J Microbiol Immunol Infect 2010;43(3):258–263

Contents lists available at ScienceDirect

Journal of Microbiology, Immunology and Infection

Journal homepage: http://www.e-jmii.com

Guideline

Guidelines for the Use of Antifungal Agents in Patients with Invasive Fungal Infections in Taiwan — Revised 2009

The Infectious Diseases Society of Taiwan; The Hematology Society of Taiwan; Taiwan Society of Pulmonary and Critical Care Medicine; 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 Vaccines.

Invasive fungal infections are associated with significant morbidity and mortality despite advances in medical care. Aggressive diagnostic approaches in "at risk" patients, coupled with prompt antifungal therapy, are essential for patient survival. Early intervention is strongly recommended, rather than waiting for microbiological or histopathological confirmation. The selection of antifungal agents depends on the severity of the illness, the most likely infecting pathogen and its antifungal susceptibility, any prior exposure to antifungal agents, drug toxicity, and the presence of organ dysfunction, as well as all available knowledge regarding the use of a particular drug in the given patient population. Antifungal agents should be used rationally. De-escalation of empirical therapy based on clinical response and laboratory results is important to avoid the selection of antifungal resistance and the unnecessary use of medical resources.

Over the last 3 years, more antifungal agents have become available and new evidence has accumulated, and so these guidelines have been updated accordingly. The aim of this document is to provide national guidance on improving the use of antifungal agents. Three principles provided the framework for these guidelines:

1. The Guidelines should be based on academic principles, rather than the regulations of the Bureau of National Health Insurance on antibiotic usage. The majority of recommendations should be evidence-based, encompassing randomized controlled clinical trials and other study results, case reports and expert opinion. Also, the Guidelines should follow the main structure of similar documents produced by the Infectious Diseases Society of America.
2. The Guidelines should be based on the local epidemiology and susceptibility patterns of pathogens. The heterogeneity of the patient population and clinical practice should also be taken into consideration.
3. The antimicrobial agents recommended in the guidelines should be available in Taiwan. These guidelines are approved by: the board of The Infectious Diseases Society of Taiwan, The Hematology Society of Taiwan, and The Taiwan Society of Pulmonary and Critical Care Medicine. The guidelines are published in the *Journal of Microbiology, Immunology and Infection* and are also available on the *Society* website. These guidelines will be updated and revised as necessary to serve as an easily accessible reference to all physicians in Taiwan.

Consensus conference participants

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Diagnosis	Drugs of choice	Alternatives[a]	Comments
1. Candidemia			Empirical therapy should be considered for critically ill patients with multiple risk factors[b] for invasive candidiasis and no other known cause of fever. Re-evaluate and modify (or discontinue) antifungal agent 48–72 hr later. Ophthalmoscopic examination is recommended for all cases. Follow-on blood cultures should be done after 48–72 hr of antifungal therapy (before next dose). For candidemia without metastatic complications, treat 14 d after the first negative blood culture result and resolution of signs and symptoms associated with candidemia. AmB-d is the treatment of choice in pregnant women.
Non-neutropenic			Remove all intravascular catheters, if possible.
Empirical therapy	AmB-d;[c] fluconazole;[d] echinocandin[e]	L-AmB;[f] voriconazole[g]	Favor fluconazole for patients who are less critically ill with no history of recent azole exposure. Favor an echinocandin for patients with moderate to severe illness or those with a history of recent azole exposure, or those who are at high risk of infection due to *C. glabrata* or *C. krusei*.
Definitive therapy	AmB-d; Fluconazole; Echinocandin	L-AmB; Voriconazole	Transfer patients who have isolates that are likely to be susceptible to fluconazole (e.g. *Candida albicans*) and who are clinically stable from an echinocandin to fluconazole. Use voriconazole as a step-down oral therapy for selected cases of candidiasis due to *C. krusei* or voriconazole-susceptible *C. glabrata*.
C. parapsilosis	Fluconazole; AmB-d	L-AmB; voriconazole; echinocandin[j]	If an echinocandin is used initially, consider changing to fluconazole.
C. glabrata	AmB-d 0.7–1.0 mg/kg/d; echinocandin;	Fluconazole; L-AmB	Continue fluconazole for patients who are clinically improved, and whose follow-up culture results are negative. Changing to fluconazole or voriconazole is not recommended without confirmation of isolate susceptibility.
C. krusei	Echinocandin; voriconazole	L-AmB; AmB-d	
Neutropenia			The comments described here are limited to those specific for neutropenia. Intravenous catheter removal is advised, but is controversial. For candidemia without persistent fungemia or metastatic complications, treat for 2 wk after the first negative blood culture result and resolution of symptoms attributable to candidemia, and resolution of neutropenia.
Empirical therapy	AmB-d 0.7–1.0 mg/kg/d iv; echinocandin	L-AmB; fluconazole; voriconazole; itraconazole[h]	Fluconazole limited to patients who are less critically ill, with no recent azole exposure, and are unlikely to have a mold infection. Voriconazole used if additional mold coverage is desired. Limited data available for micafungin and anidulafungin.

(Contd)

Diagnosis	Drugs of choice	Alternatives[a]	Comments
Neonatal candidiasis	AmB-d 1.0 mg/kg/d; fluconazole 12 mg/kg/d	L-AmB; echinocandin	A lumbar puncture and ophthalmoscopic examination are recommended in neonates with sterile body and/or urine cultures positive for *Candida*. Imaging of the genitourinary tract, liver, and spleen should be performed if the results of sterile body fluid cultures are persistently positive. For candidemia without persistent fungemia or metastatic complications, treat for 3 wk. If urinary tract involvement is excluded, L-AmB can be used. Limited data available for anidulafungin.
Chronic disseminated candidiasis	Fluconazole; AmB-d	L-AmB; echinocandin; (voriconazole)	Treatment should be continued until lesions have resolved (3–6 mo). Fluconazole (or voriconazole in selected situations) can be used as a step-down therapy in stable patients.
CNS candidiasis	AmB-d with or without 5-FC;[i] fluconazole 400–800 mg (6–12 mg/kg) daily for patients unable to tolerate AmB-d	L-AmB with or without 5-FC;[i] voriconazole	The removal of intraventricular devices is recommended. Treat until all signs and symptoms, CSF abnormalities, and radiologic abnormalities have resolved. Fluconazole (or voriconazole in selected situations) can be used as a step-down therapy in stable patients.
Candida endophthalmitis	AmB-d 0.7–1 mg/kg with 5-FC; fluconazole 6–12 mg/kg	L-AmB; voriconazole; echinocandin	Diagnostic vitreal aspiration should be done if the etiology is unknown. Surgical intervention for patients with severe endophthalmitis or vitreitis. Duration of therapy is at least 4–6wk, determined by repeated examinations to verify resolution.
Urinary tract infection			
Asymptomatic cystitis	Therapy not usually needed		Elimination of predisposing factors recommended. For high-risk surgical patients, neonates, or neutropenic patients, treat as for disseminated candidiasis. For patients undergoing urologic procedures, treat with fluconazole before and after the procedure.
Symptomatic cystitis	Fluconazole 200 mg (3 mg/kg) daily for 14 d	AmB-d 0.3–0.6 mg/kg/d for 7–14 d	AmB-d bladder irrigation limited to patients with refractory fluconazole-resistant organisms (e.g. *C. krusei* and *C. glabrata*).
Pyelonephritis	Fluconazole 200–400 mg (3–6 mg/kg) daily for 14 d	AmB-d with or without 5-FC for 7–14 d	Treat as candidemia for patients with pyelonephritis and suspected disseminated candidiasis.
Mucocutaneous candidiasis			

Oropharyngeal	Nystatin suspension 200,000–400,000 U qid; fluconazole 100–200 mg/d po	Itraconazole 200 mg/d po; AmB-d 0.3 mg/kg/d; echinocandin; voriconazole	Treat for 7–14 d (1–7 days in children) for uncomplicated disease.
Esophageal	Fluconazole 200–400 mg/d; echinocandin; AmB-d 0.3–0.7 mg/kg/d iv	Itraconazole 200 mg/d po; voriconazole	Treat for 14–21 d until clinical improvement is seen.
Candida isolated from respiratory secretions	Therapy not recommended.		Lower respiratory tract *Candida* infection is rare and requires histopathologic evidence to confirm the diagnosis.
2. Invasive aspergillosis			Treat until resolution or stabilization of all clinical and radiographic manifestations. Other factors include site of infection (e.g. osteomyelitis), level of immunosuppression, and extent of disease. Reversal of immunosuppression, if feasible, is important for a favorable outcome for invasive aspergillosis.
Empirical therapy	AmB 0.7–1.0 mg/kg/d; echinocandin; L-AmB 3 mg/kg/d	Voriconazole; Itraconazole	Initiation or modification of an antifungal regimen for patients with persist febrile neutropenia (generally 4–7 d in duration) that is without a known source and is unresponsive to appropriate antibacterial agents. No data available for micafungin and anidulafungin.
Pre-emptive therapy	AmB-d; voriconazole; L-AmB	echinocandin; itraconazole	Initiate or modify antifungal therapy to treat suspected early invasive fungal disease, but use radiologic studies, laboratory markers, or both (rather than fever alone) to stratify the likelihood of an invasive fungal infection. Favor AmB-d for patients at risk of invasive zygomycosis. Favor voriconazole when radiological presentations are consistent with invasive aspergillosis, along with a positive galactomannan antigen. No data available for anidulafungin.
Definitive therapy			
Pulmonary and tracheobronchial	Voriconazole; AmB-d	L-AmB; echinocandin; itraconazole[h]	Surgical intervention for pulmonary lesion in proximity to great vessels or pericardium, invasion of chest wall from contiguous pulmonary lesion, emphysema, and persistent hemoptysis from a single cavitary lesion. No data available for anidulafungin.
CNS	Voriconazole; L-AmB	AmB-d; echinocandin; itraconazole	Surgical resection of the infected tissue if possible. Beware of drug interaction between anticonvulsant therapy and voriconazole.

(Contd)

Diagnosis	Drugs of choice	Alternatives[a]	Comments
Sinus, endocarditis, osteomyelitis, skin and soft tissue infection	Voriconazole; AmB-d	L-AmB; echinocandin; itraconazole[h]	Surgical intervention if possible.
Chronic cavitary pulmonary aspergillosis	Itraconazole;[h] voriconazole	–	Oral therapy
Aspergilloma	–	–	Surgical resection under some circumstances.
3. Invasive zygomycosis			
CNS	L-AmB	AmB-d	Surgical resection of the infected tissue is mandatory.
Others	AmB-d	L-AmB	Aggressive eradicating surgery is mandatory. High dose can be considered when surgical intervention is not feasible.
4. Invasive Cryptococcosis			For AIDS, start HAART therapy 4–6 wk after starting antifungal therapy. For AIDS, fluconazole 200 mg/d until CD4 >100/μL and undetectable HIV RNA viral load sustained for 3 mo. For solid organ transplant recipients, treat all cryptococcosis and reduce immunosuppressive therapy; consider lowering corticosteroid dose first. Check susceptibility of persistent or relapse isolates against the original isolate.
CNS or disseminated	AmB-d plus 5-FC for 2 wk, then fluconazole for minimum 8 wk; treat for 6–18 mo for cerebral cryptococcoma	Fluconazole for 10–12 wk for mild-to-moderate disease; L-AmB for 6–10 wk; L-AmB plus 5-FC for 2 wk, then fluconazole for minimum 8 wk; AmB-d plus fluconazole for 2 wk, then fluconazole for minimum 8 wk; fluconazole plus 5-FC for 6 wk; itraconazole for 10–12 wk; voriconazole	Management of elevated intracranial pressure with symptoms. 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 wk, or earlier as clinically indicated. Follow-up for elevated pressure, if elevated pressure persists. 1. Repeated drainage until opening pressure is stable. 2. Percutaneous lumbar drain, ventriculostomy. 3. Ventriculoperitoneal shunt.
Pneumonia and others	AmB-d; fluconazole with or without 5-FC;	Itraconazole; voriconazole	Treat for 6–12 mo for immunocompetent patients. For immunocompromized patients, treat as disseminated infection.

Pulmonary cryptococcoma in immunocompetent patients	No therapy, or fluconazole 200–400 mg/d po	–	No therapy and close observation if serum antigen is negative.
5. Prophylaxis			
Invasive candidiasis	Nystatin		For leukemic patients during chemotherapy.
	Fluconazole		Limited to very high-risk patients such as hematopoietic stem cell transplant recipients prior to engraftment, solid organ transplant recipients (liver, pancreas, small bowel).
Aspergillosis	AmB-d; itraconazole; echinocandin		Limited to very high-risk patients such as allogeneic hematopoietic stem cell transplant recipients prior to engraftment, patients with GVHD. No data available for caspofungin and anidulafungin.

[a]Alternative (salvage) therapy for patients refractory to, or intolerant of, primary therapy; [b]*Candida* colonization (particularly at multiple sites), severity of illness, number and duration of broad-spectrum antibacterial agents, surgery (especially bowel surgery), dialysis, central venous catheters, parenteral nutrition, and length of ICU stay are important risk factors for invasive candidiasis; [c]Amphotericin B deoxycholate 0.5–1.0 mg/kg/d for invasive candidiasis, 0.7–1.0 mg/kg/d for cryptococcosis, 1.0–1.5mg/kg/d for invasive aspergillosis and invasive zygomycosis; [d]Intravenous, or oral, fluconazole 800 mg (12 mg/kg) on Day 1 (loading), then 400 mg (6 mg/kg) daily for invasive candidiasis, 400–800 mg (10–15 mg/kg) daily for CNS cryptococcosis; [e]Caspofungin 70 mg (loading) then 50 mg daily; micafungin: 100 mg daily; anidulafungin: 200 mg (loading), then 100 mg daily; [f]L-AmB 3–5 mg/kg daily for invasive candidiasis and invasive aspergillosis, 4–6 mg/kg/d for cryptococcosis; 3–10 mg/kg/d for invasive zygomycosis; [g]Intravenous, or oral, voriconazole 400 mg (6 mg/kg) every 12 hours for two doses on Day 1 (loading), then 200 mg (3–4 mg/kg) bid; [h]Dosage of itraconazole for treatment of invasive pulmonary aspergillosis depends on the formulation. The dosage for tablets is 600 mg/d for 3 days, followed by 400 mg/day. Although used in some case reports, oral solutions are not licensed for treatment of invasive aspergillosis. A parenteral formulation has been studied in a limited series using a dosage of 200 mg iv every 12 hours for 2 days, followed by 200 mg daily thereafter (whether this is an optimal dosage has not been defined); [i]Flucytosine 25 mg/kg 4 times daily for patients with normal renal function and is rarely administered as a single agent; [j]S-DD susceptible dose dependent. AmB-d=Deoxycholate amphotericin B; *C. parapsilosis=Candida parapsilosis; C. glabrata=Candida glabrata; C. krusei=Candida krusei*; iv=intravenous; po=orally; CNS=central nervous system; AIDS=acute immunodeficiency diseases; HAART=highly active antiretroviral therapy; HIV=human immunodeficiency virus; CSF=cerebrospinal fluid; L-AmB=liposomal amphotericin B.