC M-962*).

Penicillium marneffei is a common cause of opportunistic infection in Southeast Asia. Eight of 9 evaluable AIDS patients with systemic *P marneffei* infections were successfully treated with voriconazole, with the ninth patient dying of an unrelated cause (*ICAAC M-963*).

Predisposing factors in 12 patients with fungemia due to *Saccharomyces cerevisiae* included the presence of a central venous catheter, prior receipt of antibiotics, gastrointestinal disease, abdominal surgery, and immunocompromise (*IDSA 358*).

Seven patients with chronic granulomatous disease complicated by invasive filamentous fungal infections were treated with posaconazole after failure (6 patients) or intolerance to voriconazole (1). One patient had cervical lymphadenitis and 6 had pneumonia. Among the latter were 2 due to *Phaeoacremonium parasiticum* and 1 each to *A fumigatus*, *Paecilomyces variotti*, and *S apiospermum*. A complete response to posaconazole was achieved in 6 of the patients, with 1 patient with pneumonia due to *P parasiticum* failing to respond (*ICAAC M-1756*).

Antifungal Agents

Hemodialysis did not affect the AUC or T1/2 of either itraconazole or hydroxyitraconazole when itraconazole was administered intravenously either before or after dialysis. The major concern regarding the use of the intravenous form of itraconazole is accumulation of its cyclodextrin carrier. The clearance of cyclodextrin was significantly increased by hemodialysis (*ICAAC M-2056*).

Melanin has been demonstrated to impair the in vitro activity of caspofungin against *C neoformans* and *H capsulatum*. In contrast, the activity of voriconazole against both these organisms is not adversely affected by melaninization of the organisms (*IDSA 140*).

Lipid association reduces but does not eliminate the nephrotoxicity of amphotericin B. A retrospective review of 254 recipients of lipid formulations of amphotericin B found that approximately 15% developed nephrotoxicity, with 4.3% requiring hemodialysis. Concomitant use of cyclosporine or tacrolimus was a significant risk factor for nephrotoxicity in these patients (*A-521*).

Because the MIC may be an inaccurate measure of echinocandin activity against filamentous fungi, an alternative measure, the minimal effective concentration (MEC), has been proposed. The MEC is the lowest concentration of the echinocandin that exerts a defined morphological effect on the fungus. The use of the MEC has now been incorporated into the analysis of the pharmacodynamics of the echinocandin, caspofungin. Caspofungin demonstrated concentration-dependent pharmacodynamics in a murine model of invasive pulmonary aspergillosis with C_{max}:MEC being the parameter most closely associated with antifungal activity. Another concentration dependent ratio, AUC/MIC, is the predictive pharmacodynamic variable for caspofungin in a non-neutropenic murine model of candidiasis (*ICAAC M-476, A-1572*).

Coadministration of nelfinavir had no effect on caspofungin pharmacokinetics, while rifampin reduced caspofungin exposure without itself being affected. When given concomitantly with rifampin, the caspofungin dose should be maintained at 70 mg daily (*ICAAC A-1605*). ■