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# NEWSLETTER

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## Editors' welcome


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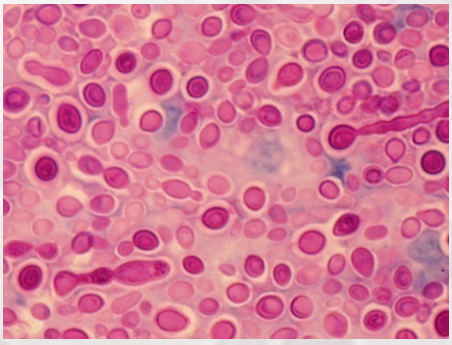
On behalf of the Asia Fungal Working Group (AFWG), we wholeheartedly welcome you to this second issue of our 2016 newsletter, dedicated to yeasts. First, we put *Cryptococcus* at center stage, devoting the discussion to its genetic diversity and optimal laboratory identification, as well as the varying clinical presentations of cryptococcal infections in the immunocompetent host versus the HIV patient. Second, *Candida* as an etiology of bloodstream infections in Asia is systematically characterized, and third is a concise update on the other emerging yeasts in Asia. Once again, we present our quick drug guide for clinicians, focusing on amphotericin B, an important element in our armamentarium against these yeast infections.

Finally, do take time to check on the latest activities and programs of the AFWG, as we look forward to further engaging you in this common interest and our commitment to optimizing the management of invasive fungal infections.

Nasal specimen (periodic acid-Schiff stain) from a *Cryptococcus*-infected immunocompromised host



Contributed by Banlunara W (Chulalongkorn University, Thailand)

# Cryptococcosis

The pathogenic yeast cell with a polysaccharide capsule, *Cryptococcus neoformans/C. gattii* complex, causes a life-threatening infection called cryptococcosis. The natural habitats of *Cryptococcus* are soil with bird (eg, pigeon) droppings, decaying wood and the bark of certain trees. Recently, evidence showed that *C. gattii* could be isolated from some tropical trees, such as almond trees (*Terminalia catappa*), pottery trees (*Ficus microcarpa*) and cassia (*Cassia grandis*).

Cryptococcosis usually affects immunocompromised hosts, especially HIV patients, via the respiratory tract. After inhalation of either sexual or asexual spores, clinical symptoms develop and manifest in the lungs, blood and, finally, the brain and meninges, sometimes spreading to the lymph nodes and skin. Severe symptoms are seen in both humans and animals. Recently, laboratory surveillance studies have illustrated the variety of *Cryptococcus*, from the serotype to the molecular level (Table 1).

**Table 1. Genus, species, serotypes and molecular types of pathogenic *Cryptococcus***

| Genus and species | Serotype | Molecular type |
|---|---|---|
| *C. neoformans* complex | | |
| *C. neoformans* var. *grubii* | A | AFLP1/VNI<br>AFLP1A, AFLP1B/VNII |
| *C. neoformans* var. *neoformans* | D | AFLP2/VNIV |
| *C. gattii* complex | | |
| *C. gattii* sensu stricto | B | AFLP4/VGI |
| *C. bacillisporus* | C | AFLP5/VGIII |
| *C. deuterogattii* | | AFLP6/VGII |
| *C. tetragattii* | | AFLP7/VGIV |
| *C. decagattii* | | AFLP10/VGIV |
| Hybrids | AD, AB, BD | AFLP3/VNIII |

Worldwide, about 1 million cases of cryptococcal meningitis occur among people with HIV/AIDS each year, resulting in nearly 625,000 deaths. This infection can be found globally, affecting sub-Saharan Africa, USA, Europe and Asia, including Thailand, where the burden of cryptococcal meningitis was estimated at 4.2/100,000 per year.

The majority of these cases in Thailand were in HIV-infected hosts and most of the isolates were *C. neoformans* var. *grubii*, serotype A/VNI, which is similar to findings in other countries. A summary of surveillance data from Southeast Asia is shown in Table 2, and includes cultures isolated from 1993 to 2011. Also similar to that seen in other countries, *C. gattii* complex has been on an upward trend in Southeast Asia from both clinical and environmental sources. A molecular study in Thailand showed a strong link between environmental and clinical strains for the VNI isolates, and similarities among the situations in Thailand and Vancouver (Canada), Australia and South America.

Moreover, a number of unique sequence types have been found in Thailand, which warrants further study in this region. Regarding the susceptibility profile, no resistance strains were presented in these studies, despite reports of resistance from other countries, such as Cambodia. Resistance should be monitored carefully, particularly since non–HIV-infected hosts have been reported.

For brain and meningeal infections, cerebrospinal fluid (CSF) and serum are the preferred specimens for laboratory diagnosis. India ink or nigrosin preparation is used to stain the background for simple direct examination. To increase the yield, one drop of sediment after 1,500 g/3,500 rpm for 10 minutes of centrifugation is recommended for CSF. Sputum, lymph node and tissue biopsy samples can also be used. The supernatant can be used for antigen detection either by lateral flow strip or latex agglutination test. To shorten the identification process, the specimens may be inoculated in the medium with phenoloxidase substrate (caffeic acid/mustard seed/cabbage seed) to induce the melanin production, which is a simple test to confirm the encapsulated yeasts as *C. neoformans*. Urease production of the encapsulated yeast is another rapid screening test for genus *Cryptococcus*. Concanavalin medium is one of the recommended tests that can be used to identify the variety. *URA5*-RFLP, multilocus sequence typing and other molecular techniques are also able to identify the genetic variation for both diagnostic and epidemiologic purposes.

## Table 2. Laboratory-based surveillance data on *C. neoformans*/*C. gattii* complex in Southeast Asia

| Country | Isolate sources | | | Identification-based | | | Susceptibility test (ug/mL) | | | | | Demography | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Clinical | Env | Feline | Serotype/ *URA5*-RFLP/ Others | *C. neoformans* | *C. gattii* | BMT/ E-test | AmB $MIC_{90}$ | FLZ $MIC_{50}$ | FLZ $MIC_{90}$ | VO $MIC_{50}$ $MIC_{90}$ | HIV +/- | Age (year) | % Male |
| **Cambodia** (Sar B, et al. 2004) | 402 (CSF) | ND | ND | A (var. *grubii*) | ND | ND | BMT | 0.50[$] 0.50[$$] | 4[$] 12[$] | 12[$] 96[$] | ND | NA | NA | NA |
| **Singapore** (Tan AL, et al. 2008) | 8 *C.n.* 2 *C.g.* | ND | ND | ND | ND | ND | E-test | 0.38 0.25 | 4 8 | 32 32 | 0.016 0.094 0.064 0.125 | NA | NA | NA |
| **Thailand** | | | | | | | | | | | | | | |
| **Northern** (Sriburee P, et al. 2004) | 75 | 9/55+ 45/100++ 2/230+++ | ND | Serotype A: all isolates | PCR fingerprinting Group 1: 129 Serotype A Group 2: 1 flower, 1 pigeon droppings | | | | ND | | | NA | NA | NA |
| **Eastern** (Tangwattanachu-leeporn M, et al. 2013) | 5 | 5/50+ | ND | Serotype A | ND | | | | ND | | | NA | NA | NA |
| **Thailand** (Kaocharoen S, et al. 2013) | 386 | 83 | 29 | M13 finger-printing/ MLST | VNI (365/386, 82/83, 25/29) VNII (8/386, 4/29) VNIV (1/82) VGI (1/386) VGII (12/386) 7 unique ST of both varieties | | | | ND | | | 88.5%/- | 6-76 (mean: 37.97) | 68.9 |
| **Thailand** (Worasilchai N, et al. 2016) | 74 (69 CSF; 5 blood) | 52 | 2 | *URA5*-RFLP | VNI (67/74, 51/52, 2/2) (1/69, 1/52) VGII (1/69) | VNII | BMT | 0.5-0.125 | 0.5-4 (5FC: $MIC_{50}$ 0.25-2) | | ND | NA | NA | NA |
| **Vietnam Ho Chi Minh city** (Day JN, et al. 2011) | 151 | NA | NA | *URA5*-RFLP | VNI (100/100); (37/51) | VGI (13/51) VGII (1/51) | | | ND | | | 100/51 | 15-62* | 63* |

5FC; 5-fluorocytosine; AmB, amphotericin B; BMT, broth microdilution test; *C.g., C. gattii; C.n., C. neoformans;* CSF, cerebrospinal fluid; Env, environment; FLZ, fluconazole; MIC50, minimum inhibitory concentration required to inhibit the growth of 50% of organisms; MIC90, minimum inhibitory concentration required to inhibit the growth of 90% of organisms; MLST, multilocus sequence typing; NA, not applicable; ND, not determined; PCR, polymerase chain reaction; RFLP, restriction fragment length polymorphism; ST, sequence type; VO, voriconazole
[$]isolates from Apr 2000-Mar 2001; [$$]isolates from Apr 2001-Mar 2002; [+]pigeon dropping samples; [++]dove dropping samples; [+++]Eucalyptus flower samples; *non-HIV group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# Cryptococcosis in HIV- and non–HIV-infected patients

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A 43-year-old female presented with progressively worsening headache, subtle fever, nausea and vomiting that developed over a few weeks. Oral candidiasis, bilateral papilledema and meningeal irritation signs without focal neurologic deficits were revealed during physical examination. Computed tomography of the brain was normal. Lumbar puncture results were: opening pressure, 30 $cmH_2O$; cerebrospinal fluid (CSF) sugar, 48 mg/dL; protein, 50 mg/dL; and white blood cell count, 40 cells/$mm^3$ with 100% mononuclear cells. India ink examination showed numerous encapsulated yeasts. Her blood and CSF cultures grew *Cryptococcus neoformans*. She also had reactive anti-HIV test, and positive CSF and serum cryptococcal antigen tests with titers of >1:5,120.

Physicians are familiar with the above scenario of cryptococcal meningitis or disseminated cryptococcal infections as AIDS-defining illnesses. Infections caused by *Cryptococcus* species can affect other populations and have a wide spectrum of clinical presentations, ranging from colonization to dissemination into any organ, with a predilection for the central nervous system (CNS) and the lungs. However, a decrease in cryptococcosis may be expected in the era of combination antiretroviral therapy (cART). This article aims to summarize the key features and treatment of cryptococcosis in HIV- and non–HIV-infected patients.

*C. neoformans* and *C. gattii* are two major pathogenic *Cryptococcus* species. Both species cause

**Table. Antifungal therapy and minimum durations of treatment for patients with cryptococcal infections[7,8]**

| | Induction | Consolidation | Maintenance |
|---|---|---|---|
| **Meningoencephalitis** | | | |
| HIV-infected | [AmBd or LAMB] plus flucytosine, 2 weeks | Fluconazole 400 mg/day, 8 weeks | Fluconazole 200 mg/day, 1 year |
| Transplant recipients | [LAMB or ABLC] plus flucytosine, 2 weeks | Fluconazole 400-800 mg/day, 8 weeks | Fluconazole 200-400 mg/day, 6-12 months |
| Non-HIV, non-transplant | [AmBd or LAMB or ABLC] plus flucytosine, 4 weeks; or AmBd, 6 weeks | Fluconazole 400-800 mg/day, 8 weeks | Fluconazole 200 mg/day, 6-12 months |
| **Non-meningeal cryptococcosis** | | | |
| **• HIV-infected** | | | |
| Extrapulmonary and diffuse pulmonary disease | | Same as CNS disease | |
| Focal pulmonary disease and isolated cryptococcal antigenemia | | Fluconazole 400 mg/day, 12 months | |
| **• Non–HIV-infected: immunosuppressed and immunocompetent patients** | | | |
| Mild-moderate pulmonary disease | | Fluconazole 400 mg/day, 6-12 months | |
| Severe pulmonary disease | | Same as CNS disease, 12 months | |
| Cryptococcemia | | Same as CNS disease, 12 months | |
| Single site of infection, no fungemia, no CNS disease, no immunosuppressive risk factors | | Fluconazole 400 mg/day, 6-12 months | |

AmBd, amphotericin B deoxycholate 0.7-1.0 mg/kg per day; LAMB, liposomal amphotericin B 3-4 mg/kg per day; ABLC, amphotericin B lipid complex 5 mg/kg per day; CNS, central nervous system

infections either in immunocompromised or immunocompetent hosts, but *C. gattii* is the cause of the majority of cryptococcosis in immunocompetent patients.[1] Besides HIV infection, other risk factors for cryptococcosis include: solid organ transplantation; corticosteroid/immunosuppressive therapy; lymphoproliferative disorders; sarcoidosis; idiopathic CD4+ lymphopenia; cirrhosis; hyper-IgE syndrome; hyper-IgM syndrome; anti–granulocyte-macrophage colony-stimulating factor (anti–GM-CSF) antibodies; rheumatic diseases; and treatment with monoclonal antibodies (eg, infliximab, alemtuzumab, adalimumab).[1] However, about one fifth of patients with cryptococcosis have no apparent risk factors.[2]

Several studies have shown that HIV-related cryptococcosis tends to affect younger patients (between 30 and 40 years) and males.[3-6] With a higher burden of yeasts and a greater degree of immunosuppression, patients with HIV infection present with headache and have higher proportions of CNS disease, cryptococcemia and extrapulmonary diseases than non–HIV-infected individuals.[3-6] Higher serum and CSF polysaccharide antigen titers, lower CSF pleocytosis and higher positive CSF India ink examination (up to 80% vs 30-50%) are more common in AIDS-related cryptococcal meningitis than in non–AIDS-related disease.[1] In HIV-infected patients with cryptococcal meningitis, there may be slower sterilization of CSF, a higher incidence of increased intracranial pressure (ICP), co-infections with other organisms, and immune reconstitution inflammatory syndrome (IRIS). Pulmonary manifestations are different in HIV-infected and in non–HIV-infected patients. One third of normal hosts present with an asymptomatic isolated lung mass or multiple nodules, while alveolar and interstitial infiltrates mimicking *Pneumocystis* infection are common in HIV-infected patients.[1]

Treatment of cryptococcosis includes antifungal therapy, management of increased ICP and hydrocephalus, and regaining host immune status. Current antifungal treatment recommendations from the Infectious Diseases Society of America and the Department of Health and Human Services for treatment of cryptococcosis in HIV- and non–HIV-infected patients are summarized in the Table.[7,8] Reduction of immunosuppressive therapy helps control cryptococcosis in non–HIV-infected patients; however, caregivers should consider deferring initiation of cART in HIV-infected patients until 2 to 10 weeks or later after the initiation of antifungal therapy and monitor carefully for increased ICP as a presentation of IRIS.[8] At least 1 year of suppressive therapy with fluconazole 200 mg is recommended for HIV-infected patients, until a CD4 count ≥100 cells/μL for at least 3 months and suppressed HIV-RNA are acheived.[8] The prognosis of non-HIV, non-transplant patients is, unfortunately, poorer than that of other groups, which is likely due to delayed diagnosis and the severity of comorbid diseases, such as malignancy.[3-5]

In conclusion, cryptococcosis has different manifestations, treatment and prognosis in HIV-infected- and non–HIV-infected patients. In the era of cART, early recognition of cryptococcosis may improve patient outcomes.


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# Emerging yeast infections in Asia

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With the advancement of modern medicine and a growing population of immunosuppressed patients, opportunistic yeast infections have become an important cause of morbidity and mortality in critically ill patients. Interestingly, certain unusual opportunistic yeast species have emerged for the first time and other known rare yeasts have appeared more often in the last decade. In the last two decades, the incidence of non-*albicans Candida* species infection has increased relative to *C. albicans* worldwide, but the shift is more marked in some Asian countries, where non-*albicans Candida* species account for ~90% of candidemia cases.

The emergence of multidrug-resistant *C. auris* is the latest threat in Asia, and the infection has spread to South Africa, United Kingdom and United States in the last 2 years. In fact, the Centers for Disease Control and Prevention (CDC) issued a clinical alert titled 'Global Emergence of Invasive Infections Caused by the Multidrug-Resistant Yeast *Candida auris'* on 24 June 2016. In addition, several unusual yeast species (*Pichia anomala, P. fabianii* and *Kodamaea ohmeri*) were found to be responsible for large outbreaks in India. *C. africana*, a cryptic species of *C. albicans*, has recently been reported to cause vulvovaginitis and balanoposthitis in China. Trichosporonosis due to multidrug-resistant *Trichosporon asahii* is frequently encountered in China, India, Japan, Taiwan and Thailand. Non-*neoformans Cryptococcus* species like *C. gattii* and *C. laurentii* have been reported in both immunocompetent and immunosuppressed patients in a few Asian countries. Other uncommon yeasts reported from Asia include *Geotrichum, Malassezia, Rhodotorula* and *Saccharomyces* species. *Malassezia japonica* and *M. arunalokei* are two new species isolated from clinical specimens in the region. *Saccharomyces* fungemia related to use of probiotics has raised concern in critically ill patients of India.

The exact reason for the emergence of these yeast infections is largely unknown. However, improved diagnostics, especially molecular techniques (eg,

**Table. Antifungal activity in emerging yeasts**

| | Azoles | | | Polyenes | Echinocandins |
|---|---|---|---|---|---|
| | Fluconazole | Voriconazole | Posaconazole | Amphotericin | All three |
| ***Candida tropicalis*** | ~10% resistant | 5-10% resistant | Susceptible | Susceptible | Susceptible |
| ***C. glabrata*** | Dose-dependent | Susceptible/ dose-dependent | Variable | Susceptible | Susceptible |
| ***C. krusei*** | Resistant | Dose-dependent | Dose-dependent | Susceptible to intermediate | Susceptible |
| ***C. parapsilosis*** | Susceptible | Susceptible | Susceptible | Susceptible | Higher MIC |
| ***C. auris*** | Resistant | Resistant in majority | Variable | ~14% resistant | ~10% resistant to caspofungin |
| ***C. rugosa*** | Low activity | Low activity | Low activity | Susceptible | Susceptible |
| ***C. guilliermondii*** | Low activity | Susceptible | Susceptible | Susceptible | Susceptible |
| ***Pichia anomala*** | Variable | Susceptible | Susceptible | Susceptible | Susceptible |
| ***Kodamaea ohmeri*** | Susceptible | Susceptible | Susceptible | Variable | Susceptible |
| ***Trichosporon asahii*** | Variable | Susceptible | Susceptible | Resistant | Resistant |
| ***Cryptococcus gattii*** | Low activity | Susceptible | Susceptible | Susceptible | Resistant |
| ***Rhodotorula* species** | Low activity | Variable | Not known | Susceptible | Resistant |
| ***Saccharomyces* species** | Variable | Susceptible | Susceptible | Susceptible | Susceptible |
| ***Malassezia* species** | Variable | Susceptible | Not known | Variable | Not known |

matrix-assisted laser desorption/ionization [MALDI], sequencing), have played important roles in the identification of the majority of emerging yeasts. The commercially available biochemical-based tests (eg, VITEK-2, API strips) cannot correctly identify all yeasts, so molecular techniques are required. The accurate identification of yeasts is of paramount importance when choosing the proper antifungal agent, as yeasts differ in virulence and drug resistance. The usual antifungal susceptibility of emerging yeasts in Asia is summarized in the Table.

### *Candida auris*

*C. auris* was first isolated in 2009 from external ear discharge of a patient from Japan. Since that report, the infection has been reported in South Korea, India, Pakistan and Kuwait. In a recent study of ICU-acquired candidemia in 27 ICUs in India, the pathogen was isolated from 5.2% of 1,400 candidemia cases – the 6th most common isolate – and ranked as the 4th most common isolate in neutropenic patients. The study showed that, before acquiring the infection, a significant number of *C. auris* candidemia cases underwent invasive interventions, including vascular surgery, total parenteral nutrition, urinary catheterization, post-operative drain and prolonged central venous line days. The duration of ICU stay prior to acquisition of *C. auris* candidemia was significantly longer (median 25 days, interquartile range [IQR] 12-45 days) than for non-*auris* candidemia patients (median 15 days, IQR 9-28 days; $p<0.001$), suggesting nosocomial transmission. However, the exact mode of transmission and source in the hospital environment were not identified.

*C. auris* is now considered a superbug because of its resistance to azoles and polyenes, and its association with high mortality rates. To combat such a threat, clinicians and microbiologists should heighten vigilance and surveillance for this organism, and improve infection control practices. The agent is not easily identified by phenotypic methods; confirmation would require molecular methods.

### *Trichosporon* species

Of the *Trichosporon* species, *T. asahii* is the most common agent causing fungemia, pulmonary and soft tissue infections and meningitis in both immunocompetent and immunosuppressed patients. The majority of invasive infections are associated with malignancies, previous antibiotic therapy, use of a central catheter and admission to ICUs. In Asia, trichosporonosis is the second most common deep-seated yeast infection in China, India, Japan, Taiwan and Thailand. In Thailand, it accounts for 6% of all fungemia cases, with the majority being ICU patients. In Japan, breakthrough infection is common after micafungin therapy and linked to high mortality (76%). In China, the infection commonly affects the urinary system, lungs and blood. Rare *Trichosporon* species causing infection in Asia include *T. dermatis, T. inkin, T. montevideense, T. asteroides, T. faecale, T. ovoides, T. domesticum, T. japonicum* and *T. jirovecii.* The high mortality from trichosporonosis is due to delay in identifying the causative agent and poor susceptibility to antifungal agents.

## Conclusion

Asian countries harbor a wide spectrum of new yeasts that are potentially pathogenic in susceptible hosts. The emergence of multidrug-resistant *C. auris* infection and trichosporonosis is a matter of serious concern. There is an urgent need to work on awareness of clinicians, improvement of mycology laboratory facilities, and bridging gaps in infection control practices in the region.


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# AMPHOTERICIN B: A quick reference for practicing clinicians

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Amphotericin B is a polyene antifungal agent derived from *Streptomyces nodosus*.[1] Although it was discovered more than 60 years ago, it remains a first-line agent for the treatment of many life-threatening invasive fungal infections.

Amphotericin B is amphipathic (ie, it possesses both hydrophilic and hydrophobic moieties) and, hence, is insoluble in water.[1] Aqueous solubility is therefore achieved by formulation with deoxycholate (DAmB) or a lipid carrier. The former has been available since the late 1950s, but its clinical utility is limited by a high frequency of adverse effects, particularly nephrotoxicity.[1,2] There are various lipid formulations (Table) that reduce the parent drug nephrotoxicity while retaining the drug's activity, providing a better therapeutic index for the drug.[1,2] All are administered intravenously (IV). Aerosolized formulations could be a valuable alternative, because inhalation administration ensures a high drug concentration in the respiratory tract, while potentially minimizing systemic toxicities.[3-5]

**Table. Lipid formulations of amphotericin B**

| Formulation | Complex |
|---|---|
| Amphotericin B lipid complex (ABLC) | Complexed with dimyristoylphosphatidylcholine and dimyristoylphosphatidylglycerol |
| Amphotericin B colloidal dispersion (ABCD) | Complexed with cholesteryl sulphate |
| Liposomal amphotericin B (LAmB) | Complexed with hydrogenated soy phosphatidylcholine, distearoyl, phosphatidylglycerol and cholesterol |

## Spectrum of activity

Amphotericin B has a broad spectrum of activity, with efficacy in candidiasis, cryptococcosis, aspergillosis, histoplasmosis, blastomycosis, coccidioidomycosis, zygomycosis, sporotrichosis, fusariosis and phaeohyphomycosis.[2]

Fungi with intrinsic resistance include rare pathogens such as *Trichosporon* species, *Aspergillus terreus, Scedosporium* species and *Malassezia furfur.*[2]

## Pharmacokinetic parameters

Pharmacokinetic properties differ among the various formulations. For DAmB, peak plasma concentrations typically range from 0.5 to 2 mg/L, with slow excretion by the kidneys over weeks or months.[6] Among the formulations with a lipid carrier, ABLC and ABCD are rapidly cleared from the bloodstream and taken up primarily by the reticuloendothelial system, with peak plasma levels ≤5 mg/L when given at therapeutic doses.[7] In contrast, LAmB given at similar doses is associated with peak plasma levels up to 200 times higher.[7] However, all three lipid carrier formulations have non-linear pharmacokinetics, such that there are greater than (LAmB) or less than (ABLC, ABCD) proportional increases in serum concentrations with increasing doses.[8-10] **LAmB achieves 4- to 7-fold higher brain parenchymal concentration than other preparations, making this molecule useful for treating fungal infections involving the CNS.**

## Dosage recommendations

The dosing of IV amphotericin B depends on both the formulation used and the specific indication. DAmB should be given over a period of 2-6 hours. Because patient tolerance can vary substantially, the dosage should be individualized and adjusted according to clinical status.[3] A test dose may be desirable to assess tolerance. In patients with good cardio-renal function and a well-tolerated test dose, therapy is usually initiated at 0.25 mg/kg/day, gradually increasing to 0.5-0.7 mg/kg/day.[6]

Prehydration with 500 mL of intravenous normal saline and prolonged infusion of DAmB for 7-10 hours is associated with better tolerance and reduced nephrotoxicity. Avoid concomitant saline infusion in the same line of DAmB as saline may precipitate DAmB.

With ABLC, the recommended daily dosage for adults and pediatric patients is 5 mg/kg/day, administered at a rate of 2.5 mg/kg/hour.[8]

Meanwhile, with ABCD, the recommended dose for adults and pediatric patients is 3-4 mg/kg/day, initially at a rate of 1 mg/kg/hour, although this can be shortened to a minimum of 2 hours if there is no evidence of intolerance or infusion-related reactions.[9]

Finally, LAmB may be given to adult and pediatric patients at doses of 3-6 mg/kg/day depending on the specific indication, initially administered over 2 hours, although this can be reduced to around 1 hour if the drug is well tolerated.[10]

## Drug-drug interactions

Drug interactions associated with amphotericin B are often based on their potential to cause nephrotoxicity.[3] For example, compounds such as aminoglycosides, cyclosporine, pentamidine and antineoplastic agents can enhance the potential for drug-induced renal toxicity, and should be used with great caution if given concomitantly.[6,8-10] Intensive monitoring of renal function and electrolytes is recommended in patients requiring any combination of nephrotoxic medications.

Furthermore, concurrent use of flucytosine with amphotericin B may increase the toxicity of flucytosine, possibly by increasing its cellular uptake and/or impairing its renal excretion.[6,8-10]

Animal studies also suggest possible antagonism between amphotericin B and imidazole derivatives (eg, miconazole, ketoconazole), although the clinical significance of these findings is not known.[6,8-10]

## Therapeutic drug monitoring

At present, there is no evidence to support the routine use of therapeutic drug monitoring with amphotericin B.[11] However, this could change in the future, should our understanding of the exposure-response relationships improve.

## Adverse drug reactions

The most common adverse events associated with amphotericin B are transient chills and/or fever during infusion of the drug.[6,8-10] Infusion-related reactions are due to toll-like receptor-2 activation, resulting in a proinflammatory cytokine response. Pretreatment with nonsteroidal anti-inflammatory agents, antihistamines and corticosteroids may reduce such reactions. However, the clinical use of DAmB is limited primarily by nephrotoxicity. In some cases, this can be associated with permanent renal impairment, particularly when given alongside other nephrotoxic drugs.[2] Lipid carrier formulations have lower rates of nephrotoxicity, and these effects are only weakly correlated with dose.[2] Hence, higher effective dosages can be given with lipid-formulated amphotericin B compared with DAmB, with a lower risk of treatment-limiting renal dysfunction.


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# Candidemia in Asia: A laboratory-based surveillance study

## Background and methods

Efforts to improve outcomes of *Candida* infections must be supported by adequate epidemiologic data describing infection frequency and species distribution. As no large-scale, cross-sectional study of candidiasis across Asia had been performed, members of the AFWG collaborated to conduct a 12-month, laboratory-based surveillance of candidemia at 25 hospitals from 6 countries/regions in Asia. The goal was to determine the incidence and distribution of candidemia at the surveillance sites, as a first step in collecting data that could help guide prevention and treatment strategies against *Candida* infection in these regions.

This surveillance study was conducted with the cooperation of the microbiology/mycology labs of 25 hospitals – 10 in China, 1 in Hong Kong, 4 in India, 1 in Singapore, 6 in Taiwan and 3 in Thailand. Data were collected on fungi isolated from clinical specimens from 1 July 2010 through 30 June 2011.

## Results

Overall, there were 1,601 episodes of candidemia, which yielded 1,910 non-duplicate *Candida* blood isolates identified to species level. The calculated incidence of candidemia was 1.22 episodes/1,000 discharges or 0.15 episodes/1,000 patient-days. Incidence varied markedly among the participating hospitals and countries/regions.

*C. albicans* was the most frequently isolated species (41%), followed by *C. tropicalis* (25%), *C. glabrata* (14%) and *C. parapsilosis* (12%). Although *C. albicans* was the most common species overall, it accounted for <40% of candidemia in 12 of 25 hospitals. The spectrum and incidence of *Candida* species varied among hospitals, with the relative contributions of the four common species differing among the countries/regions (Figure).

*C. tropicalis* was the leading non-*albicans* species overall; the proportion of *C. tropicalis* was significantly higher in tropical areas (India, Thailand and Singapore) than in other geographical regions (46.2% vs 18.9%; p=0.04). For 3 of the 25 hospitals (2 in China; 1 in Taiwan), *C. glabrata* was the most common non-*albicans* species. Up to 26% of candidemia cases were caused by *C. glabrata* in two hospitals (1 in China; 1 in Singapore).

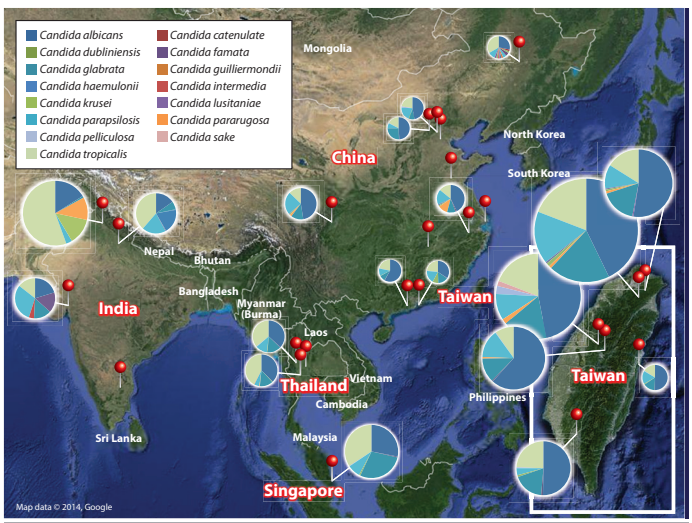
## Discussion

These data reveal substantial variability in the incidence of candidemia and species distribution of *Candida* isolates among the hospitals, although the reasons for the differences are difficult to ascertain from these surveillance data.

As in Europe and North America, *C. albicans* is typically the most common cause of candidemia in the Asian sites surveyed in this study. However, *C. tropicalis* tended to be the most frequently identified non-*albicans* species in this study, in contrast to the USA and the UK, where *C. glabrata* is the leading non-*albicans* species.

Asia is a large and heterogeneous region and, although this study included 25 hospitals, it cannot claim to provide a sample representative of the region. Other study limitations include: all but one of the participating hospitals were referral centers; not all *Candida* isolates were successfully identified to species level; and isolate identification was performed at local laboratories, not a central reference laboratory.

Figure. Distribution of *Candida* species in blood isolates by study site




The size of the circles indicates the relative number of candidemia episodes in each site. Only *Candida* species of 20 or more episodes at each study site are shown. The inset represents Taiwan.

Despite the acknowledged limitations, the findings of this surveillance study provide an overview of the incidence of candidemia and distribution of causative species in Asia. The authors suggest that these results support the importance of a proper and detailed microbiologic diagnosis, including the speciation of *Candida* blood isolates, for optimal patient care and appropriate infection control.

**Reference:**
Tan BH, Chakrabarti A, Li RY, et al; Asia Fungal Working Group (AFWG). Incidence and species distribution of candidaemia in Asia: a laboratory-based surveillance study. *Clin Microbiol Infect* 2015;21:946-953.

AFWG UPDATES

## The Asia Fungal Working Group (AFWG) is dedicated to advancing the understanding, diagnostics and management of invasive fungal infections and augmenting fungal surveillance data to support best practices in the Asia-Pacific region.

### MMTN – Philippines a success

The Medical Mycology Training Network (MMTN) regional series was established by the AFWG to provide essential knowledge and practical experience in medical mycoses, ultimately helping to improve patient outcomes across the Asia-Pacific region. As an offshoot of the highly successful regional series, we held the first local, country-based MMTN in the Philippines. This MMTN was held jointly with the 5th Philippine Clinical Mycology Network Meeting on 13-14 May 2016 at the Cebu Institute of Medicine in Cebu, Philippines. Around 60 physicians and medical technologists from the Philippines attended the 2-day event. Overall, the feedback for the first MMTN Philippines was positive, and showed the participants benefited greatly from the unique and "highly informative" educational experience.

AFWG Executive Committee member Dr Mitzi Chua from the Philippines opened the meeting, followed by presentations on fungal infections by AFWG colleagues, Chair Professor Arunaloke Chakrabarti (India) and Dr Ariya Chindamporn (Thailand). Dr Virginia Mesola (Philippines) shared data on Philippine epidemiology of invasive fungal infections and local fungal diagnostics.

AFWG UPDATES

## Official AFWG website launched

We are very excited to announce that the official AFWG website (www.AFWGonline.com) is now up and running. It is designed to be the primary site for all AFWG updates and announcements, as well as a comprehensive portal for networking and delivery of updated mycology information tailored to researchers and healthcare professionals in Asia.

The website features educational modules and videos for continuing medical education, a collection of various resources and research publications for easy access to material that can help your practice, schedules of upcoming events of interest, and other useful content. We look forward to your visit and hope to receive feedback on how we can improve the site further.

# Contribute to our online surveys

The AFWG would like to thank everyone who has already participated in our online surveys, “Diagnostic mycology laboratory services in Asia” and “Clinical management of invasive fungal infections in Asia”. The collated results will also be posted as soon as possible, and will hopefully help us identify real-life gaps and needs, and help advance mycology services and clinical practices across the region.

**You can still contribute!**

### Diagnostic mycology laboratory services in Asia

- A survey on the capacity and services of your diagnostic mycology laboratory
- To be completed by the person in charge of the mycology laboratory (or personnel assigned by the person-in-charge)
- One survey per mycology lab

https://www.surveymonkey.com/r/afwglabonline

### Clinical management of invasive fungal infections in Asia

- A survey on your current practices in managing IFIs at your hospital
- Any infectious disease physician, hematologist/oncologist, transplant physician/surgeon, or critical care specialist
- One survey per physician

https://www.surveymonkey.com/r/afwgclinonline