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Editors' welcome

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We are proud to showcase the latest edition of our newsletter, where we focus on some of the excellent presentations enjoyed by delegates at the recent Medical Mycology Training Network (MMTN) Conference held in Kuala Lumpur, Malaysia (5–6 August 2017). The MMTN typically provides an integrated educational forum, based on practical training for microbiologists and laboratory personnel, case workshops for clinicians, and combined plenary sessions with updates on diagnostics and management.

Our Kuala Lumpur event brought together an international panel of expert speakers from across the region, and welcomed more than 90 delegates from Malaysia, with attendees from the Philippines and Indonesia, as well.

In the following pages, we feature highlights from the plenary sessions. These focused on 4 main themes: fungal infection challenges in the 21st century; practical issues in antifungal therapy; hot topics in Asian medical mycology; and optimizing diagnosis and patient management.

Eleven outstanding presentations are summarized. We particularly draw your attention to Dr Atul Patel's lecture on '*New antifungal agents*', offering several reasons to be optimistic about the future of our practice, and Professor Arunaloke Chakrabarti's talk on the '*Outbreak of superbug* Candida auris: *Asian scenario and interventions*', which offers relevant advice on this important fungal concern in the region.

As ever, we invite you to visit our official website, www.AFWGonline.com, or to drop us a line on Facebook, Instagram or LinkedIn. Thank you for your support!

Evolving fungal landscape in Asia

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Fungal pathogens pose a significant threat to public health, food biosecurity and biodiversity. Despite this, they are largely ignored by the public, the press and funding bodies. From a public health perspective, there remains relatively little global recognition that over 300 million people suffer from serious fungal-related diseases, or that fungi are responsible for an estimated 1.6 million deaths each year – a higher mortality rate than that of malaria.[1]

Cryptococcosis

Around 21–36% of cryptococcosis cases occur in patients with cirrhosis, making it the most common host factor associated with these infections in HIV-uninfected patients.[2-4] Furthermore, in a recent multivariate analysis, cirrhosis was 1 of 2 factors (along with cerebrospinal fluid antigen titer) shown to be an independent predictor of mortality.[4] The minimum inhibitory concentration (MIC) of different antifungal agents, particularly fluconazole, may vary according to genotype; hence it is important to determine MICs for clinical isolates.

Candidemia

A recent laboratory-based surveillance study conducted in 25 hospitals across Asia demonstrated that candidemia is common across the region, with an overall incidence of more than 1 episode per 1,000 discharges, and a wide distribution across services (Figure 1).[5] *Candida tropicalis* was the most frequently isolated non-*albicans* species, particularly in tropical countries.[5,6] Risk factors for candidemia include age, moderate-to-severe renal diseases, leukemia, lymphoma, gastrointestinal malignancies, metastatic solid tumors and chronic pulmonary diseases.[7]

In a pan-Asian study, reduced susceptibility to fluconazole was common in non-*albicans Candida* species, suggesting that echinocandins should be the antifungal of choice in clinically unstable or high-risk patients with documented candidemia.[6] International guidelines recommend echinocandins as initial therapy for candidemia in most cases.[8,9]

Aspergillosis

In a recent study conducted in 5 Asian countries, *Aspergillus* species was the most common etiology of microbiologically confirmed cases with proven/probable invasive mold infection (71.6%) – largely due to *A. fumigatus* and *A. flavus*.[10] The most frequently observed host factor was prolonged steroid use (39.4%) and the most common underlying condition was diabetes (30.9%).[10]

Azole resistance in *A. fumigatus* is an emerging global health problem, including in Asia.[11-13] This could affect the current primary treatment recommendation, which is based around voriconazole monotherapy.[14] Alternative treatment strategies, including azole-echinocandin combinations or liposomal amphotericin B, may be necessary in areas with environmental resistance rates of ≥10%.[15]

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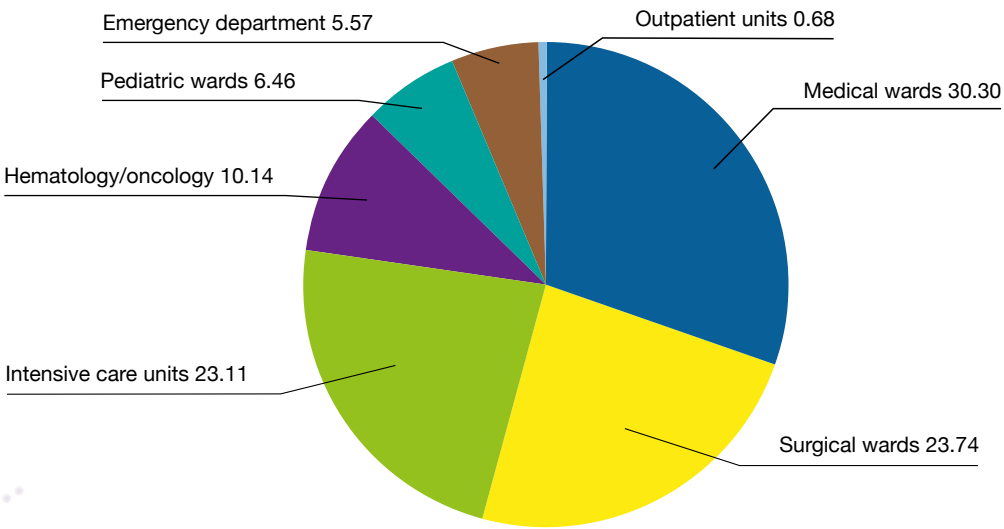
Figure 1. Distribution of patients with candidemia by hospital service (numbers denote percentages)[5]



Strengths and limitations of imaging for diagnosis of invasive fungal infections

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In the most recent iteration of the European Organization for Research and Treatment of Cancer/Mycoses Study Group consensus, the clinical criteria for defining probable lower respiratory tract fungal disease are all radiologic.[1] They are based on the presence of 1 or more of the following signs on computed tomography (CT)[1]:

- Dense, well-circumscribed lesions(s) with or without a halo sign;
- Air-crescent sign; or
- Cavity.

These criteria were developed more for research use rather than usual clinical practice, but they nonetheless provide potentially valuable guidance.

Halo sign

The CT halo sign indicates ground glass attenuation surrounding a pulmonary nodule.[2] It is caused by angioinvasion and tissue infarction, with surrounding hemorrhage.

The halo sign is not unique to invasive fungal infections (IFI), and can be caused by other pathologies, such as Wegener's granulomatosis and Kaposi's sarcoma.[2] However, in an autopsy-based study of neutropenic patients with hematologic malignancy, with or without invasive pulmonary aspergillosis (IPA), the halo sign appeared to be the most specific for IPA: it was evident in 13/17 IPA versus 0/31 non-IPA patients ($p<0.0001$).[3]

However, the halo sign is transient and therefore will not be visible on CT in all patients with IPA.[4] Thus, early CT is valuable. Furthermore, the halo sign is prognostic: initiation of antifungal treatment based on identification of a halo is associated with significantly improved treatment response and survival.[5]

Air-crescent and reversed halo sign

In the context of IPA, an air-crescent sign requires no pre-existing cavity, and is caused by parenchymal cavitation.[6] It typically occurs about 2 weeks after detection of the initial radiographic abnormality, and often coincides with white blood cell recovery.[6]

Meanwhile, a reversed halo sign may be an indicator of pulmonary mucormycosis, and detection may allow the early initiation of appropriate therapy.[7]

Overall, used appropriately and in context, lung CT remains a key pillar of the diagnostic process for IFI, particularly in neutropenic patients.

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Candidemia: Lessons learned from Asian studies for intervention

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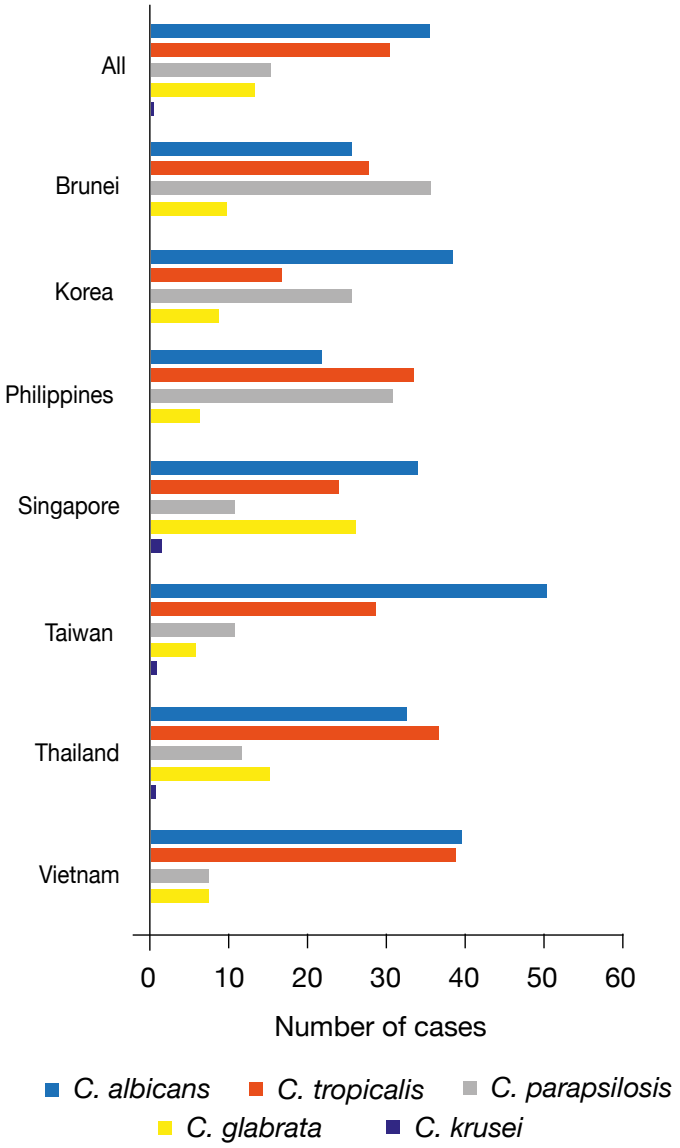
Worldwide, candidemia affects over 250,000 people per year, leading to more than 50,000 deaths.[1] Key risk factors are largely healthcare-related, including critical illness (particularly long-term stay in the intensive care unit), abdominal surgery, broad-spectrum antibiotic use and central vascular catheter/total parenteral nutrition.[1,2]

In general, these risk factors appear to be similar in Asia, as compared with Western countries. Despite this, the incidence of candidemia appears to be higher in Asia – ranging from 0.39 to 14.2 cases per 1,000 admissions/discharges, compared with incidences typically below 1 case per 1,000 admissions/discharges in Western countries.[3,4] Potentially modifiable causes of this disparity may include: limited awareness in fungal diseases; overuse and/or misuse of antibiotics and corticosteroids; suboptimal infection control; and the use of management strategies that are largely based on clinical assessment and empiric therapy.[3]

Species distribution

Two recent studies have examined the distribution of *Candida* species across multiple Asian countries.[4,5] In the first, based on 1,910 isolates from 6 countries, *C. albicans* (41.36%) and *C. tropicalis* (25.45%) were the most common.[4] This finding was confirmed in the second analysis, which included 861 isolates from 7 countries.[5] Both studies found that the incidence of *C. tropicalis* was typically higher in tropical countries compared with more temperate areas. Furthermore, there were substantial variations between countries (Figure 2), with some of the less common species being observed more frequently in particular countries (eg, *C. parapsilosis* in Brunei and the Philippines, *C. glabrata* in Singapore).[5]

Figure 2. Species distribution of *Candida* in 7 Asian countries[5]



Improving future strategies for candidemia management

There are a number of ways in which candidemia management could be improved across many Asian countries:

- Develop and implement diagnostic tools that are more widely available and have shorter turnaround time (for both identification and antifungal susceptibility);
- Improve infection control;
- Perform local epidemiology studies; and
- Improve antifungal treatment, including greater access to echinocandins (particularly in light of recent evidence showing reduced susceptibility to fluconazole in non-*albicans* species in Asia[5]), greater education on appropriate drug selection, and improved antifungal stewardship.

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Do we need modification of recent IDSA & ECIL Guidelines while managing patients in Asia?

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Guidelines are very important in the management of fungal infections. They play a crucial role in summarizing the current evidence base, standardizing care and improving outcomes. However, there are many reasons why clinicians in Asia (or, indeed, elsewhere in the world) might want to deviate from recommendations:

- The importance of individualized clinical judgment over generic pathways;
- Differences between trial data and 'real-life' practice;
- Local epidemiology and resistance patterns;
- Varying patient demographics;
- Drug intolerance; and
- Cost concerns.

Invasive candidiasis

According to both the Infectious Diseases Society of America (IDSA) and the European Conference on Infections in Leukemia (ECIL), echinocandins are now the recommended initial therapy for candidemia in both neutropenic and non-neutropenic patients.[1,2] There remains an allowance for the use of azoles and liposomal amphotericin B in some circumstances.

However, in an Asian context, local circumstances may dictate some divergence from guidelines. In particular, epidemiology may differ substantially in this region compared with North America and Europe – most notably in a higher incidence of *C. tropicalis* and a lower incidence of *C. glabrata*.[3,4]

In addition, cost is a concern. A recent Asian study assessed the cost-effectiveness of individual echinocandins (caspofungin, micafungin and anidulafungin) versus non-echinocandins for *C. albicans* and non-*albicans* spp., taking into account the probability of treatment success, mortality rates, adverse drug events, etc.[5] Importantly, the study found that echinocandins – particularly anidulafungin – were cost-effective compared with other therapies.

Invasive aspergillosis

In recent guidance from IDSA and ECIL, recommendations for the primary therapy of invasive aspergillosis (IA) were based largely around voriconazole and isavuconazole.[1,6] ECIL-6 recommends against first-line use of amphotericin B deoxycholate on the grounds of low efficacy and high toxicity.[6]

However, the reality of IA management may come down to whether or not a given center can take a diagnosis-driven approach, based on the latest tools and rapid diagnostic turnaround times. For many centers in Asia, this is not yet possible because the capacity to investigate the underlying etiology is limited. Instead, an empiric approach must be taken, based on the treatment of a presumed fungal infection, triggered by persistent fever in a high-risk (neutropenic) patient. The choice of empiric therapy may include agents such as voriconazole, fluconazole, liposomal amphotericin B and caspofungin.

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New antifungal agents

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There remains a pressing need for new antifungal agents, for a wide variety of reasons – including an increasing incidence of IFI, high levels of associated mortality, limitations among existing agents (eg, toxicity, drug-drug interactions and resistance), and the need for agents against difficult-to-treat infections like *Scedosporium* and *Fusarium*.

A number of potent new agents are currently in Phase 1 and 2 development, many of which offer a broad spectrum of activity and potential synergy with approved antifungals (Table 1).[1] In addition, several drugs that have been approved for indications outside fungal infection – such as cyclosporine/tacrolimus/rapamycin, rifampin and verapamil – have potentially broad-spectrum antifungal activity that could be useful in combination with existing treatments.[1] The antidepressant sertraline has also shown promising activity against cryptococcal meningitis.[2,3]

Newer formulations of posaconazole

Among currently approved antifungal agents, 2 new formulations of posaconazole have potential to improve the usability of this compound. The major drawback of the older, oral-suspension formulation was the requirement of frequent dosing (4 times daily during week 1 followed by twice daily), preferably following a full meal, to ensure adequate oral absorption.[4] This was needed because absorption requires dissolution of the drug in the stomach, which is maximized by taking smaller, more frequent doses with food, to lower the gastric pH and prolong residence time.

The new formulations of posaconazole – a delayed-release tablet and an injectable preparation – circumvent these absorption problems. The tablet formulation uses pH-sensitive polymers to release posaconazole at a controlled rate in the duodenum, thereby improving the absorption profile and allowing once-daily maintenance dosing.[4] However, it has the downside of disallowing division/crushing of the tablet, thus preventing administration through a gastric feeding tube. The injectable formulation has the advantage of early achievement of steady-state plasma levels, but must be administered via a central line and may be contraindicated in patients with renal impairment.[4]

Isavuconazole

Isavuconazole is a recently approved, second-generation triazole antifungal agent, available in oral and intravenous (IV) formulations. The oral preparation has high bioavailability, and absorption is not significantly affected by food intake.[5] It is approved for use against IA and mucormycosis,[5] although efficacy against the latter appears to be similar to amphotericin B.[6]

In vitro data suggest that isavuconazole has broad-spectrum antifungal activity, including against *Candida* spp., *Cryptococcus neoformans* and *Trichosporon* spp.[7] However, it has little or no activity against difficult-to-treat *Scedosporium prolificans* and *Fusarium* spp.

Table 1. New antifungal agents in the pipeline[1]

Compound	Activity	Target	Stage
APX001	**Glycosyl phosphatidylinositol synthesis**	• Broad-spectrum potency against pathogens including Mucorales, *Candida* spp., *Aspergillus* spp., *Fusarium* spp. and *Scedosporium* spp. • Synergizes with approved antifungals	Phase 1, Phase 2
AR 12	Probably blocks fungal acetyl-CoA synthetase 1; increases host immune response by downregulating host chaperone proteins	• *Cryptococcus neoformans* • *Candida albicans* • Mucorales molds • Hyalohyphomycosis, including those caused by *Fusarium* spp. and *Scedosporium* spp.	Phase 1
Efungumab	**Hsp90**	• *Candida* spp.	Phase 2
MGCD290	Hos2	• Broad spectrum • Synergizes with approved antifungals	Phase 2
Nikkomycin Z	**Chitin synthase**	• Coccidioidomycosis, histoplasmosis and blastomycosis • Synergizes with approved antifungals	Phase 1

It has many potential advantages over other azole antifungals[5,7,8]:

- High prodrug water solubility, obviating the need for cyclodextrin (which is associated with nephrotoxicity) in the IV formulation;
- High oral bioavailability, which therefore allows for 1-to-1 dosage conversions from the IV formulation;
- A prolonged half-life of >75 hours, allowing for convenient once-daily dosing;
- Predictable, linear pharmacokinetics with no relevant food effect; and
- Potentially fewer drug–drug interactions than other azoles, although it should not be administered with strong inducers or inhibitors of CYP3A4.

Isavuconazole therefore represents a valuable new option within the antifungal armamentarium.

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Recent advances of fungal diagnostics and application in Asian laboratories

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Mortality due to invasive fungal infection is up to 100% if not treated and about 50% even with proper treatment. The poor outcome is attributed to absence of diagnosis due to nonspecific clinical signs and symptoms. Common clinical situations include inappropriate use of broad-spectrum antibacterial drugs in inaccurately diagnosed fungal sepsis and failure to diagnose chronic pulmonary aspergillosis in smear-negative pulmonary tuberculosis, among others.[1] These scenarios point to the importance of access to advanced fungal diagnostics to improve clinical outcomes, promote antimicrobial stewardship and control antimicrobial resistance.

Current methods detect clinical infection

Currently available methods include T2 magnetic resonance for detection of candidemia,[2] molecular identification of the fungus in the tissue – immunohistochemistry, DNA sequencing and fluorescence in situ hybridization (FISH)[3] and the proteomic-based matrix-assisted laser desorption ionization (MALDI) for the identification of various fungi.[4] These methods, however, are only able to detect pathogens upon clinical infection. Improvement of outcomes, however, will rely on detection at biological infection and prompt administration of targeted prophylaxis or pre-emptive therapy.

New diagnostic tests

Several new prospective diagnostic tests have been developed in recent years, each with their own pros and cons. These include the combination of polymerase chain reaction (PCR) and galactomannan tests,[5] proximity ligation assay,[6] detection of siderophore production[6] and electronic nose technology for *Aspergillus* detection,[7] and cryptococcal antigen lateral flow assay.[8] These methods have various rates of success and need further validation. Current consensus for diagnostic tests serves as a guide for choosing appropriate methods (Table 2).

Present scenario in Asian countries

A recent study involving 241 laboratories in 7 Asian countries revealed poor access to biomarker tests like galactomannan, β-D-glucan and PCR in Indonesia, Philippines and Thailand.[9] The authors called for the need for the development of quality laboratories, accreditation and training of manpower in existing laboratories, as well as access to advanced non-culture–based diagnostic tests for improved diagnosis of fungal infections in Asia.

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Table 2. Current consensus on diagnostic tests for fungal infections

Infection	Culture/histopathology	Biomarker (antibody)	Biomarker (antigen)	Response to treatment
Aspergillosis	Yes – invasive	No	GM/BDG/PCR	Increasing evidence
Cryptococcosis	Routine	No	Antigen/PCR	Yes (CSF antigen)
Histoplasmosis	Culture – delay	Limited	Antigen	Yes (antigen)
Mucormycosis	Yes – invasive	No	Investigational	No
Other molds	Yes – invasive	No	Investigational	No
Candidiasis	Routine	Investigational (anti-mannan)	PCR/mannan/BDG	No

BDG, β-D-glucan; CSF, cerebrospinal fluid; GM, galactomannan; PCR, polymerase chain reaction

Mucormycosis and pythiosis – new insights

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The revised taxonomy classifies fungi causing mucormycosis in the new subphylum Mucoromycotina.[1] This subphylum and the subphylum entomophthoromycotina were formerly among the 2 orders that were members of the zygomycota division.[1] The 2 subphyla are pathogens similar in size and both have aseptate hyphae; however, they differ in their infected host, clinical manifestation and spore types.[1] *Rhizopus* species is the most common mucormycosis-causing agent.[2]

Studies performed in mucormycosis patients worldwide revealed that the underlying conditions differ between patients in developed countries and those in developing countries. The European continent sees higher cases of underlying hematological malignancies in mucormycosis patients[3] in contrast with countries such as India[4] and Mexico,[5] which report diabetes as the predominant underlying condition in their patients.

Pathogenesis of mucormycosis: Role of CotH receptor agents

The regulatory protein CotH on the surface of the mucorales fungi specifically bind to the glucose receptor protein GRP78 on the surface of the host endothelial cells. This interaction facilitates fungal invasion of the cell, subsequently causing damage to the endothelial cells, promoting angioinvasion and dissemination.[6] Investigations show that interruption of CotH in *Rhizopus oryzae* is able to disrupt the invasive potential of the pathogen, making CotH a promising therapeutic target.[6]

Pythiosis: A fungus-like organism

An increasing trend in cases of human pythiosis has been observed in the past 10 years, with Thailand reported to have the highest number of cases worldwide.[7] Clinical manifestations of human pythiosis can be classified into 4 types: cutaneous/subcutaneous; ocular; vascular; and disseminated pythiosis. In vascular pythiosis, 4 classic clinical presentations that should be of concern are underlying thalassemia, no atherosclerotic risk, history of previous leg wound and presentation with acute or chronic limb ischemia.[8] The ocular form, on the other hand, is commonly linked to a history of eye contact with water, such as through contact lens wear and swimming pool use. Rapid and definite diagnosis and treatment are crucial to patients' survival and preservation of the eye globe.

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Chronic pulmonary aspergillosis – diagnosis and management in a resource-limited setting

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Chronic pulmonary aspergillosis (CPA) is a long-term lung infection that is progressive and incurable.[1] It is caused by the same pathogens of the acute form of the disease, mainly *Aspergillus fumigatus* and, less frequently, *A. niger* and *A. flavus*; however, the 2 forms of the disease have different pathologic pathways.[2] Untreated CPA may result in fibrosis and death.

CPA affects more than 3 million individuals worldwide.[3] Of these patients, approximately 1.2 million have a history of tuberculosis (TB) infection. This is of particular importance in Asia, as the majority of patients with active or residual TB are in India, China and Indonesia.[4]

Pathogenesis of CPA

CPA arises from underlying conditions that accommodate cavity formation or cause tissue damage.[5] These prove to be fertile sites for the growth of *Aspergillus*. *Aspergillus* destroys lung tissue, which is further worsened by the production of proteolytic enzymes, toxins and other metabolites. The following underlying conditions are risk factors of CPA[6]:

- Deterioration in local and systemic defenses against infection due to alcohol and tobacco abuse, and diabetes
- Presence of cavity due to bronchopulmonary disease such as active/residual TB, bronchial dilatation, sarcoidosis or chronic obstructive pulmonary disease
- Prolonged use of low-dose oral or inhaled corticosteroids
- Absence of or presence of very little vascular invasion

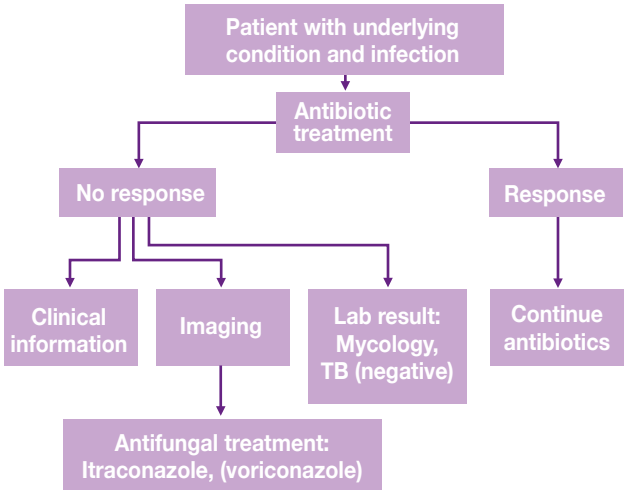
Signs and symptoms of CPA

Symptoms of CPA are often similar to that of other chronic infections, therefore, imaging and mycology investigations are important in supplementing clinical presentation when making a diagnosis. Symptoms commonly last more than 3 months and include weight loss, fatigue, cough, hemoptysis and breathlessness. Chest X-ray shows presence of at least 1 cavity or nodules in early stage CPA. The precipitin test is a key diagnostic test that detects the presence of antibodies against *Aspergillus* in bodily fluids.

Management in a resource-limited setting

In centers with limited resources, diagnosis of CPA can be made based on the clinical presentation. It is crucial to obtain an accurate history of underlying conditions to determine the likelihood of CPA. Conventional mycology tests can also be used to aid diagnosis; however, sensitivity and specificity, contamination and colonization issues should be considered when interpreting test results. Treatment can be initiated with antibiotics and the response observed (Figure 3). Itraconazole is the widely used antifungal agent for invasive infections such as aspergillosis, as well as for superficial infections. The widespread use of this agent has unfortunately led to the emergence of strains resistant to itraconazole.

Figure 3. Treatment algorithm for CPA in a resource-limited setting



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Outbreak of superbug *Candida auris*: Asian scenario and interventions

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Candida auris was first described in 2009 following isolation of the pathogen from the external ear canal of a patient in Japan; identification of the pathogen was only possible by sequencing the organism's genome.[1] It was soon detected in Korea[2] and, in less than a decade, emerged in all 5 continents of the world.[3,4] Its multidrug-resistant clonal strains that appear to be nosocomially transmitted is reason for concern.

The prevalence of *C. auris* infections remains inconclusive. A study in India which analyzed samples of patients from 27 intensive care units reported a prevalence of 5.3%.[3] Further analysis to ascertain unique features of *C. auris* revealed the following risk factors[5]:

- Admission to a public hospital
- Underlying respiratory illness
- Vascular surgery
- Prior antifungal exposure
- Multiple interventions

The authors concluded that patients with sepsis, undergoing invasive management for longer durations and exposed to antifungal agents should be investigated for *C. auris* candidemia.[5]

Characteristics of *C. auris*

C. auris is commonly misidentified as other species because of the lack of a reference database for several laboratory commercial phenotypic systems. Currently, accurate identification can be performed using matrix assisted laser desorption ionization time-of-flight mass spectrometry (MALDI-TOF MS)[6] following a database update, as well as with DNA sequencing.[7] *C. auris* may be suspected by its growth at 42°C but not in the presence of 0.01% or 0.1% cycloheximide.[8] Another phenotypic feature of the pathogen is its ability to ferment dextrose, dulcitol and mannitol.[9] However, the isolate can only be confirmed by sequencing.

In vitro properties of *C. auris* include the following:

- Thermotolerance, with optimal growth at 37°C and viability up to 42°C, and salt tolerance[8]
- Adheres to polymeric surfaces, forms biofilms and resists antifungal agents[9]
- Significantly thinner biofilm compared with other *Candida* species[10]
- Minimal ability to adhere to silicone elastomer relative to *C. albicans*[10]

Studies from Public Health Laboratory, UK, have found that *C. auris* presents in 2 types, aggregate-forming and non-aggregate–forming isolates.[11,12] The non-aggregative isolates were found to be more pathogenic than the other type and has better biofilm-forming capability. A study also found *C. auris* to be more virulent than other key pathogenic non-*albicans Candida* species but comparable to that of *C. albicans*.[11] However, an unpublished study showed higher biofilm formation in non-aggregative *C. auris* compared with *C. albicans*, suggesting variation in properties that is yet to be understood.

Multidrug resistance in *C. auris*

C. auris is inherently resistant to all classes of antifungal agents, with alarmingly high rates of mortality and therapeutic failure reported worldwide.[13] Recent reports show extremely high resistance to fluconazole and elevated MIC against voriconazole, as well as against other drugs (Figure 4).[3,14,15]

Figure 4. Drug resistance in *C. auris* in Asian countries

Fluconazole	90% resistant
Voriconazole	Elevated minimum inhibitory concentration (MIC) in 50% of isolates
Amphotericin B	Variable susceptibility; 15–30% of the isolates exhibit high (>2 µg/mL) MICs
Echinocandin	2–8% resistant
Multidrug resistant	50% resistant to ≥2 antifungal classes
All classes resistant	4%
Indian intensive care units	Fluconazole, 58.1% (resistant); amphotericin B, 13.5%; caspofungin, 9.5% (high MIC); 16.2% multidrug resistant

Treating *C. auris* infections

At present, no consensus exists on the optimal treatment of *C. auris* candidemia. Echinocandins remain as first-line therapy, however, caspofungin has been shown to be inactive against *C. auris* biofilms. Flucytosine may be used for renal or urinary tract infections, whereas posaconazole and isavuconazole have shown excellent in vitro activity against *C. auris*. New drugs SCY-078 and pulmocide are anticipated to exhibit potent antifungal activity against *C. auris* isolates.

Prevention and control of outbreak

Surveillance of *C. auris* colonization in an Indian hospital showed that by Day 4, all patients in the ICU were colonized although none were at the time of admission. Persistence of *C. auris* in the hospital environment were mainly observed in the hands of healthcare workers, equipment such as ventilator, temperature probes and echocardiography leads, as well as bed surfaces, blankets and linen. Decontamination was successful using chlorhexidine body wash, oral nystatin tablets, and hand washing with soap and water and various disinfectants, however, success depended on the use of correct methods and sufficient exposure time of the agents to the infected surfaces.

Red flags of *C. auris* candidemia

In summary, *C. auris* infection should be considered in patients in the ICU or high-dependency units, those who have been transferred from another hospital following a long stay, and patients receiving multiple interventions and with prior antifungal exposure. Additionally, the identification of the pathogen as other *Candida* species via a commercial system and finding that the pathogen appears to be resistant to fluconazole and exhibits high MIC to voriconazole are also red flags of *C. auris* infection.

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New risk factors for invasive aspergillosis: How to suspect and manage

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Primary host factors that should arouse suspicion for IA include recent history of neutropenia, receipt of allogeneic stem cell or solid organ transplantation, prolonged use of corticosteroids and immunodeficiency.[1,2] These criteria are meant to ensure a fairly homogenous population for inclusion in clinical trials. Nevertheless, the absence of any of these host factors should not be reason to withhold antifungal therapy in patients with clinical, radiological and/or mycological data suggesting IA.[1]

Other clinical circumstances that point to IA

The *Asp*ICU diagnostic criteria[3] stemmed from the *Asp*ICU study[4] that revealed IA in critically ill patients without any malignancy. The authors found that 77% of patients in the cohort were not classifiable by the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) criteria, paving the way for the development of the *Asp*ICU diagnostic criteria according to 3 categories, namely, proven, putative and colonized. Among the underlying diagnoses in proven/putative cases are chronic obstructive pulmonary disease (COPD), liver disease and alcohol abuse.

Defenses against *Aspergillus*

T-cell immunity and Th1 response are important for protection against *Aspergillus*, which is among the most prevalent airborne pathogens worldwide.[5] In the immunocompetent individual, several of the body's defense mechanisms line up to defend the body against this ubiquitous pathogen:

- The mucociliary tree prevents most *Aspergillus* conidia from reaching the alveoli
- Alveolar macrophages play a major role in the phagocytosis and killing of the pathogen
- Recruited polymorphonuclear leukocytes are able to ingest and kill conidia not previously killed by macrophages

In patients with sepsis, an immunoparalysis state characterized by both innate and adaptive immunodysfunction is induced, resulting in ineffective clearance of septic foci, increased vulnerability towards secondary infections and reactivation of latent infections, leading to death.[6]

Unconventional risk factors

Various studies and case reports have highlighted other risk factors that may indicate IA (Figure 5).[1] These include patients with COPD on steroids (particularly with isolation of *Aspergillus* in respiratory secretions), hepatic failure and severe influenza. Additionally, in patients who do not meet the consensus criteria for host factors, it is also probable that 2 or more risk factors may precipitate the occurrence of IA.

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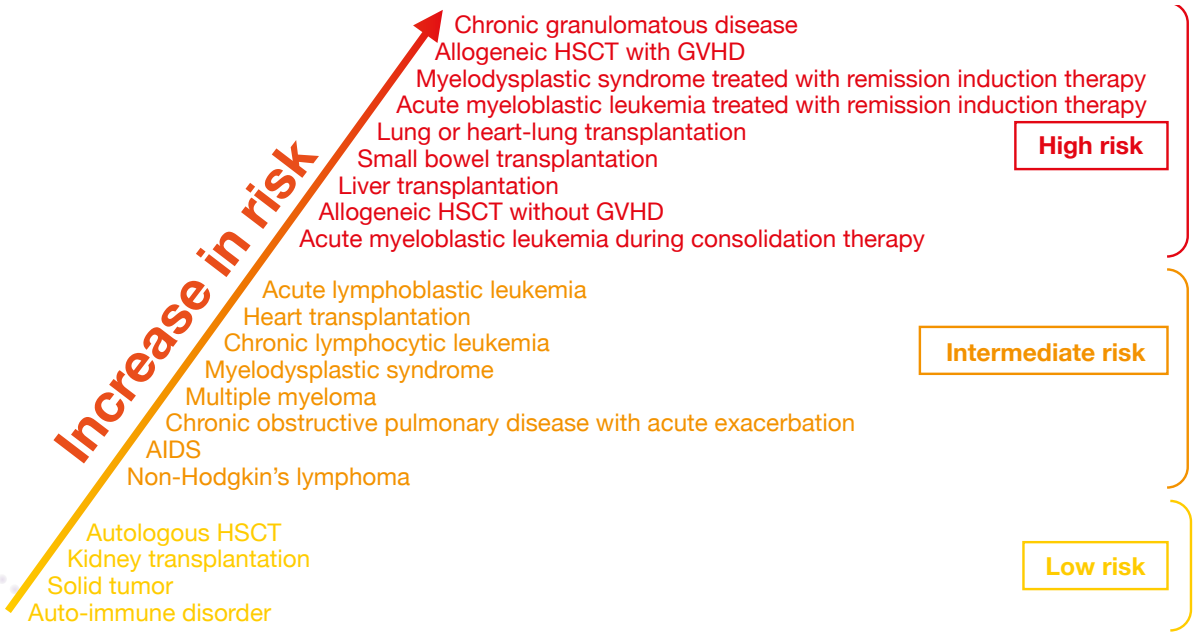
Figure 5. Risk of IA based on primary host factors[1]



HSCT, hematopoietic stem cell transplantation; GVHD, graft-versus-host disease

Antifungal prophylaxis: Whom, what and when

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Invasive fungal disease causes substantial morbidity and mortality, largely due to difficulty in obtaining a timely diagnosis that has been attributed to limitations of available diagnostic tests. This further causes delays in treatment initiation, suboptimal response to treatment and the use of substantial resources. These factors form the rationale for antifungal prophylaxis administration. However, debates regarding the universal systemic primary prophylaxis remain due to resistance, toxicity and cost considerations.

Cost-effectiveness

Primary prophylaxis has been proven to be cost-effective in selected high-risk patients with hematologic malignancies. A network meta-analysis and pharmacoeconomic analysis of 21 randomized controlled trials evaluating triazole prophylaxis showed that, overall, posaconazole was superior in reducing IFI and all-cause deaths among patients receiving chemotherapy for acute myelogenous leukemia (AML) and was considered cost-effective.[1] Itraconazole solution, on the other hand, was least costly, particularly as prophylaxis in the AML cohort; however, this needs to be weighed against the efficacy and tolerability of the agent.

The right patient and right prophylaxis

Prophylactic strategy should be individualized based on risk-benefit assessment at each hospital, or, even for each patient, after considering factors such as, epidemiology, diagnostic tools, therapeutics and cost-effectiveness. Neutropenia remains the most important risk factor for IFI,[2] while others include underlying conditions such as graft-versus-host disease and progressive cancer, immunogenetic factors and environmental factors.

The selection of a prophylactic agent should be based on knowledge of the host, the antifungal agents and the strategies available (Table 3).[3] Consideration should be given to the efficacy, bioavailability, toxicity, drug-drug interaction, compliance and cost.

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Table 3. Selection of primary antifungal prophylaxis

Diagnosis or status of the hosts	Primary	Alternative	Comments
AML and MDS patients receiving induction chemotherapy	Nystatin (S/L)	Posaconazole (S/H) Itraconazole (W/H) Fluconazole 50–400 mg (W/H) AmB-d (W/H)	Clinical trials for fluconazole showed various results.
Allogeneic HSCT, initial neutropenic phase	Nystatin (S/L) Fluconazole 400 mg IV or po (S/H) Micafungin 50 mg (W/H)	Voriconazole 200 mg (4 mg/kg) bid po (W/H) Itraconazole (W/H) AmB-d (W/H)	
Allogeneic HSCT, GVHD phase	Nystatin (S/L) Posaconazole (S/H) Voriconazole (S/H)	Itraconazole (W/H) Fluconazole (W/H) AmB-d (W/H)	Prophylactic use of anti-mold agents is recommended in patients with severe GVHD under treatment with high-dose steroid or equivalent immunosuppressants.

AmB-d, amphotericin B deoxycholate; AML, acute myeloid leukemia; bid, twice a day; IV, intravenous; GVHD, graft-versus-host disease; HSCT, hematopoietic stem cell transplantation; MDS, myelodysplastic syndrome; po, orally
Grading: S/H, strong recommendation, high-quality evidence; S/L, strong recommendation, low-quality evidence; W/H, weak recommendation, high-quality evidence

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