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Review Article

2016 guidelines for the use of antifungal agents in patients with invasive fungal diseases in Taiwan

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Abstract The 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 Vaccines have updated the guidelines for the use of antifungal agents in adult patients with invasive fungal diseases in Taiwan. This guideline replaces the 2009 version. Recommendations are provided for *Candida*, *Cryptococcus*, *Aspergillus* and Mucormycetes. The focus is based on up-to-date evidence on indications for treatment or prophylaxis of the most common clinical

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problems. To support the recommendations in this guideline, the committee considered the rationale, purpose, local epidemiology, and key clinical features of invasive fungal diseases to select the primary and alternative antifungal agents. This is the first guideline that explicitly describes the quality and strength of the evidence to support these recommendations. The strengths of the recommendations are the quality of the evidence, the balance between benefits and harms, resource and cost. The guidelines are not intended nor recommended as a substitute for bedside judgment in the management of individual patients, the advice of qualified health care professionals, and more recent evidence concerning therapeutic efficacy and emergence of resistance. Practical considerations for individualized selection of antifungal agents include patient factors, pathogen, site of infection and drug-related factors, such as drug—drug interaction, drug-food intervention, cost and convenience. The guidelines are published in the *Journal of Microbiology, Immunology and Infection* and are also available on the *Society* website.

Introduction

Invasive fungal diseases (IFDs) continue to increase in frequency and produce significant morbidity and mortality in association with advances in medical care that tend to weaken host defense mechanisms.[1—8] This guideline aims to identify opportunities to improve the management of adults with IFDs and those at risk of developing IFDs by creating explicit and feasible recommendations to implement in clinical practice. The goals are to promote judicious and optimal use of antifungal agents, provide the rationale for selecting antifungal agents, and emphasize risk assessment and management. The guideline is intended for all clinicians who are likely to diagnose and manage adult patients with IFDs and those at risk for developing IFDs (see Tables 1—4).

Clinical practice guidelines are considered to be the essence of evidence-based medicine. The guidelines are defined by the Institute of Medicine, USA as "systematically developed statements to assist practitioners and patients in making decisions about appropriate health care for specific clinical circumstances."[9] The first and second versions of the Taiwan antifungal guidelines were published in 2006 and 2009.[10,11] The current 2016 guidelines update the previous recommendations based on more recent evidence-based studies. This is the first guideline that explicitly describes the quality and strength of the evidence to support these recommendations. The guideline was approved by the members of the council and endorsed by the Infectious Diseases Society of Taiwan (IDST).

Methods

The IDST coordinated the process of updating the guideline. The recommendations, strength, and the quality of the evidence were extensively reviewed and discussed in a series of multidisciplinary conferences and forums. The process consisted of development and validation phases to assure the quality of recommendations and facilitate integration of opinions from multidisciplinary professionals. In the development phase authors reviewed available guidelines, new primary studies and systematic reviews and local epidemiology. Authors prepared the draft recommendations and had open discussions with panel members until consensus was achieved. In the validation phase the drafts were revised accordingly and sent to the IDST for final approval.

Three principles provided the framework for this and the previous guidelines.[10,11] First, the guidelines were generated based on evidence and academic principles, rather than the regulations of the Bureau of National Health Insurance on antimicrobial usage. The majority of the recommendations were evidence-based, encompassing randomized controlled clinical trials and other well conducted studies. Because high-quality evidence for antifungal use is limited, we incorporated *in vitro* data, case reports and expert opinions. Second, the guidelines were based on the local epidemiology and susceptibility patterns of invasive fungal pathogens. The heterogeneity of the patient population and current clinical practice were also taken into consideration. Third, the antimicrobial agents recommended in the guidelines were available in Taiwan.

The target populations are adult patients with IFDs or those at risk of developing IFDs. The recommendations are restricted to *Candida*, *Cryptococcus*, *Aspergillus* and Mucormycetes. The focus is on the most commonly encountered clinical problems. The IFDs are also classified by certainty of the diagnosis, host factors, clinical findings including symptoms/signs and imaging studies, into proven, probable and possible IFDs according to international consensus recommendations for research purposes.[12] For example, proven invasive aspergillosis (IA) include microbiological or histopathological confirmation. For probable IA there include relevant clinical presentations (fever, cough, and high resolution CT scans showing halo signs), and positive biomarkers suggestive of IA such as the serum galactomannan antigen assay in high-risk patients. We did not distinguish possible or suspect IFDs as an explicit entity in the guideline because therapeutic decisions need to be individualized. We recognize that not all infections in patients at high risk for IFDs are caused by fungal pathogens and can be very difficult to distinguish presumed fungal from bacterial, mycobacterial or viral infections.

Table 1 Summary of recommendations for the treatment of candidiasis.

Diagnosis or status of the hosts	Primary	Alternative[a]	Comments
Candidemia			1. Strategies to prevent infection by modifying or eliminating risk factors[b] predisposing to candidemia and other invasive candidiasis are likely to have more impact on the outcome related to invasive candidiasis in critically ill or immunocompromised patients than any of the other strategies addressed in these guidelines. Implementing such strategies should be a priority for all healthcare facilities. 2. Empirical therapy should be considered for critically ill patients with multiple risk factors[b] for invasive candidiasis and no other known cause of fever (S/M), and followed by re-evaluation and modify (or discontinue) antifungal agent 48—72 h later as indicated. 3. A dilated ophthalmological examination is recommended within the first week of therapy in non-neutropenic patients to establish if endophthalmitis is present (S/L), particularly for patients have visual complaints, or those with altered mental status and use antifungal with limited intraocular levels, such as echinocandins. For neutropenic patients, the optimal timing for examination is the first week after recovery from neutropenia (S/L). 4. Central venous catheters (CVCs) should be removed as early as possible in the course of candidemia for non-neutropenic patients when the source is presumed to be the CVC and the catheter can be removed safely (S/M). Catheter removal should be considered on an individual basis for each patient (S/L for neutropenic patients). 5. Follow-on blood cultures should be performed after 48—72 h of antifungal therapy and then every other day to establish the time point at which candidemia has been cleared (before the next dose) (S/L). 6. Recommended duration of therapy for candidemia without obvious metastatic complications is for 14 d after documented clearance of *Candida* from the bloodstream and resolution of signs and symptoms attributable to candidemia (S/M). 7. AmB-d is the treatment of choice in pregnant women. 8. Testing for antifungal susceptibility should be considered for those when there is treatment failure or prior exposure of antifungals. Testing for azole susceptibility is recommended for all bloodstream and other clinically relevant *Candida* isolates (S/L). 9. Monotherapy with 5-FC should be avoided as resistance develops rapidly (S/L).
Non-neutropenic			
Empirical therapy[b]	AmB-d[c,d] (S/L) Fluconazole (S/H)[c,e] Echinocandin (S/H)[c,f]	L-AmB[c,g] (S/H) Voriconazole (S/L)[c,h]	1. 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 fluconazole-resistant *Candida* species (S/H), such as *C. glabrata* or *C. krusei*. 2. Favor fluconazole for patients who are not critically ill and who are considered unlikely to have a fluconazole-resistant *Candida* species. (S/H)

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Table 1 (*continued*)

Diagnosis or status of the hosts	Primary	Alternative[a]	Comments
			3. Favor amphotericin-B if there's limited availability, intolerance, or other pharmacokinetic or pharmacodynamic considerations.[a] (S/M)
Definitive therapy	AmB-d (S/H) Fluconazole (S/H) Echinocandin (S/H)	L-AmB (S/H) Voriconazole (S/M)	1. Transition from an echinocandin or AmB to fluconazole (usually after 5—7 days) is recommended for patients who are clinically stable, have isolates that are susceptible or very likely susceptible to fluconazole (e.g., *C. albicans*), and, in optimal condition, have negative follow-up blood cultures. (S/M for echinocandin; S/H for AmB) 2. Favor amphotericin-B if there's limited availability of other antifungal agents or other pharmacokinetic or pharmacodynamic considerations.[a] 3. Among patients with suspected azole- and echinocandin-resistant *Candida* infections, L-AmB is recommended (S/L). 4. Use voriconazole as a step-down oral therapy for selected cases of candidiasis due to *C. krusei* or voriconazole-susceptible *C. glabrata*. (S/L)
C. parapsilosis	Fluconazole (S/L) AmB-d	L-AmB Voriconazole Echinocandin	If an echinocandin is used initially, consider changing to fluconazole. (W/L)
C. glabrata	AmB-d 0.7—1.0 mg/kg/d Echinocandin (S/L)	Fluconazole L-AmB	1. Continue fluconazole for patients who are clinically improved, and whose follow-up blood culture results are negative. (S/L) 2. Transition from echinocandin to higher-dose fluconazole 800 mg (12 mg/kg) daily or voriconazole 200—300 mg (3—4 mg/kg) twice daily should only be considered among patients with susceptible isolates. Changing to fluconazole or voriconazole is not recommended without confirmation of isolate susceptibility. (S/L) 3. Flucytosine may be used in combination with echinocandin for the treatment of urinary candidiasis with sepsis. (S/L)
C. krusei	Echinocandin (S/L) Voriconazole (S/L)	L-AmB (S/L) AmB-d	
Neutropenia	Echinocandin (S/M) AmB-d 0.7—1.0 mg/kg/d iv	L-AmB (S/M) Fluconazole (W/L) Voriconazole (W/L) Itraconazole[a]	1. The comments described here are limited to those definite therapy specific for neutropenia. 2. Recommended minimum duration of therapy for candidemia without metastatic complications is 2 weeks after documented clearance of Candida from the bloodstream, provided neutropenia and signs/symptoms attributable to candidemia have resolved. (S/L)
Chronic disseminated candidiasis	Fluconazole (S/L) AmB-d (S/L)	L-AmB Echinocandin (Voriconazole)	1. Initial therapy with L-AmB or an echinocandin, followed by oral fluconazole for patients who are unlikely to have a fluconazole-resistant isolate (S/L). 2. Treatment should be continued until lesions resolved on repeat imaging, which is usually several months. 3. Antifungal therapy should be continued throughout the period of high risk to prevent relapse in patients receive subsequent chemotherapy or hematopoietic cell transplantation (S/L).

Table 1 (*continued*)

Diagnosis or status of the hosts	Primary	Alternative[a]	Comments
CNS candidiasis	L-AmB ± 5-FC[i] (S/L) Fluconazole (S/L)	Voriconazole (S/L) AmB-d + 5-FC[i] (W/L)	1. L-AmB (5 mg/kg daily) with or without flucytosine for initial therapy, and step-down to fluconazole 400—800 mg (6—12 mg/kg) daily after the patient has responded to initial treatment and has susceptible isolates (S/L). 2. Therapy should continue until all signs and symptoms and CSF and radiological abnormalities have resolved (S/L). 3. Infected CNS devices should be removed if possible (S/L).
Endophthalmitis	Fluconazole (S/L)	Voriconazole (S/L) L-AmB ± 5-FC (S/L) AmB-d + 5-FC (W/L)	Decisions regarding antifungal treatment and surgical intervention should be made jointly by an ophthalmologist and an infectious diseases physician (S/L). 1. Diagnostic vitreal aspiration should be done if the etiology is unknown. (S/M) 2. With macular involvement or vitritis, intravitreal injection of either AmB-d or voriconazole is recommended in addition to systemic treatment (S/L). Vitrectomy should be considered for vitritis (S/L). 3. For fluconazole-susceptible isolates, fluconazole 800 mg (12 mg/kg) loading, then 400—800 mg (6—12 mg/kg) daily (S/L). 4. Duration of therapy is at least 4—6 weeks or until resolution of the lesions (S/L).
Intravascular infection, including endocarditis, infections of implantable cardiac devices, or suppurative thrombophlebitis	L-AmB ± 5-FC (S/L) Echinocandin (S/L) Fluconazole (S/L)	Voriconazole (W/V) Posaconazole (W/V)	1. For native valve endocarditis, L-AmB ± 5-FC or echinocandins is recommended for initial therapy (S/L). Step-down to fluconazole 400—800 mg (6—12 mg/kg) daily for patients who have susceptible *Candia* isolates, have demonstrated clinical stability, and have cleared *Candida* from the bloodstream (S/L). 2. Valve replacement is recommended; and antifungal treatment should continue for at least 6 weeks after surgery and for a longer duration in those with perivalvular abscess and other complications (S/L). 3. Long term antifungal suppression is recommended for patients who cannot undergo valve replacement and for prosthetic valve endocarditis (S/L). 4. For pacemaker and implantable cardiac defibrillator infections, the entire device should be removed (S/M). Antifungal therapy for 4 weeks after removal of the device for infections limited to generator pockets, or at least 6 weeks after wire removal for infections involving the wires (S/L). 5. For suppurative thrombophlebitis, catheter removal and incision and drainage or resection of the vein, if feasible, is recommended (S/L). L-AmB or echinocandins for at least 2 weeks after candidemia (if present) has cleared, and step-down to fluconazole if susceptible (S/L). Resolution of the thrombus can be used as evidence to discontinue antifungal therapy if clinical and culture data are supportive (S/L).

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Table 1 (*continued*)

Diagnosis or status of the hosts	Primary	Alternative[a]	Comments
Osteoarticular infection	Fluconazole (S/L)	Echinocandins (S/L) AmB-d (W/L) L-AmB (W/L)	1. Surgical intervention is indicated for all septic arthritis (S/M), and in selected cases with osteomyelitis (S/L). 2. May consider echinocandins (S/L), AmB-d (W/L) or L-AmB (W/L) for initial 2 weeks. 3. Fluconazole 400 mg (6 mg/kg) daily for 4—6 weeks for septic arthritis, and 6—12 months for osteomyelitis (S/L). 4. For infection involving a prosthetic device, device removal is recommended (S/M). If the prosthetic device cannot be removed, chronic suppression with fluconazole, if the isolate is susceptible, is recommended (S/L).
Urinary tract infection			Elimination of predisposing factors, such as indwelling bladder catheters, is recommended whenever feasible. (S/L)
Asymptomatic cystitis			1. Antifungal treatment is NOT recommended unless the patients belongs to a group at high risk for dissemination: neutropenic patients, very-low-birth-weight infants (<1500 g), and patients who will undergo urologic procedures (S/L). 2. Neutropenic patients and very-low-birth-weight infants are treated as recommended for candidemia. 3. Patients who will undergo urologic procedures are treated with fluconazole or AmB-d 0.3—0.6 mg/kg daily for several days before and after the procedure (S/L).
Symptomatic cystitis	Fluconazole 200 mg (3 mg/kg) daily for 14 d (S/M)	AmB-d 0.3—0.6 mg/kg/d for 1—7 d (S/L)	1. AmB-d bladder irrigation limited to patients with refractory infection due to fluconazole-resistant species (e.g. *C. krusei* and *C. glabrata*) (W/L).
Ascending pyelonephritis	Fluconazole for 14 d (S/L)	AmB-d ± 5-FC for 1—7 d (S/L)	2. Elimination of urinary tract obstruction is strongly recommended (S/L). 3. For patient who have nephrostomy tubes or stents in place, consider removal or replacement, if feasible (W/L). 4. Surgical intervention is strongly recommended in adults with fungus balls or casts in the pyelum or urinary bladder (S/L). Irrigation through nephrostomy tubes, if present, with AmB-d is recommended (S/L). 5. Use of echinocandin in patients with *Candida* urinary tract infection and candidemia may lead to treatment failure due to inadequate concentrations of echinocandin in urine. (S/L) 6 . Treat as candidemia for patients with pyelonephritis as a part of presumed disseminated candidiasis.
Mucocutaneous candidiasis			
Oropharyngeal	Nystatin suspension (S/M) Fluconazole 100—200 mg daily po (S/H)	Itraconazole 200 mg daily po (S/M) AmB-d 0.3 mg/kg/d Voriconazole (S/M) Posaconazole (S/M) Echinocandin (W/M)	1. Treat for 7—14 d for uncomplicated disease (S/M). 2. For HIV-infected patients antiretroviral therapy is strongly recommended to prevent recurrence (S/H). 3. Disinfection of the denture is recommended for denture-related candidiasis (S/M).

Table 1 (*continued*)

Diagnosis or status of the hosts	Primary	Alternative[a]	Comments
Esophageal	Fluconazole 400 mg/d (S/H)	Echinocandin (B-II, S/H) AmB-d 0.3—0.7 mg/kg/d iv (S/H) Itraconazole 200 mg/d po (S/H) Voriconazole (S/H) Posaconazole (W/L)	Treat for 14—21 d until clinical improvement is seen. Use of alternatives for *Candida krusei*.
Candida isolated from respiratory secretions	Rarely required (S/M)		Lower respiratory tract *Candida* infection is rare and requires histopathologic evidence to confirm the infection.

[a] Alternative agents are considered in the following conditions: local resistance profiles (before patient data are available); allergy, pharmacokinetics/pharmacodynamics, refractory to or intolerant of primary regimen, or breakthrough infection during or prior use of primary regimen.

[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] Dosages suggested in the following are for adults (unless otherwise indicated) with clinically severe (often life-threatening) infection. Dosages also assume normal renal function, and not severe hepatic dysfunction. Dosages for focal infections are described in the tables.

[d] Amphotericin B deoxycholate 0.5—1.0 mg/kg/d.

[e] Intravenous, or oral, fluconazole 800 mg (12 mg/kg, loading) then 400 mg (6 mg/kg) daily.

[f] Caspofungin 70 mg (loading) then 50 mg daily; micafungin 100 mg daily; anidulafungin 200 mg (loading) then 100 mg daily.

[g] L-AmB 3—5 mg/kg daily.

[h] Intravenous, or oral, voriconazole 400 mg (6 mg/kg) every 12 h for two doses on Day 1 (loading), then 200 mg (3—4 mg/kg) bid.

[i] Flucytosine 25 mg/kg 4 times daily for patients with normal renal function and is rarely administered as a single agent.

Abbreviation: 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; CSF = cerebrospinal fluid; L-AmB = liposomal amphotericin B; 5-FC, flucytosine.

Grading of recommendation and evidence: S/H, strong recommendation, high-quality evidence; S/M, strong recommendation, moderate-quality evidence; S/L, strong recommendation, low-quality evidence; S/V, strong recommendation, very low-quality evidence; W/H, weak recommendation, high-quality evidence; W/M, weak recommendation, moderate-quality evidence; W/L, weak recommendation, low-quality evidence; W/V, weak recommendation, very low-quality evidence.

Each author was assigned to review the recent literature for a single topic, evaluate the evidence, determine the strength of the recommendations, and prepare a written draft of recommendations. PubMed was searched to identify the relevant English literature published from January 1, 2009 through June 30, 2016. Contents were reviewed and presented for each PICO (population/patient, intervention/indicator, comparator/control, outcome) question. We also reviewed the latest guidelines of Infectious Diseases Society of America (IDSA),[13—15] the Infectious Diseases Working Party (AGIHO) of the German Society of Hematology and Oncology (DGHO),[16] the Third European Conference on Infections in Leukaemia (ECIL-3),[17,18] the European Society of Clinical Microbiology and Infectious Diseases (ESCMID)[19,20] published during 2009—2016. Literature published prior to 2009 were reviewed when they were considered to provide the key evidence that support the recommendations.

The evidence was reviewed based on the GRADE method.[21—23] The panel followed a guideline development process that has been adopted by IDSA. This includes a systematic method of grading both the quality of evidence (very low, low, moderate, and high) and the strength of the recommendation (weak or strong).[7,8] The strengths of recommendations are based on, but not limited to quality (certainty) of evidence. For these reasons the Taiwan guidelines have included conventional amphotericin B in this and the previous versions. However, when there were an abundance of options we took into consideration the balance between benefits (treatment efficacy and benefit of early intervention) and harms (potential toxicity and drug—drug interaction), the negative impact of delay in intervention, burdens, resources and cost.

This document summarizes the rationale, purpose, pertinent review of local epidemiology, and key recommendations. These are summarized in the tables with corresponding description in the texts and footnotes. The document and tables are designed to achieve a balance between theoretical and practical applications for specialists, generalists, house staff and students. The guideline also emphasizes the limitation of current medical knowledge and gaps between daily practice and research needs. The references provide background information and key publications not included in international guidelines.

These guidelines are not intended nor recommended as a substitute for bedside judgment for the management of individual patients, advice of qualified health care

professional or search for updated evidence. The guidelines are published in the *Journal of Microbiology, Immunology and Infection* and are also available on the *Society* website.

Invasive candidiasis

Candidemia and other invasive candidiasis (IC) are important healthcare-associated infections. They have increased significantly in the past decade worldwide.[2–4,24–28] The Taiwan Nosocomial Infection Surveillance data show that *Candida* species have become the second most common cause of healthcare-associated bloodstream infection in intensive care units and are the leading pathogens that cause healthcare-associated urinary tract infections.[29] IC is associated with high mortality rate, increased length of hospital stay, and excess medical costs for hospitalized patients.[3,4,25,27,30–32]

In Taiwan, *Candida albicans* remains a major cause of IC, accounting for over 50% of all cases.[32,33] The three non-*albicans Candida* species are *Candida tropicalis*, *Candida glabrata* and *Candida parapsilosis*. These four *Candida* species account for more than 90% strains of IC in Taiwan. The emergence of non-*albicans Candida* species is particularly important for hemato-oncology patients as well as for non-neutropenic critically ill and non-critically ill patients.[3,8,24,26,33,34] For example, *C. tropicalis* is more likely to be isolated from neutropenic patients receiving chemotherapy on hemato-oncology services.[2,24,33,35] Although most invasive *Candida* isolates were often susceptible to fluconazole in the past,[36] azole non-susceptibility (including susceptible-dose dependent [S-DD] and resistant strains) have become a major concern. Cross resistance to other triazoles has been noted for *C. glabrata* and *C. tropicalis*.[37] *C. glabrata* that are non-susceptible to azoles are associated with prior use of azoles[32,37,38] rather than clonal spread in hospital settings.[39,40] *Candida krusei*, is intrinsically resistant to fluconazole, but is rarely isolated from the hospitals in Taiwan.[32–34,38] Antifungal susceptibility testing and search for intravascular lesions or a metastatic focus are often helpful in guiding therapy for patients with breakthrough infection or who fail treatment.[41]

In view of the poor outcome and the difficulty in making a timely diagnosis of IC, special efforts are needed to prevent infection by reducing risk factors for acquiring IC. Risk factors associated IC include the use of antibiotics, central venous catheters, surgical procedures, parenteral nutrition, sepsis, severity of illness, neutropenia, renal failure, mechanical ventilation, use of immunosuppressive agents, and *Candida* colonization.[2,3,14,24,42–44] Clinical and molecular epidemiology studies have shown that the majority of *Candida* blood isolates are similar or identical to prior colonization in the patient's urinary and gastrointestinal tracts.[40,45–48] However, exogenous infections can occur from cross transmission.[46] Therefore standard precautions including hand hygiene need to be implemented.

Empiric therapy including a fungicidal agent should be considered for critically ill and neutropenic patients with persistent fever despite antibacterial therapy, multiple risk factors, multiple and heavy colonization of Candida, and without an established cause for fever. Patients should be re-evaluated at 48–72 h and antifungal therapy can be de-escalated after IC is ruled out by blood cultures and other diagnostic measures.[14]

Antifungal therapy is not indicated for patients with asymptomatic candiduria. Candidemia is rarely encountered even in critically ill patients with candiduria (<5%).[40,48,49] Removal of an indwelling urinary catheter is often sufficient to clear candiduria without antifungal therapy. On the other hand, candiduria in the absence of a urinary catheter may be a manifestation of disseminated candidiasis in neutropenic patients with persistent unexplained fever,[14,50] high-risk surgical patients,[51] neonates,[52,53] and immunocompromised patients.[14,43]

Cryptococcosis

There are 70 species in the genus *Cryptococcus*, but only *Cryptococcus gattii* and *Cryptococcus neoformans* are the predominant cause of infections in immunocompromised or immunocompetent hosts. More than 95% of isolates in Taiwan are *C. neoformans*.[5] The disease spectrum includes meningoencephalitis, pneumonia, cryptococcemia, sepsis and fever of unknown origin. The human immunodeficiency virus (HIV) epidemic has substantially increased the burden of cryptococcal disease worldwide. In addition to HIV infection and T-cell immunodeficiency (including the use of steroids for autoimmune diseases),[74] chronic liver diseases are the most common underlying diseases in Taiwan. Cirrhosis of the liver is an independent predictor of mortality in patients with cryptococcemia or cryptococcal meningitis.[5,54]

Treatment for cryptococcosis needs to be tailored according to the immune status of the host site of infection, access to health care facilities and availability of antifungal drugs.[13] For central nervous system treatment must be tailored according to intracranial pressure (ICP), treatment phase (induction, consolidation, and maintenance phases. The best evidence is for management of HIV-infected patients and solid organ transplant recipients. There are only limited studies for immunocompetent hosts. Treatment of disseminated cryptococcosis and CNS diseases consists of at least 2 weeks of induction therapy followed by 8 weeks or more of consolidation therapy, and maintenance therapy to prevent recurrence in selected patients.

Antifungal agents with activity against *Cryptococcus* include polyenes (amphotericin B), flucytosine, and azoles. Echinocandins have no *in vivo* activity against cryptococci. Combination therapy with deoxycholate amphotericin B (AmB-d) and flucytosine is recommended as the first-line induction treatment for disseminated cryptococcosis and CNS disease. The combination has been shown in a randomized controlled trial[55] to be superior to AmB-d alone to increase survival and the rates of yeast clearance in meningoencephalitis. However, the use of flucytosine is frequently compromised by lack of availability and adverse reactions such as bone marrow toxicity. For transplant recipients with meningoencephalitis, lipid formulation amphotericin B such as liposomal amphotericin B (L-AmB) is preferable as induction therapy in view of the high proportion of patients with renal insufficiency and concurrent use of nephrotoxic drugs.[56] Fluconazole is the drug of

Table 2 Summary of recommendations for the treatment of cryptococcosis.

Diagnosis or status of the hosts	Primary	Alternative[a]	Comments
Meningoencephalitis			1. Intracranial hypertension (ICP) is commonly found in cryptococcal meningitis and is associated with increased mortality. One of the most critical determinants of outcome is control of CSF pressure. — Determine ICP at baseline. — If CSF pressure is $\geq$ 25 cm of CSF and there are symptoms of increased ICP during induction therapy, relieve by CSF drainage by intermittent lumbar punctures (LP) to reduce opening pressure (OP) by 50% if it is extremely high or to a normal pressure of 20 cm of CSF. — If there is persistent pressure elevation $\geq$25 cm of CSF and symptoms, repeat LP daily until the ICP and symptoms have been stabilized for 12 days; — Consider temporary percutaneous lumbar drains or ventriculostomy for patients who require daily LPs. — Permanent ventriculoperitoneal shunts should be placed only with appropriate antifungal therapy when conservative measures to control ICP have failed, to avoid infectious seeding. — Mannitol has no proven benefit and is not routinely recommended (S/L). — Acetazolamide and corticosteroids (unless part of IRIS treatment) should be avoided to control increased ICP (S/M). 2. Cryptococcal isolates should be stored to test antifungal susceptibility in case of treatment failure or relapse (S/L).
HIV-infected patients			
Induction therapy	AmB-d[b,c] +5-FC[b,e] (S/H) L-AmB[b,d] +5-FC (S/M)	AmB-d (S/M) L-AmB (S/M) AmB-d + fluconazole[b,f] (W/M)	AmB-d or L-AmB plus flucytosine for 2 weeks. For flucytosine-intolerable patients, AmB-d or L-AmB alone for 4—6 weeks; or AmB-d plus high dose fluconazole 800 mg daily for 8 weeks.
Consolidation therapy	Fluconazole (S/H)		Fluconazole 400 mg daily for $\geq$ 8 wk.
Maintenance therapy	Fluconazole (S/H)	Itraconazole[b,g](W/H) AmB-d (W/H)	Fluconazole 200—400 mg daily for 1 year. Consider discontinue after CD4 $>$ 100 and undetectable viral load for over 3 months.
Organ transplant recipients			
Induction therapy	L-AmB + 5-FC (S/L)	L-AmB (S/L) AmB-d (S/L)	1. For flucytosine-intolerable patients, AmB-d or L-AmB 6 mg/kg/d alone for 4—6 weeks. 2. Immunosuppressive management should include sequential or step-wise reduction of immunosuppressants, with consideration of lowering the corticosteroid dose first (S/L).
Consolidation therapy	Fluconazole (S/M)		Fluconazole 400—800 mg (6—12 mg/kg) daily for 8 weeks.
Maintenance therapy	Fluconazole (S/L)		Fluconazole 200—400 mg daily for 6—12 months.
HIV-negative, non-transplant patients			1. Check HIV status and CD4 cell count for patients with disseminated cryptococcosis.
Induction therapy	AmB-d + 5-FC (S/M)	L-AmB (S/L)	2. Duration varied due to heterogeneity in patient population, pathogen variety and their response to antifungal therapy.

(*continued on next page*)

Table 2 (*continued*)

Diagnosis or status of the hosts	Primary	Alternative[a]	Comments
			3. Usually up to 4 wks is required for patients without neurological complications and CSF cultures become negative after 2 wks of therapy; otherwise may need 6wks. Alternatively, in patients with low risk of therapeutic failure, consider induction therapy for 2 wks followed by fluconazole (800 mg/d) consolidation therapy for 8 wks (S/L). 4. If 5-FC is not given or treatment is interrupted, consider lengthening AmB-d or L-AmB induction therapy for at least 2 wks (S/L).
Consolidation therapy	Fluconazole (S/M)		Fluconazole 400—600 mg daily for 8 wk.
Maintenance therapy	Fluconazole (S/L)		Fluconazole 200 mg (3 mg/kg) daily for 6—12 months.
Non-meningeal cryptococcosis			
Severe diseases	Same as CNS disease (S/L)		Treat as CNS diseases for 12 months for the following conditions: (S/L) 1. cryptococcemia 2. dissemination (involvement of at least 2 noncontiguous sites), 3. high fungal burden, e.g, severe pulmonary cryptococcosis, cryptococcal antigen titer $\geq$1:512
Others	Fluconazole (S/L)		Fluconazole 400 mg daily for 6—12 months for patients who fulfill all of the followings 1. There are no immunosuppressive risk factors 2. Infection occurs at single site, such as mild-to-moderate pulmonary cryptococcosis 3. Blood culture is negative of Cryptococcus 4. Serum cryptococcal antigen titer is not high, for example, $<$ 1:512 5. CNS disease has been ruled out, that is, India ink preparation, antigen assay and culture of CSF are all negative if CSF study is indicated.

[a] Alternative agents are considered in the following conditions: local resistance profiles (before patient data are available); allergy, pharmacokinetics/pharmacodynamics, refractory to or intolerant of primary regimen, or breakthrough infection during or prior use of primary regimen.
[b] Dosages suggested are for adults (unless otherwise indicated) with clinically severe (often life-threatening) infection. Dosages also assume normal renal function, and not severe hepatic dysfunction.
[c] Amphotericin B deoxycholate 0.7—1.0 mg/kg/d in combination therapy, or 1 mg/kg/d alone.
[d] L-AmB 3—4 mg/kg daily.
[e] Flucytosine 25 mg/kg 4 times daily for patients with normal renal function and is rarely administered as a single agent.
[f] Intravenous, or oral, fluconazole 800 mg (12 mg/kg, loading) then 400 mg (6 mg/kg) daily.
[g] Itraconazole 200 mg twice per day orally.
Abbreviations: AmB-d, Deoxycholate amphotericin B; L-AmB, liposomal amphotericin B; 5-FC, flucytosine; iv, intravenous; po, orally; CNS, central nervous system; AIDS, acquired immunodeficiency syndrome; HIV, human immunodeficiency virus; CSF, cerebrospinal fluid.
Grading of recommendation and evidence: S/H, strong recommendation, high-quality evidence; S/M, strong recommendation, moderate-quality evidence; S/L, strong recommendation, low-quality evidence; S/V, strong recommendation, very low-quality evidence; W/H, weak recommendation, high-quality evidence; W/M, weak recommendation, moderate-quality evidence; W/L, weak recommendation, low-quality evidence; W/V, weak recommendation, very low-quality evidence.

choice for localized infections of mild-to-moderate severity. There are limited data for other azoles.

Elevated ICP is common in cryptococcal meningoencephalitis and can lead to changes in mental status, facial palsy, loss of vision and hearing and early mortality. The importance of aggressive control of elevated ICP cannot be overemphasized.[13,57] The benefits of therapeutic lumbar punctures on survival have been shown to be independent of the initial ICP.[58] Medications, such as mannitol, acetazolamide and corticosteroids, are not recommended to control increased ICP.[13]

In HIV-infected patients with cryptococcal meningoencephalitis, early initiation of current potent antiretroviral therapy may increase the risk of the immune reconstitution

Table 3 Summary of recommendations for the treatment of invasive aspergillosis (IA).

Diagnosis	Primary	Alternative[a]	Comments
Invasive aspergillosis			1. Patients with immunocompromised condition are high risk for IA, such as neutropenia, prolonged steroid use, transplantation, T cell immunosuppressants, etc. 2. Hospitalized allogeneic hematopoietic stem cell transplantation recipients should be place in a protected environment, if feasible (S/L). 3. Patients should be educated for reasonable precautions to reduce mold exposure (S/L). 4. Identification of causing etiology to species level and saving the isolate for future antifungal susceptibility testing are recommended. 5. Triazoles are preferred agents for treatment and prevention of IA in most patients (S/H). 6. AmB-d and L-AmB are alternative therapeutic options when voriconazole cannot be administered. AmB-d for use if no alternative agents are available. L-AmB for use if azoles are contraindicated or not tolerated (S/M). 7. Echinocandins are not recommended as primary monotherapy for IA, but are effective in salvage therapy (either alone or in combination) (S/M). 8. When facing breakthrough infections or treatment failures, one should consider review the evidence of IA, test antifungal susceptibility (W/M), review potential interacting drugs (S/M), perform therapeutic drug monitoring (S/M), reduce doses of immunosuppression if feasible (S/L), surgical resection of necrotic tissue, diagnostic approach for potential new etiology (S/L), and switch to a different class of antifungal agent or combination therapy (W/M). 9. For patients with successfully treated IA who require subsequent immunosuppression, secondary prophylaxis should be initiated to prevent recurrence (S/M).
Invasive pulmonary aspergillosis (IPA)	Voriconazole[b] (S/H)	L-AmB[c] (S/M) AmB-d[d] (S/M) Itraconazole[e] (W/M) Posaconazole[f] (W/M) Echinocandin[g] (W/M)	1. Primary combination therapy is not routinely recommended. 2. Treatment is continued for a minimum of 6—12 weeks and vary by site of disease, evidence of disease improvement, degree and duration of immunosuppression (S/L). 3. Surgical intervention recommended, if feasible, for pulmonary lesions in proximity to great vessels or pericardium, invasion of chest wall from contiguous pulmonary lesion, emphysema, and persistent hemoptysis from a single cavitary lesion (S/M).
Invasive sinonasal aspergillosis	Similar to IPA	Similar to IPA	1. Initial therapy with polyene should be considered in the presence of risks or evidences suggestive of mucormycosis until excluded otherwise. 2. Surgical debridement should be considered as adjunctive treatment to antifungal therapy if possible (S/M).
Tracheobronchial aspergillosis	Similar to IPA	Similar to IPA	1. Therapy with aerosolized polyene for inhalation remains investigational and non-standardized.
CNS aspergillosis	Voriconazole (S/M)	L-AmB (S/M)	1. Surgical resection of the infected tissue if feasible. 2. Be aware of drug interactions between anticonvulsants and triazoles. 3. Combination therapy may be considered in selected patients with proven or probable IA.

(*continued on next page*)

Table 3 (*continued*)

Diagnosis	Primary	Alternative[a]	Comments
			4. Intra-thecal antifungal therapy with polyene is not recommended due to poor pia matter penetration, and it may induce chemical arachnoiditis, seizure, headache and altered mental status. Corticosteroid should be avoided if possible.
Endocarditis	Voriconazole (S/L) L-AmB (S/L)		1. Early surgical intervention to prevent embolic complications and valvular decompensation (S/M). 2. Post-operation lifelong antifungal therapy in couple with frequent monitoring of clinical and radiological status (S/L).
Osteoarthritis	Voriconazole (S/M)		Surgical intervention if feasible
Skin and soft tissue aspergillus infections	Similar to IPA	Similar to IPA	1. Cutaneous aspergillosis may reflect disseminated disease, look for primary focus of infection. 2. Surgical debridement in burns or massive soft tissue wounds.

[a] Alternative agents are considered in the following conditions: local resistance profiles (before patient data are available); allergy, pharmacokinetics/pharmacodynamics, refractory to or intolerant of primary regimen, or breakthrough infection during or prior use of primary regimen. Dosages suggested below are for adults (unless otherwise indicated) with clinically severe (often life-threatening) infection, and they also assume normal renal function, and not severe hepatic dysfunction.

[b] Intravenous, or po, voriconazole 400 mg (6 mg/kg) every 12 h for two doses on day 1 (loading), then 200 mg (4 mg/kg) every 12 h; higher dosages are suggested for *Aspergillus flavus* and *Aspergillus terreus* than those for *Aspergillus fumigatus;* further dosage adjustment is based on therapeutic drug monitoring.

[c] Liposomal amphotericin B 3—5 mg/kg iv daily.

[d] Amphotericin B deoxycholate 1.0—1.5 mg/kg iv daily.

[e] Dosage of itraconazole for treatment of invasive aspergillosis depends on the formulation. The dosage for itraconazole capsule is 200 mg po twice a day. Itraconazole oral solutions, itraconazole oral tablets and parenteral itraconazole are not available in Taiwan.

[f] Dosage of posaconazole depends on the formulation.

(1) Posaconazole oral suspension 200 mg (5 ml) four times a day initially or for diet or nutritional supplement intolerant patients, then 400 mg (10 ml) twice a day after stabilization of disease; posaconazole oral suspension is best taken with greasy food;

(2) Posaconazole oral tablets 300 mg po twice a day on day 1 (loading), then 300 mg po daily;

(3) Posaconazole parenteral formulation 300 mg iv twice a day on day 1 (loading), then 300 mg iv daily;

[g] Caspofungin 70 mg iv on day 1 (loading), then 50 mg iv daily; micafungin 100—150 mg iv daily; anidulafungin 200 mg iv on day 1 (loading), then 100 mg iv daily.

Abbreviation: IA = invasive aspergillosis; AmB-d = amphotericin B deoxycholate; CNS = central nervous system; iv = intravenous; L-AmB = liposomal amphotericin B; MIC = minimum inhibitory concentration; po = orally.

Grading of recommendation and evidence: S/H, strong recommendation, high-quality evidence; S/M, strong recommendation, moderate-quality evidence; S/L, strong recommendation, low-quality evidence; S/V, strong recommendation, very low-quality evidence; W/H, weak recommendation, high-quality evidence; W/M, weak recommendation, moderate-quality evidence; W/L, weak recommendation, low-quality evidence; W/V, weak recommendation, very low-quality evidence.

inflammatory syndrome and mortality.[59] This issue is beyond the scope of the present guideline.

Invasive aspergillosis

Invasive aspergillosis (IA) has emerged as the most important fungal pathogen during the past decade for both immune and structurally compromised patients. The immunocompromised group includes hematological malignancies, prolonged neutropenia, long-term steroid use, stem cell and solid organ transplantation. The structurally compromised group includes patients in intensive care units, chronic obstructive pulmonary disease, cirrhosis, and undergoing dialysis. IA is associated with significant morbidity and mortality.[15,60—62]

Aspergillus fumigatus and *Aspergillus flavus* are the most common species in Taiwan.[6,63] *A. flavus* is the most common causative pathogen for invasive fungal sinusitis in Taiwan. It also tends to be less susceptible to antifungal drugs than *A. fumigatus*.[6,64] A recent small-scale study demonstrated up to 7.9% of *A. fumigatus* isolates are azole-resistant in Taiwan.[65] An additional problem is the emergence of amphotericin-B resistant *Aspergillus terreus*.[66] It is therefore increasingly important to request microbiological confirmation and pathogen identification at the species level to select the most appropriate antifungal agent in patients with IFDs.

There has been a major change in the approach to the management of IA during the past decade. This includes better diagnostic procedures and earlier intervention. Diagnosis has been improved by use of high-resolution chest CT scans, diagnostic bronchoscopy, and rapid diagnostic tests such as the galactomannan antigen assay. Therapy has improved by use of antifungal agents with better safety

Table 4 Summary of recommendations for the treatment of mucormycosis.

Diagnosis or status of the hosts	Primary	Alternative[a]	Comments
Invasive mucormycosis			Management should include antifungal therapy, control of underlying conditions and surgery. (S/M)
CNS	L-AmB (S/M)[b]	AmB-d (S/M)[c] Posaconazole[d] (S/M)	
Others	AmB-d (S/M)	L-AmB (S/M) Posaconazole[d] (S/M)	Surgical resection of the infected tissue is mandatory (S/M) but not recommended in disseminated cases. (W/L)

[a] Alternative agents are considered in the following concerns or conditions: allergy, pharmacology/pharmacokinetics, local resistance profiles, intolerant of or refractory to primary agent.
[b] Liposomal amphotericin B 5 mg/kg iv daily. High dose L-AMB up to 10 mg/kg/d may be considered in selected cases before operation or when surgical intervention is not feasible.
[c] Amphotericin B deoxycholate 1.0—1.5 mg/kg iv daily.
[d] Dosage of posaconazole depends on the formulation.
(1) Posaconazole oral suspension 200 mg (5 ml) four times a day initially or for diet or nutritional supplement intolerant patients, then 400 mg (10 ml) twice a day after stabilization of disease; posaconazole oral suspension is best taken with greasy food;
(2) Posaconazole oral tablets 300 mg po twice a day on day 1 (loading), then 300 mg po daily;
(3) Posaconazole parenteral formulation 300 mg iv twice a day on day 1 (loading), then 300 mg iv daily.

Abbrivations: AmB-d = Deoxycholate amphotericin B; iv = intravenous; po = orally; CNS = central nervous system; L-AmB = liposomal amphotericin B.
Grading of recommendation and evidence: S/H, strong recommendation, high-quality evidence; S/M, strong recommendation, moderate-quality evidence; S/L, strong recommendation, low-quality evidence; S/V, strong recommendation, very low-quality evidence; W/H, weak recommendation, high-quality evidence; W/M, weak recommendation, moderate-quality evidence; W/L, weak recommendation, low-quality evidence; W/V, weak recommendation, very low-quality evidence.

profiles. This includes triazoles and L-AmB rather than AmB-d and voriconazole instead of AmB-d. New therapeutic strategies include symptom-driven [empirical] and diagnostic-driven [pre-emptive] in addition to definitive therapy and prophylaxis.[15,67] Thus far there is inadequate evidence to support routine primary combinational antifungal therapy. But it could be considered as a salvage option for immunocompromised patients with proven/probable IA when surgical resection is not feasible.[15,68] Surgical intervention is recommended for selected patients with pulmonary lesions in proximity to the great vessels or pericardium, invasion of the chest wall from a contiguous pulmonary lesion, emphysema, persistent hemoptysis from a single cavitary lesion, cerebral lesions, osteomyelitis, endocarditis, sinusitis, and cutaneous lesions.[15]

A growing body of evidence has shown that serum levels of triazoles vary among individuals and even in the same patient due to alterations in absorption. This is particularly problematic for itraconazole and posaconazole. There are also drug—drug interactions for all triazoles, and pharmacogenetic polymorphisms for voriconazole.[69] Data supporting the value of therapeutic drug monitoring (TDM) is too limited to establish recommendations. Nevertheless, there are accumulating reports that indicate that TDM can have an important role in optimizing safety for voriconazole and flucytosine and efficacy for itraconazole, posaconazole, and possibly, voriconazole. TDM may be helpful in selected clinical scenarios such as suspected toxicity, breakthrough infection, treatment failure, changing gastrointestinal, hepatic, or renal function, and drug—drug interactions and in conjunction of antifungal stewardship programs.[15,69]

AmB-d remains as the therapeutic agent of choice in this guideline for the following reasons. It has broad spectrum activity; is the preferred agent for pregnant women and neonates and provides an alternative choice when confronting drug—drug interactions with azoles. However, up to 24% of patients receiving AmB-d developed nephrotoxicity in a multicenter prospective observational study in Taiwan.[1] Thus, when considering the use of AmB-d, it is of paramount importance to carefully inform patients and caregivers of the side effects of this drug and implement measures to prevent anaphylaxis and reduce nephrotoxicity and infusion related toxicity. These measures include slow infusion, adequate saline hydration, pre-infusion medications and close monitoring of serum creatinine and electrolytes.[1] Substitution of L-AmB for AmB-d has reduced infusion reactions and nephrotoxicity and can achieve better CNS concentration with higher doses. In addition, L-AmB, but not AmB-d is active against *Candida* biofilms.[70]

Environmental control is an essential strategy for preventing aspergillosis. Reconstruction and renovation may increase risk and cause outbreaks of mold infections, particularly for aspergillosis in immunocompromised patients. Hospital infection control programs need to include elimination of environmental fungal exposures to plants, new construction and mold in areas where patients are at greatest risk of developing aspergillosis.[71]

Mucormycosis

Previously termed zygomycosis, mucormycosis must be dealt with as a medical emergency. The majority of pathogens in the order Mucorales are *Rhizopus*, *Mucor*, *Rhizomucor*, *Lichtheimia* (previously classified as *Absidia*), *Cunninghamella*, *Apophysomyces* and *Saksenaea*. It is less common than IA in patients with hematological diseases, but the prognosis is

remarkably poor. The most important predisposing conditions associated with mucormycosis include granulocytopenia, immunosuppression, diabetes, penetrating trauma, and iron overload.[72,73] The most prevalent sites of infection are the paranasal sinuses, followed by the lung, brain, and skin. Rhinocerebral mucormycosis is the most common form in patients with diabetes. Pulmonary mucormycosis occurs most often in patients with hematologic malignancies.[72]

AmB and posaconazole are the only active agents for these infections.[74] AmB is currently the recommended systemic antifungal agent. L-AmB is, often preferred over AmB-d because it is less nephrotoxic and allows the administration of higher doses. It has been demonstrated in animal models to be more effective in reducing brain fungal burdens.[75] Posaconazole is an option for salvage or maintenance therapy.[17] Surgical debridement is recommended in addition to antifungal therapy.[16,17,19,73] Correction of underlying conditions, such as neutropenia, hyperglycemia and ketoacidosis, and reduction of immunosuppressants is also crucial for successful management.

Conclusion

Although great care has been taken to develop these guidelines the field continues to be in flux. Changes will be needed to the current approach in diagnosis and management as new agents and diagnostic tools become available. The patient's physician has the primary responsibility to provide care, request consultations, and make decisions for specific procedures, choice of drug and dosage according to the best available information. These decisions must be made after consideration of all the relevant clinical findings and interests of the patient. Consultation with an infectious diseases physician is recommended for complex or life-threatening situations. There needs to be close collaboration with the pertinent hematologists, transplant experts, surgeons and critical care physicians. Review of the manufacturer's product information, consultations with a knowledgeable clinical pharmacist and the antibiotic stewardship team are often helpful. It is particularly important that there be awareness of drug interactions particularly for critically ill patients who are receiving multiple drugs. Emergence of resistance is a critical problem for all antimicrobial drugs including antifungal agents. It is therefore important to avoid inappropriate or excessive use of these agents when not indicated or no longer needed.

Author contributions

YC Chen, coordinate and chair the review and guideline development process, prepare the manuscript; HC Kung, review and prepare cryptococcosis and mucormycosis section; PY Huang reviewed and prepared candidiasis section; WT Chen reviewed and prepared aspergillosis section; other authors including panel members of the IDST involve in content development and critical review of the manuscript.

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