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Guidelines for the use of antifungal agents in patients with invasive fungal infections in Taiwan

Infectious Diseases Society of Taiwan; Medical Foundation in Memory of Dr. Deh-Lin Cheng; Foundation of Professor Wei-Chuan Hsieh for Infectious Diseases Research and Education; and CY Lee's Research Foundation for Pediatric Infectious Diseases and Vaccine

Invasive fungal infections are associated with significant morbidity and mortality despite advances in medical care. Facing the transition to the era of managed care, requiring both cost containment and quality assurance, there is an increasing need of better management of patients with invasive fungal infections. An aggressive diagnostic approach in patients at risk and prompt institution of antifungal therapy may be essential for patient survival. Early intervention is strongly recommended rather than waiting for microbiological or histopathological confirmation, especially with the availability of relatively safe options. Conventional amphotericin B has been the main therapeutic agent for the treatment of most invasive fungal infections for four decades due to its broad spectrum of activity. However, such use must be accompanied by strategies to reduce amphotericin B-related toxicity. Drug-related adverse effects are associated with a significantly prolonged length of stay, increased economic burden, and increased risk of death. Thus, the total cost of antifungal treatment should not be limited to drug costs alone and the overall cost of health care must be taken into consideration in the era of global cost-containment.

Selection of antifungal agents is not just a choice between old versus new agents, but depends on the clinical status of the patient, the physician's knowledge of the species and/or antifungal susceptibility of the infecting isolate, the relative drug toxicity, the presence of organ dysfunction that would affect drug clearance as well as available knowledge of use of the drug in the given patient population, and the patient's prior exposure to antifungal agents. In addition, antifungal agents should be used rationally to avoid or prevent the selection of antifungal resistance and unnecessary use of medical resources.

A series of symposia was held over the last two years in order to develop these guidelines. Participants included experts in the field of infectious diseases, hemato-oncology, neurology and surgery. A consensus conference was held on March 11, 2006 in conjunction with the Infectious Diseases Society of Taiwan, the Medical Foundation in Memory of Dr. Deh-Lin Cheng, Foundation of Professor Wei-Chuan Hsieh for Infectious Diseases Research and Education, and CY Lee's Research Foundation for Pediatric Infectious Diseases and Vaccine. Participants included board members of the Infectious Disease Society of Taiwan and aforementioned experts*. These guidelines are limited to the most common invasive fungal infections including candidiasis, aspergillosis, zygomycosis and cryptococcosis. The aim of the guidelines is to provide national guidance to improve the use of antifungal agents. Three principles were maintained in establishing these guidelines:

1. Guidelines were based on academic principles rather than the regulations of the Bureau of National Health Insurance on antifungal usage. The majority of recommendations were evidence-based, considering randomized controlled clinical trials and other study results, case reports and expert opinions. Guidelines follow the main structure of the Infectious Diseases Society of America's guidelines.
2. Guidelines are based on local epidemiology and susceptibility patterns of pathogens.
3. Antifungal agents recommended in the guidelines are agents already marketed in Taiwan.

These guidelines are approved by the board of the Infectious Diseases Society of Taiwan, and a copy will be sent to physicians in hospitals. The guidelines are published in the *Journal of Immunology, Microbiology and Infection* and also available at the Journal's website (www.jmii.org). These guidelines will be updated and revised yearly as necessary to serve as an easily accessible reference to all physicians in Taiwan.

Guidelines for the use of antifungal agents in patients with invasive fungal infections

Diagnosis	Drugs of choice	Alternative
1. Candidiasis		
Candidemia	Remove all intravascular catheters, if possible	
Non-neutropenia	AmB 0.6-1.0 mg/kg/d iv;	Casp 50 mg/d iv[a];
	Flu 400-800 mg/d iv or po for 14 days after last positive blood culture	Vor 4 mg/kg bid iv or po[b];
		AmB 0.7 mg/kg/d iv plus Flu 800 mg/d iv or po for 4-7 days, then Flu 800 mg/d po
Neutropenia	AmB 0.7-1.0 mg/kg/d iv for 14 days after last positive blood culture	Flu 400-800 mg/d iv or po;
		L-AmB 3-6 mg/kg/d iv;
		Casp 50 mg/d iv;
		Vor 4 mg/kg bid iv or po
Neonates	AmB 1.0 mg/kg/d iv;	L-AmB 3-6 mg/kg/d iv;
	Flu 8-12 mg/kg/d iv for 14-21 days after negative repeat blood culture	Casp 50 mg/m^2 BSA/d iv
Chronic invasive candidiasis	AmB 0.6-1.0 mg/kg/d iv;	L-AmB 3-5 mg/kg/d iv;
	Flu 400-800 mg/d iv or po for total 3-6 months and resolution or calcification of radiologic lesions	Casp 50 mg/d iv
Intra-abdominal	Remove catheters, if possible	
	AmB 0.6-1.0 mg/kg/d iv;	Casp 50 mg/d iv;
	Flu 400-800 mg/d iv or po for 14-21 days	Vor 4 mg/kg bid iv or po
Urinary	Remove or replace urinary instruments	
	None for asymptomatic candiduria	
	Flu 100-400 mg iv or po;	Casp 50 mg/d iv;
	AmB 0.3-1.0 mg/kg/d iv for 7-14 days	Vor 4 mg/kg bid iv or po
Oropharyngeal	Nys 200,000-400,000 U 5 times/d;	Itr 200 mg/d po[c];
	Flu 100-200 mg/d po for 1-7 days (children) or 7-14 days (adults) after clinical improvement	AmB 0.3-0.6 mg/kg/d iv for refractory cases[d]
Esophageal	Flu 200-400 mg/d iv or po;	Casp 50 mg/d iv;
	Itr 200 mg/d po[c];	Vor 4 mg/kg bid iv or po
	AmB 0.3-0.7 mg/kg/d iv for 14-21 days after clinical improvement	
2. Empirical antifungal treatment of neutropenic patients with prolonged fever despite antibacterial therapy		
	AmB 0.5-1.0 mg/kg/d iv;	Casp 50 mg/d iv;
	Flu 400-800 mg/d iv or po (in selected patients)[e] until resolution of neutropenia	Vor 4 mg/kg bid iv or po (in selected patients)[f];
		L-AmB 3-5 mg/kg/d iv
3. Aspergillosis		
Pulmonary	Surgical resection, if feasible	
	Vor 4 mg/kg bid iv po;	L-AmB 3-5 mg/kg/d iv;
	AmB 1-1.5 mg/kg/d iv in good partial response and neutrophil recovery, then change to Vor 4 mg/kg bid po or Itr 400 mg/d po[g]	Casp 50 mg/d iv;
		Itr 400 mg/d po[g];
ENT	Surgical debridement, if possible	
	Same as pulmonary	
Disseminated (excluding cerebral)	Surgical debridement, if possible	
	Same as pulmonary	
Cerebral	Surgical debridement, if possible	
	Vor 4 mg/kg bid iv or po;	AmB 1-1.5 mg/kg/d iv
	L-AmB 3-5 mg/kg/d iv for 4-6 weeks, then change to Vor 4 mg/kg bid po	
4. Zygomycosis		
Rhino-cerebral	Aggressive eradicating surgery, if possible	
	L-AmB 3-10 mg/kg/d iv;	

	AmB 1-1.5 mg/kg/d iv	
Disseminated (excluding CNS)	Aggressive eradicating surgery, if possible	
	Same as rhino-cerebral	
Pulmonary	Aggressive eradicating surgery, if possible	
	AmB 1-1.5 mg/kg/d iv	L-AmB 3-10 mg/kg/d iv
5. Cryptococcosis		
Pulmonary		
Cryptococcoma and immunocompetent	Close observation, if negative serum antigen; Flu 200-400 mg/d po, if positive serum antigen	
Pneumonia	AmB 0.5-1.0 mg/kg/d iv for total 1000-2000 mg; Flu 200-40 mg/d iv or po for 6-12 months For AIDS, Flu 200-400 mg/d lifelong, discontinues if CD4 >200/mm^3 post-HAART therapy	Flu 400 mg/d iv or po plus 5-FC 100-150 mg/kg/d po for 10 weeks; Itr 200-400 mg/d for 6-12 months
CNS, disseminated	AmB 0.7-1.0 mg/kg/d iv plus 5-FC 100-150 mg/kg/d po for 2 weeks, then Flu 400 mg/d po for 10 weeks; AmB 0.7-1.0 mg/kg/d iv plus 5-FC 100-150 mg/kg/d po for 6-10 weeks; AmB 0.7-1.0 mg/kg/d iv for 6-10 weeks; Flu 10-15 mg/kg/d (max. 800 mg/day) iv or po for 10-12 weeks For AIDS, Flu 400 mg/d lifelong, discontinues if CD4 >200/mm^3 post-HAART therapy	L-AmB 3-6 mg/kg/d iv for 6-10 weeks; Flu 10-15 mg/kg/d iv or po plus 5-FC 100-150 mg/kg/d po for 6 weeks; Itr 400 mg/po[g] for 10-12 weeks

Management of elevated intracranial pressure

Keep initial CSF opening pressure <200 mm H_2O

1. If CSF opening pressure >250 mm H_2O, serial lumbar drainage to achieve closing pressure <200 mm H_2O or 50% of initial opening pressure
2. If CSF opening pressure <200 mm H_2O, initiate medical therapy and follow-up lumbar puncture at second week or earlier as clinically indicated

Follow-up for elevated pressure, if elevated pressure persists

1. Repeat drainage until opening pressure is stable
2. Ventriculoperitoneal shunt

Abbreviations: AmB = conventional deoxycholate amphotericin B; Flu = fluconazole; Casp = caspofungin; Vor = voriconazole; L-AmB = lipid formulation of amphotericin B; BSA = body surface area; Nys = nystatin; Itr = itraconazole; bid = twice a day; ENT = ear, nose and throat area; CNS = central nervous system; 5-FC = 5-flucytosine; AIDS = acquired immunodeficiency syndrome; HAART = highly active antiretroviral therapy; CSF = cerebrospinal fluid; iv = intravenously; po = orally

[a]Caspofungin dosing in adults consists of 70 mg loading dose followed by 50 mg per day.

[b]Voriconazole dosing consists of 6 mg/kg bid on day 1 (loading dose) followed by 4 mg/kg bid.

[c]The formulation of itraconazole is tablet.

[d]Only in azole-refractory infections.

[e]*P*atients at low risk for invasive aspergillosis, who have not received an azole antifungal agent as prophylaxis; change to an antifungal agent if there is no response after 3 days of treatment.

[f]*A*llogeneic bone marrow transplant recipients and individuals with relapse of leukemia.

[g]The formulation of itraconazole is solution.

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