Cryptococcosis in AIDS Patients: From Research to Practices in Resource-Limited Settings

Somnuek Sungkanuparph*. Division of Infectious Diseases, Department of Medicine, Faculty of Medicine Ramathibodi Hospital, Mahidol University, Bangkok, Thailand

Cryptococcosis is the most common life-threatening fungal infection among AIDS patients in resource-limited settings. It almost always occurs in patients with severe immunodeficiency and HIV-infected patients in resource-limited settings usually present with advanced HIV disease. The mortality rate from cryptococcosis in these settings is relatively high even with antifungal treatment. Several randomized clinical trials have demonstrated that primary prophylaxis with fluconazole reduces the incidence of cryptococcosis in patients with advanced HIV disease, particularly those with CD4 counts <100 cells/μL. A controlled trial in Thailand also demonstrated a survival benefit. Although primary prophylaxis for cryptococcosis is not generally recommended in high-income countries, it may be more beneficial in resource-limited countries because of the higher incidence of disease and the limited capacity of diagnosis and treatment. Primary prophylaxis with fluconazole is recommended in Thailand for years while the recent WHO guidelines for essential prevention and the limited capacity of diagnosis and treatment. The studies of ART initiation among patients with cryptococcosis in resource-limited settings have shown that the incidence of new cases and rate of relapsed disease are dramatically reduced, and the survival has markedly increased. Prospective studies from resource-limited settings have also demonstrated that discontinuation of secondary prophylaxis is safe when patients achieve successful immune restoration from ART. Cryptococcal immune reconstitution inflammatory syndrome (C-IRIS) is characterized a clinical deterioration of cryptococcosis following initiation of ART. Some studies report that C-IRIS is observed more frequently in severely immunocompromised patients with disseminated infection or early ART initiation after cryptococcosis. This may partly explain the high incidence of C-IRIS in resource-limited settings. However, a standard case definition of C-IRIS has not been available. The International Network for the Study of HIV-associated IRIS has been working for the practical case definition of C-IRIS to provide a tool for clinical use, particularly in resource-limited settings, and future epidemiologic studies.

Harnessing Multidrug Resistance Gene Expression for Effective Antifungal Strategies by a Natural Product Berberine

Lixin Zhang*. Institute of Microbiology, Chinese Academy of Sciences, Beijing, China

The effectiveness of existing drugs is increasingly compromised by the emergence of drug-resistant pathogens. Upregulating multidrug-resistance (MDR) pumps, which confers enhanced resistance to chemically unrelated alien substances, is a major source of microbial drug resistance. A major challenge in developing efficacious antibiotics against drug-resistant pathogens is to identify compounds that could counteract MDR functions. In the human pathogen Candida albicans, Mdr1p plays a key role in azole-resistant clinical isolates. Here we report an unexpected consequence of MDR1 upregulation: it confers enhanced sensitivity to a natural product, berberine. This effect of MDR1 overexpression is at least in part due to enhanced accumulation of berberine inside cells. In support of this notion, a number of berberine structural analogues exhibited a similar MDR1-dependent antifungal activity. We also show that berberine is indeed highly efficacious in inhibiting the growth of azole-resistant clinical C. albicans isolates with upregulated MDR1 from HIV infected patients. Our study reveals a novel function of MDR1 in raising sensitivity of drug-resistant fungal pathogens to selected natural products. Thus, the drug resistance phenotype conferred by MDR1 overexpression could be harnessed through the use of MDR1-dependent cytotoxic agents, such as berberine, for effective antifungal strategies.

Combination Antifungals - Is There a Role?

B.H. Tan*. Department of Internal Medicine, Singapore General Hospital, Singapore

Traditionally, antibiotics have been combined to treat polymicrobial infections, in initial therapy, and to prevent the emergence of resistance. For years, the hope has been that combining antifungals would produce the same effects. In medical mycology, however, very few combinations have made it to standard recommendations. The combination of amphotericin B and flucytosine in the initial treatment of cryptococcal meningitis is a case in point. That combining antifungals is not yet quite standard practice stems from problems in interpreting the literature. The same combination of drugs have produced different results in different laboratories! This likely has to do with the fact that most of the tests are not standardized. Further, the best clinical data come only from retrospective studies. In this talk the literature on combinato antifungals will be reviewed.

The Echinocandins and Formulary Decision

Mamie Hui*. Department of Microbiology, the Chinese University of Hong Kong, Hong Kong, China

Invasive fungal infections have always been a difficult to treat infectious diseases with high mortality. This is due to the immunocompromised state of the patients as well as toxicities of antifungal treatments. Traditionally, only the azoles and the polyenes are available for treatment of these patients. Recently, a novel class of antifungal agents, the echinocandins, have emerged with promising safety profiles. These agents act by inhibiting the synthesis of 1,3-β-D-glucan of fungal cell wall.