Adopting International Guidelines for Management of Invasive Fungal Diseases in Thailand - How to Make It Optimal

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The prevalence of invasive fungal diseases (IFD) has been increasing during the last decade, partly because of the advances in modern medical technologies and therapies resulting in patients' immune disruptions. Besides HIV infection, robust chemotherapy for cancers and hematological malignancies, as well as transplantations, are among the risk factors to acquire invasive fungal infections.1,2 Moreover, the epidemiology of IFD has evolved during the past decade due to the use of fluconazole prophylaxis in leukemic patients in some centers.3 Fungal pathogens have become an important cause of sepsis in the United States and the rate of sepsis caused by fungal organisms increased by 207 percent.4 On the other hand, management of IFD has been significantly changed to improve survival and quality of life.

Amphotericin B was the first approved antifungal agent to treat systemic fungal infections and it has been used as a first-line antifungal therapy for more than 50 years, until its lipid formulations became available in the late 1990s. In addition, the novel second-generation triazoles, voriconazole and posaconazole, were approved in 2002 and 2006, respectively. Furthermore, echinocandins, the antifungal agents with a new antifungal mechanism that are active against fungal cell walls, were launched during the 2000s. These included caspofungin (approved in 2001), micafungin (approved in 2005) and anidulafungin (approved in 2006). All of the novel antifungal drugs provide not only a more potent activity and a broader spectrum against certain fungal organisms, but also a safer profile. However, the new antifungal agents are pricey.

Because of the newly available antifungal agents, recent international guidelines for treatment of IFD have been updated and endorsed, and the recommendations for management of IFD were dramatically changed from the previous guidelines. In 2008, the Infectious Diseases Society of America (IDSA) issued the clinical practice guidelines for treatment of Aspergillosis.5 In these guidelines, voriconazole replaced amphotericin B for use as a first-line antifungal treatment of invasive aspergillosis. Similarly, the echinocandins substituted amphotericin B for the first-line treatment of candidiasis in the updated 2009 IDSA clinical practice guidelines for the management of candidiasis.6 In 2010, the IDSA suggested practice guidelines for management of cryptococcal diseases.7 The guidelines recommended amphotericin B...
deoxycholate in combination with flucytosine as a first-line induction therapy. Amphotericin B deoxycholate in combination with fluconazole may be used as an alternative induction treatment.

Recently, the European Society for Clinical Microbiology and Infectious Diseases (ESCMID) announced 2012 guidelines for management of Candida diseases in both non-neutropenic and hematological patients. These guidelines also recommended an echinocandin as the first choice of treatment for invasive candidiasis. Finally, in 2013, the third European Conference on Infections in Leukemia (ECIL-3) issued the guidelines for diagnosis and treatment of mucormycosis in patients with hematological malignancies. The mucormycosis guidelines were endorsed for the first time and it was developed upon evidences without a randomized controlled trial. In the mucormycosis guidelines, amphotericin B (preferably lipid formulations) was the first-line antifungal treatment. However, a novel triazole, and posaconazole, were added for use as an oral maintenance therapy.

In addition to guidelines for specific fungal diseases, guidelines for antifungal management in leukemia and hematopoietic stem cell transplant recipients have also been developed by ECIL-3. These guidelines provided recommendations for antifungal prophylaxis and management for high risk hematological patients.

It has been brought into attention about the cost-effectiveness of these clinical practice guidelines for invasive fungal diseases. A study in Spain showed that, in two years (2007-2009), antifungal consumption increased by 27%, which was 67 times more than antibacterial consumption. Therefore, totally adopting these international guidelines in resource-limited countries may result in a higher healthcare cost. In Thailand, amphotericin B deoxycholate, fluconazole and itraconazole are commonly used for systemic mycoses. These 3 agents are in the National List of Essential Medicines (NLEM) and can be used without restriction in patients with all healthcare programs. Flucytosine is not available in Thailand. Recently, liposomal amphotericin B and then voriconazole were added into the NLEM in a specific class called "J2". This class of drugs requires specific conditions to receive approval for use. Liposomal amphotericin B is approved for use in patients with significant renal impairment that prevents the use of amphotericin B deoxycholate. Voriconazole is approved only for patients with proven or probable invasive aspergillosis. All echinocandins and posaconazole are not listed in the NLEM. The endorsement of NLEM should be concordant with the guidelines for IFD and balance with the cost. Therefore, there are some issues that need to be reconsidered.

1. Voriconazole has been included into the J2 class of NLEM supported by the international guidelines for treatment of aspergillosis. However, NLEM uses serum galactomannan as a marker to determine "probable aspergillosis" for approval to use voriconazole. However, serum galactomannan is not an ideal serological testing for diagnosis of aspergillosis, as it only has moderate sensitivity and specificity. Therefore, some aspergillosis cases that require treatment may not be eligible for voriconazole treatment. In fact, a typical halo or air crescent sign seen in a chest computed tomography is more suggestive of invasive aspergillosis in a high risk patient.

2. In a resource-limited setting where the new antifungal agents are expensive, cases with
"possible aspergillosis" can be treated safely with amphotericin B deoxycholate followed by itraconazole (preferred oral suspension formula). Careful hydration and follow up are essential to improve outcomes and reduce complications.

3. Liposomal amphotericin B is the only drug approved to use in patients who have renal toxicity following amphotericin B deoxycholate. Therefore, all patients receiving amphotericin B deoxycholate for all indications with renal impairment will be eligible to use liposomal amphotericin B. This will increase the antifungal cost from 200 Baht/day to approximately 40,000 Baht/day. In fact, some patients can be treated with a less costly antifungal agent. For instance, patients with proven candidiasis due to fluconazole-resistant Candida may be treated with an echinocandin which cost about 6,000-10,000 Baht/day, 4-7 times cheaper than liposomal amphotericin B. Patients with mucormycorsis who have renal impairment may receive posaconazole for maintenance therapy instead of liposomal amphotericin B, which is about 10 times cheaper.

4. Echinocandins is effective and fungicidal to Candida, especially those with fluconazole and voriconazole resistance. These drugs may be considered to include in the NLEM to use in patients with azole-resistant candidiasis who have nephrotoxicity from amphotericin B deoxycholate. As mentioned above, it will be more cost-effective than liposomal amphotericin B.

5. Fluycytosine is not available in Thailand and some centers use amphotericin B in combination with fluconazole for alternative induction treatment of cryptococcal meningitis, according to the IDSA guidelines. However, a recent study in Vietnam revealed that amphotericin B in combination with flucytosine, but not with fluconazole, as compared with amphotericin B alone, is associated with improved survival among patients with cryptococcal meningitis. Nevertheless, a cost effectiveness analysis for resource-limited countries (including Thailand) revealed that a short-course (7 days) amphotericin induction therapy in combination with high-dose (1,200 mg/d) fluconazole is very cost effective for cryptococcal meningitis induction. Therefore, this is still an open question whether flucytosine should be made available or fluconazole should be recommended in combination with amphotericin B deoxycholate for induction therapy in cryptococcal meningitis.

References