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# NEWSLETTER
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## Editors' welcome

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In this latest issue of our newsletter, we would like to turn your attention to some of the highlights at the last Medical Mycology Training Network (MMTN) Conference, held in Ho Chi Minh City, Vietnam (1–3 December 2017).

This recent conference in Ho Chi Minh City brought together a panel of international and regional mycology experts. We covered a broad range of topics from the recent updates on antifungal agents to the management of fungal infections. More than 60 delegates from Vietnam and Malaysia attended the conference. The delegates had the chance to attend workshops facilitated by our esteemed international experts.

It is our pleasure to present this issue featuring highlights from the plenary forums, topical sessions and case workshops. We are also pleased to share with you highlights from the case studies presented by Dr Atul Patel and Dr Methee Chayakulkeere. Both Dr Patel and Dr Chayakulkeere shared their experience in the management of challenging cases from their respective countries with focus on aspergillosis and histoplasmosis.

Do check out our official website, www.AFWGonline.com, or drop us a message on Facebook, Instagram or LinkedIn to find out more about our exciting educational activities. Thank you for your support!

# Know your fungal landscape in Vietnam

**Professor Jeremy Day**
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There are an estimated 2 million life-threatening infections due to invasive fungal infections every year, and more than 90% of these are due to 4 species – *Candida*, *Cryptococcus*, *Aspergillus* and *Pneumocystis*.[1] Immunosuppression and co-morbidities play a significant role in the risk of developing these infections. In Vietnam, tuberculosis, HIV infection, and air pollution are key drivers for fungal infections. A study to estimate the burden of fungal infection in Vietnam offered new insights into the prevalence of AIDS-associated mycoses, aspergillosis and candidiasis.[2] In the study, the authors used an actuarial approach to estimate the prevalence of fungal diseases based on the population structure of Vietnam, available incidence and prevalence data from literature.[2]

The estimated incidence and prevalence of selected fungal infections seemed to be lower compared to several countries; Professor Day noted that the numbers may be underestimated due to a lack of high quality data.[2-5] If anything, this study raised more questions about the large unrecognized burden of disease, which warranted further epidemiological research.

## Clinical pearls

- Fungal infections are a growing concern in Vietnam
- Possible causes include more sophisticated medical treatment and increased pollution
- There is an urgent need to improve fungal diagnostics and fungal infection reporting in Vietnam

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# Management of cryptococcosis and penicilliosis

**Professor Jeremy Day**
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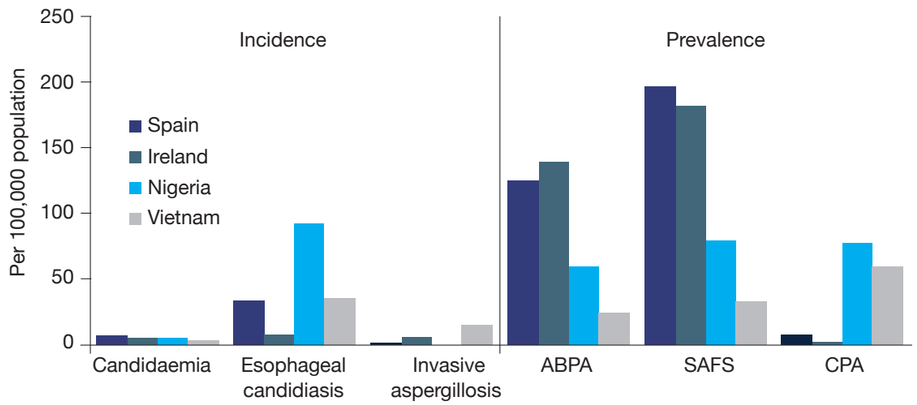
## Cryptococcal meningitis

The global incidence of HIV-associated cryptococcal meningitis is estimated to be around 223,100 cases per year, resulting in 181,000 deaths.[1] Few drugs are available for treatment and many have poor efficacy presented with toxicities. Combination antifungal therapy is the recommended treatment for cryptococcal meningitis.

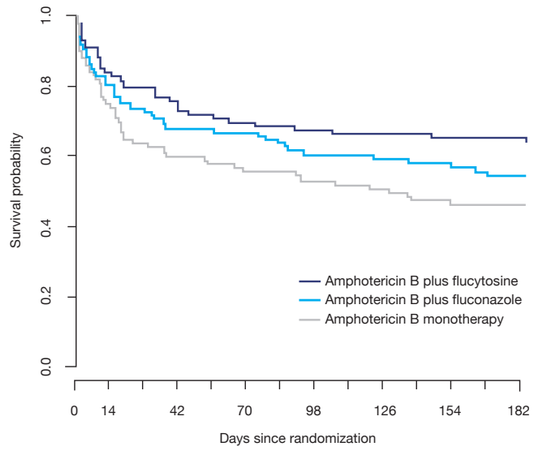
Previous data from a randomized controlled trial conducted in Vietnam showed that amphotericin B plus flucytosine was associated with improved survival compared with amphotericin B alone (15 vs 25 deaths at day 14; hazard ratio [HR]: 0.57; p=0.08; and 30 vs 44 deaths at day 70; HR: 0.61; unadjusted p=0.04) (Figure 2).[2] This combination also resulted in faster yeast clearance from cerebral spinal fluid (CSF) than amphotericin B monotherapy or amphotericin B combined with fluconazole 800 mg/day. Rates of adverse events were similar across both groups. Access to both amphotericin B and flucytosine has the potential to reduce the mortality of HIV-associated cryptococcal meningitis. In contrast, combining fluconazole with amphotericin B for 2 weeks offered no survival benefit compared with 4 weeks of amphotericin B monotherapy. The rate of CSF fungal clearance is associated with the survival outcome; this measure has utility in evaluating novel antifungal treatment regimens, but trials powered to important clinical endpoints are still needed. Recently, the Antifungal Combinations for Treatment of Cryptococcal Meningitis in Africa (ACTA) trial has been published, which has demonstrated the key role that flucytosine can play in delivering more efficacious oral treatment and allowing shortened durations of amphotericin therapy.[3]

Figure 1. Incidence and prevalence of selected invasive mycoses, selected countries[2-5]



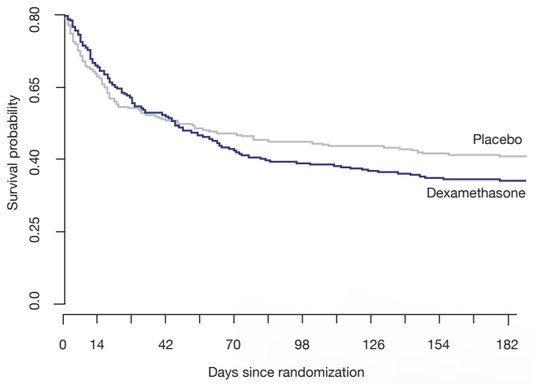

ABPA, allergic bronchopulmonary aspergillosis; SAFS, severe asthma with fungal sensitization; CPA, chronic pulmonary aspergillosis

Figure 2. Kaplan-Meier survival estimates according to treatment groups[2]




Professor Day also presented the results of the CryptoDex trial of adjunctive treatment with dexamethasone in HIV associated cryptococcal meningitis.[4] In this trial, patients were randomized to dexamethasone or placebo for 6 weeks, in addition to best available antifungal treatment.[4] The mortality rate was 57% vs 49% by 6 months, respectively (HR: 1.18; p=0.20) (Figure 3). Patients in the dexamethasone group also experienced higher risk of death or disability compared with placebo with 13% vs 25% having pre-specified good outcomes (odds ratio [OR]: 0.42; p<0.001). The use of dexamethasone is harmful and should not be given as an adjunctive treatment.

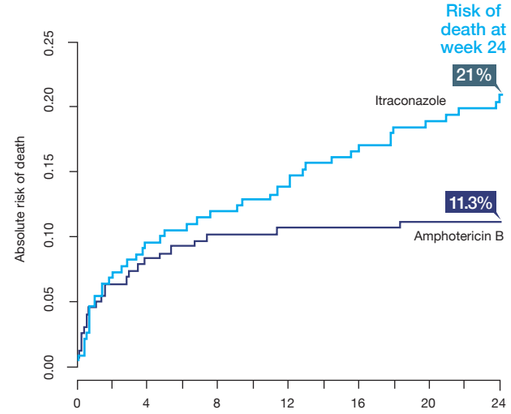
Figure 3. Kaplan-Meier survival estimates during the 6 months follow-up[4]




## Talaromycosis (penicilliosis)

Talaromycosis infection is a common cause of HIV-related deaths in Asia. The American and British treatment guidelines recommend initial treatment with amphotericin B followed by itraconazole.[5,6] This regimen is based on a non-comparative trial conducted in Thailand that showed 97% treatment response in 74 patients.[7] A non-inferiority trial comparing amphotericin B and itraconazole demonstrated lower risk of death with the former at week 24 (11.3% vs 21%; p=0.006) (Figure 3).[8] Amphotericin B also resulted in significantly faster fungal clearance and clinical resolution compared with itraconazole. However, more patients experienced anemia and electrolyte disturbances. Based on the outcomes of this trial, amphotericin B must be considered the treatment of choice for talaromycosis.

Figure 4. Estimated risk of death at week 24 in patients receiving itraconazole vs amphotericin B for HIV-associated talaromycosis[8]




## Clinical pearls

- Combination of amphotericin B and flucytosine for 2 weeks is the gold standard for cryptococcal meningitis induction treatment
- Dexamethasone should not be given as an adjunctive treatment for cryptococcal meningitis due to poor outcome, increased adverse events and disability
- Amphotericin B is superior to itraconazole and should be considered as induction therapy for talaromycosis

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# Management of fungal infections in high-risk patients

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Immunocompromised patients are at risk of IFI that can result in death. Dr Tan's presentation discussed different strategies for the treatment of IFI in high-risk patients experiencing prolonged febrile neutropenia.

## Empirical approach

In the late 1980s, it became obvious that clinical examination and cultures were not sufficiently sensitive for early detection of IFI. Two pivotal clinical trials demonstrated that the early introduction of antifungals could reduce the frequency of IFI in febrile neutropenic patients,[1,2] leading the Infectious Diseases Society of America (IDSA) to recommend this strategy in their practice guidelines.[3] This strategy is known as the empirical approach. Experts today feel that these studies were underpowered, used prophylaxis of dubious value, and did not prove their primary hypothesis.[4]

## Diagnostic-driven (pre-emptive) approach

With improved diagnostics, patients can be treated using the diagnostic-driven approach. In this approach, antifungal therapy is initiated when patients exhibit clinical evidence of IFI. Hence, antifungal treatment and its side effects are obviated in a proportion of patients. As one nonrandomized prospective study found, a diagnosis-driven approach reduced the use of antifungals from an estimated 35% to 7.7%.[5] In this study, patients received antifungal therapy after they had a positive result from the *Aspergillus* galactomannan assay or a computed tomography (CT) scan.

In a head-to-head study, patients were randomized to either a standard diagnostic strategy (based on culture and histology) or a biomarker-based diagnostic strategy (*Aspergillus* galactomannan and polymerase chain reaction [PCR]) to direct antifungal treatment. There were fewer patients who received antifungal therapy in the biomarker-based group compared with the standard diagnosis group (15% vs 32%; p=0.002) (Table 1).[6] Another group of investigators explored the diagnostic-driven approach, giving antifungal therapy to selected patients with persistent febrile neutropenia. In this study, the overall sensitivity, specificity and negative predictive value (selecting patients who do not need antifungal therapy) for this approach were 100%, 52.4% and 100%, respectively.[7] These results indicated that the diagnostic-driven approach is useful for identifying patients who are not likely to develop IFI and therefore do not require antifungal therapy. These findings have a clinical and economic impact on the treatment strategy and continue to be a subject of debate and investigation.

## Posaconazole prophylaxis

Posaconazole is a triazole antifungal drug that is used to treat IFI caused by *Candida* and *Aspergillus*. Posaconazole is recommended by the IDSA as an antifungal prophylactic against invasive aspergillosis.[8] Although posaconazole. is an effective prophylaxis, a consistent proportion (about 30%) of patients still require subsequent systemic antifungal treatment.[9] A prospective study investigated the impact of posaconazole prophylaxis on subsequent antifungal treatment strategy.[9] Among patients who received posaconazole prophylaxis and needed systemic antifungal treatment, an empirical approach was utilized in 80% of the patients, a pre-emptive approach in 15% of the patients and targeted treatment in 5% of the patients. There was no difference in IFI-attributable mortality between the empirical and pre-emptive approach (25% vs 21%; p=0.2). The study concluded that posaconazole prophylaxis did not modify the efficacy of subsequent systemic antifungal used, regardless of the treatment approach.

## Costs: Empirical vs diagnostic-driven

Diagnostic-driven treatment is not inferior to empirical treatment in terms of survival.[10] Hence cost might be a consideration. According to a study, the reduced use of antifungal agents contributed to the lower cost of the diagnostic-driven strategy compared with an empirical approach (£1,561.29 vs £2,301.93).[11] In addition, more patients are able to avoid the adverse effects caused by antifungal treatment. These results suggested that the diagnostic-driven approach may provide cost-savings for high-risk patients who are neutropenic and have persistent fever.

**Table 1. Comparison of outcomes for standard versus biomarker-based diagnostic strategy to direct antifungal treatment in high-risk hematology patients[6]**

| | Standard diagnosis group (n=122) | Biomarker-based diagnosis group (n=118) | p |
|---|---|---|---|
| Received antifungal therapy | 32% | 15% | 0.002 |
| Probably invasive aspergillosis | 0 | 14% | 0.0001 |
| Mortality | 15% | 10% | 0.31 |
| Invasive aspergillosis-related mortality | 15% | 10% | 0.30 |
| Hepatotoxicity | 17% | 10% | 0.11 |
| Nephrotoxicity | 43% | 51% | 0.20 |

### Clinical pearls

- Both the empirical and diagnostic-driven approaches are common antifungal treatment strategies for high-risk patients
- In the empirical approach, patients are given antifungals based on the fever trend
- In the diagnostic-driven approach, diagnostic assays and CT scans are used to trigger antifungal treatment
- There is a potential for overtreatment of non-fungal fever, resulting in increased toxicity and costs with the empirical approach

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# Case challenge 1: Invasive infections in a patient with sarcoidosis

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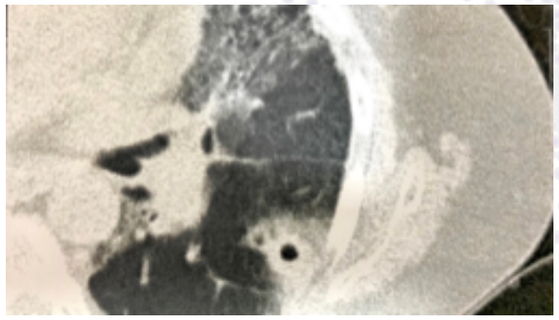
A 49-year-old female patient was previously diagnosed with sarcoidosis and interstitial lung disease, and has been receiving steroids for her medical condition over the last 15 years. She previous received empirical anti-tuberculosis treatment but has stopped after a few months due to adverse drug reaction. Pulmonary function test showed severe restriction with diffusion defects. Two-dimensional echocardiography and antinuclear antibody were normal. High-resolution chromatography showed end-stage fibrotic changes in bilateral lung parenchyma with honeycombing, secondary bronchiectasis in bilateral upper and lower lobes.

## Clinical presentation

Earlier in June 2017, the patient was admitted to the hospital with fever, worsening respiratory symptoms and peripheral cyanosis. She had a total leukocyte count (TLC) of 16,200 and a galactomannan reading of 1.36. Her bronchoscopy appeared normal. *Aspergillus fumigatus* was identified in her bronchoalveolar lavage fluid. She was started on itraconazole 200 mg/day but had no clinical response.

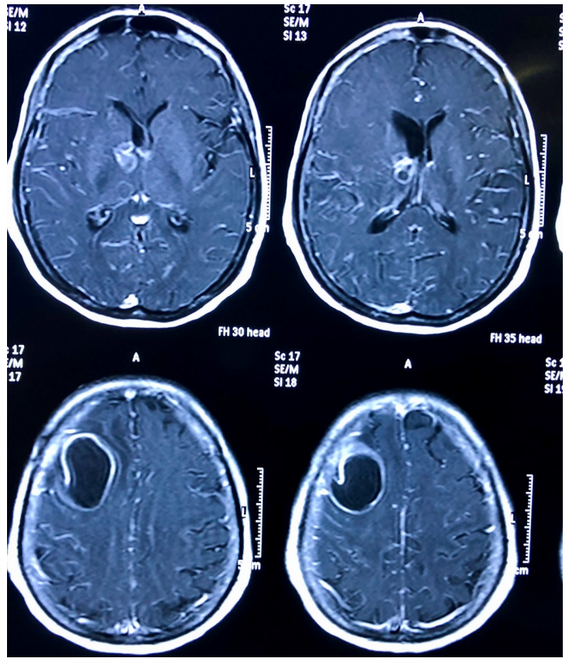
The patient went to consult another pulmonologist. Two-dimensional echocardiography showed left ventricular ejection fraction at 55% and right ventricular systolic pressure at 11 mmHg signaling moderate to severe pulmonary hypertension. The patient was tested negative for anti-cyclic citrullinated peptide. Repeat CT scan of the thorax revealed thick-walled cavity with a surrounding halo sign in left lower lobe (Figure 5). Since she was diagnosed with invasive aspergillosis, her antifungal was changed to voriconazole 200 mg BID.

**Figure 5. CT scan of the thorax showed thick-walled cavity with a surrounding halo sign in left lower lobe**



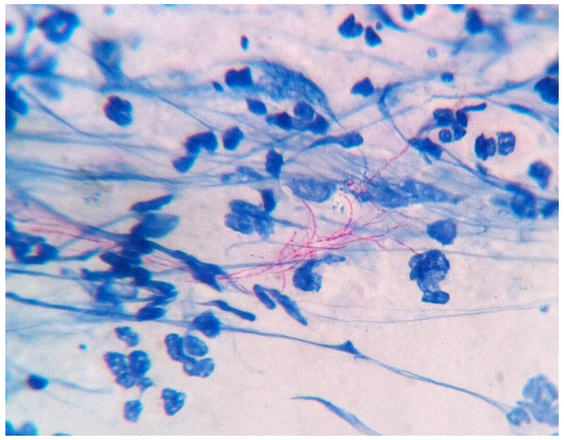
In October 2017, the patient was admitted to the emergency room with fever, headache and an episode of convulsion on the same day. Examination revealed the patient was drowsy but arousable and could follow verbal commands. She had tachycardia and hypoxia but was afebrile. She was anemic with a hemoglobin level of 10.7 g/dL, and TLC was 16,600. She had a pro-brain natriuretic peptide value of 1,419 pg/mL and elevated C-reactive protein of 4.5 mg/L. Her liver enzymes were normal and no abnormalities were detected in her chest X-ray and ultrasound. Neurological reference advised a CSF examination and a magnetic resonance imaging (MRI) of the brain. CSF examination reported the following: glucose 68mg/dL; protein: 105mg/dL; white blood cell count 120/cmm with 20% neutrophils and 80% lymphocytes. No organism was detected on Gram or Ziehl-Neelsen stain. CSF cryptococcal antigen and CSF GenXpert MTB/RIF assays were negative; CSF adenosine deaminase level was 3.38 and CSF galactomannan test yielded 4.06. The MRI showed an abscess in the left frontal parietal region. Contrasts also showed multiple lesions located at the basal ganglia region (Figure 6). Serum IgG antibodies against toxoplasma was negative.

Figure 6. MRI with contrast showed a large abscess in the left frontoparietal region with multiple lesions located at the left basal ganglia region




Neurophysician suggested anti-tuberculosis therapy (isoniazid, rifampin, ethambutol, and pyrazinamide) with steroids. At this point, an infectious disease consultation was requested. The patient's history and treatment reviewed two important observations: 1) The patient experienced clinical deterioration with brain involvement after more than 6 weeks on voriconazole. 2) Voriconazole trough level were not measured. The infectious disease physician advised to stop anti-tuberculosis treatment and continued with voriconazole, requested voriconazole trough levels be measured and neurosurgical reference for draining the brain abscess. The patient was started with 2 g ceftriaxone injection every 12 hours and anti-seizure treatment. Direct microscopic examination of the sample from the brain abscess revealed partially acid-fast beaded filaments (Figure 7). Microbiological culture grew Nocardia farcinica, which was confirmed with matrix-assisted laser desorption/ionization time of flight (MALDI-TOF) mass spectrometry. Her voriconazole trough level was 5.72 mg/L. She was given ceftriaxone and trimethoprim/sulfamethoxazole for her nocardia infection and had a clinical response to the antimicrobials.

Figure 7. Direct microscopic examination of the brain abscess sample revealed partially acid-fast beaded filaments



## Discussion

The first important learning objective from this case was the selection of antifungal agent and dosage for a patient diagnosed with invasive pulmonary aspergillosis (IPA). Itraconazole, initially selected by the pulmonologist of this case, is generally not recommended as a first choice in the management of IPA due to erratic absorption and significant drug-drug interactions with acid-suppressing agents. Voriconazole is a treatment of choice for IPA. Cerebral aspergillosis is a likely possibility in an immunocompromised patient diagnosed with IPA. The second learning point is how one should evaluate disease progression on appropriate antifungal therapy for >6 weeks. This could be due to inadequate voriconazole trough level leading to treatment failure. Clinicians should check voriconazole trough levels in every patient with IFI because it is associated with high mortality. Brain abscess aspiration and microbiologic examination can confirm the diagnosis of CNS aspergillosis. CSF fungal biomarkers, eg, CSF galactomannan and β-D-glucan, are useful in making a diagnosis of CNS fungal infection in a situation where brain aspiration or biopsy is not possible.

Galactomannan detection is one of the microbiological criteria for the diagnosis of cerebral aspergillosis. CSF galactomannan with an optical density index (ODI) cutoff of 0.5 to 2.0 has high specificity and sensitivity (Table 2), and could be used to diagnose cerebral aspergillosis without needing cerebral biopsy.[1] β-D-glucan in cerebrospinal fluid is also a useful biomarker for the diagnosis of CNS fungal infections.[2]

**Table 2.** Diagnosis performance of galactomannan in CSF according to different cutoffs.[1]

| | Value (%) with CSF galactomannan ODI cutoff of | | | | | |
|---|---|---|---|---|---|---|
| Parameter | 0.5 | 1.0 | 2.0 | 3.0 | 4.0 | 5.0 |
| Sensitivity | 88.2 | 88.2 | 88.2 | 76.5 | 70.6 | 58.8 |
| Specificity | 96.3 | 96.3 | 96.3 | 96.3 | 96.3 | 96.3 |
| Positive predictive value | 93.8 | 93.8 | 93.8 | 92.9 | 92.3 | 90.9 |
| Negative predictive value 92.9 | 92.9 | 92.9 | 92.9 | 86.7 | 83.9 | 78.8 |

CSF, cerebral spinal fluid; ODI, optical density index



Monitoring trough levels for voriconazole may be important for patients who are not responding optimally or have drug interactions that may decrease voriconazole levels. Although voriconazole resistance is rising globally, lack of response is mostly due to significant drug-drug interactions and the variation in metabolism in patients with CYP2C19 polymorphisms.

### Clinical pearls

- Polymicrobial infections are common in immunocompromised patients
- Proper clinical, radiological and hematological evaluation with direct histopathological examination and culture are necessary for the accurate diagnosis of CNS aspergillosis
- Voriconazole is an effective therapy to treat IFI and trough levels have to be monitored to ensure optimal therapeutic levels are maintained

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# Case challenge 2: Diagnosis and monitoring treatment of histoplasmosis

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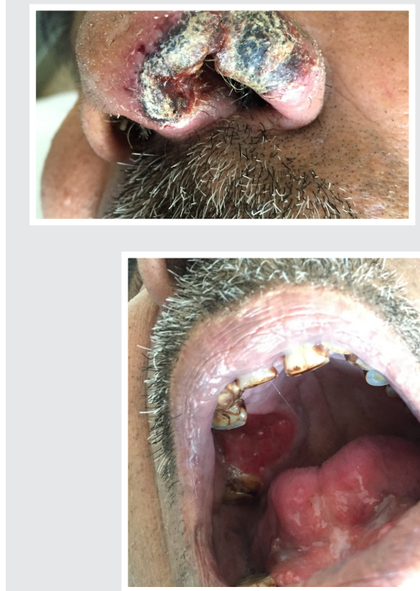
## Clinical presentation

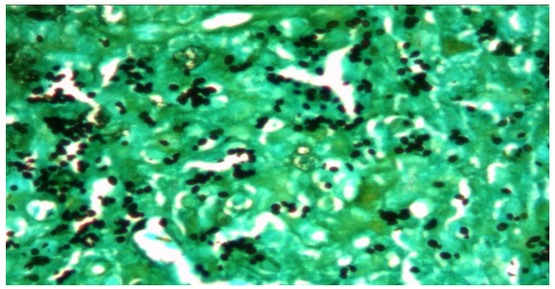
A 68-year-old patient with diabetes and chronic kidney disease was presented with fever, progressive nasal ulcer with crusting and painful palatal ulcer (Figure 8A). His work up for fever showed bilateral enlarged adrenal glands on abdominal CT scan. Biopsy from the palatal ulcer showed intracellular yeasts consistent with a diagnosis of histoplasmosis (Figures 8B & 8C). As *Histoplasma* antigen test was not available, a serum galactomannan test was conducted and yielded 3.48 ng/mL.

Figure 8. Clinical presentation of the patient with progressive nasal ulcer with crusting and painful palatal ulcer (A); and silver stain (B) and hematoxylin and eosin (H&E) stain (C) of the biopsy sample from the palatal ulcer

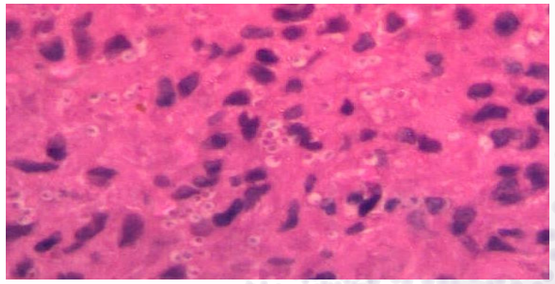
**A**



**B**

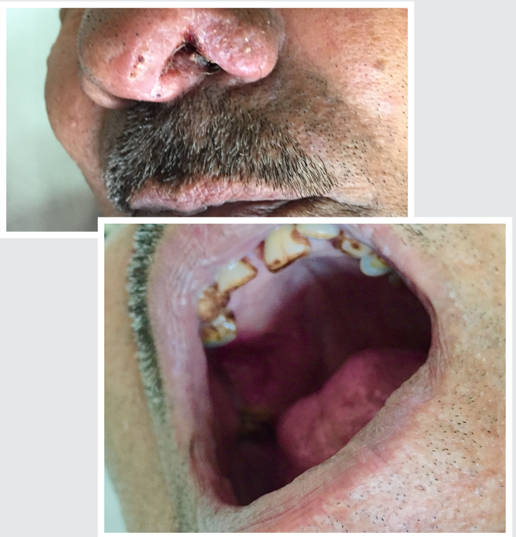


**C**



The patient was treated with oral itraconazole and had a good clinical response with marked regression in nasal and palatal ulcers (Figure 9) and a decrease in serum galactomannan level (2.48 ng/mL) after 6 weeks of therapy. The patient had complete clinical response after 7 months on antifungal treatment with further decrease of the serum galactomannan level to 1.45 ng/mL. His antifungal treatment was stopped at 9 months when the serum galactomannan level was at 0.68ng/mL. The patient had no sign of relapse 3 months follow-up after treatment completion. This case showed positive correlation of serum galactomannan levels with clinical response for histoplasmosis.

Figure 9. Marked regression in the nasal and palatal ulcers after 6 weeks on oral itraconazole therapy



### Discussion

The diagnosis of histoplasmosis is challenging as serological tests are not reliable, and culture is positive in only 50–70% and takes several weeks before it becomes positive.[1]

Detection of *Histoplasma* antigen from serum, urine and CSF is a sensitive and specific assay for diagnosing histoplasmosis but it is not available in many parts of world, including India. It may also be negative in localized diseases and only positive in progressive disseminated form of histoplasmosis. Histoplasmosis shares many clinical presentations and radiological features of tuberculosis, eg, fever of unknown origin, lymphadenopathy, adrenal gland enlargement, pulmonary nodules, etc. In regions of high tuberculosis prevalence, like India, histoplasmosis is generally not suspected. Diagnosis of histoplasmosis is generally made from the demonstration of intracellular yeasts in histopathological examination.

Positive *Aspergillus* galactomannan test can be used as a surrogate marker of *Histoplasma* infection. The minimum cutoff threshold for serum galactomannan to detect histoplasmosis is 0.4, giving a sensitivity of 82.1% and specificity of 100%.[2] False-positive results from *Aspergillus* galactomannan assay has been reported in solid organ transplant recipients with histoplasmosis.3 Cross-reactivity between *Histoplasma* antigen and *Aspergillus* galactomannan has also been described in an HIV-infected patient with histoplasmosis.4 Therefore, physicians need to differentiate the 2 disease entities, especially when it comes to treatment decision making. In countries where *Histoplasma* antigen assay is not available, the cross-reactivity between *Histoplasma* and galactomannan antigens could be helpful surrogate marker for making a diagnosis of histoplasmosis in appropriate clinical and laboratory settings.

### Clinical pearls

- Aspergillus galactomannan assay with a cutoff ODI of 0.4 can be used as a reliable surrogate marker to detect for histoplasmosis
- Decline in serum galactomannan correlates with clinical response in patient with histoplasmosis
- Cross-reactivity between *Aspergillus* galactomannan and *Histoplasma* antigen can lead to false-positive results especially in immunocompromised patients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# Case challenge 3: Treatment of a patient with disseminated histoplasmosis and tuberculosis with adrenal insufficiency


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### Clinical presentation

A 65-year-old man presented to the hospital with prolonged fever of 3 months. His underlying medical conditions included type 2 diabetes (managed with premix insulin twice a day), hypertension, coronary heart disease, dyslipidemia and cervical cord tumor with paraplegia. He complained of weight loss of 25 kg within the last 6 months. His test for HIV was negative.

Ultrasonography of the abdomen showed an oval-shaped, hypoechoic, right suprarenal mass (3.9x2.4 cm). CT scan of the abdomen showed lipid-poor masses at both adrenal glands with central necrosis (Figure 10A). There was no internal calcification or adjacent organ invasion. CT scan of his chest revealed enhancing mass at right upper lobe (RUL) with central necrosis, internal calcification and speculate border (Figure 11A). There was also multiple heterogeneous enhancing masses at the RUL intrapulmonary nodules and right middle lobe (RML) with interlobular septal thickening. The patient was suspected to have bronchogenic carcinoma with intrapulmonary, lymphangitic and adrenal metastases.

The patient developed hypotension, adrenal insufficiency and was tested positive for tuberculosis in the bronchoalveolar lavage fluid. He was diagnosed with disseminated tuberculosis and commenced treatment with isoniazid, rifampicin, ethambutol and pyrazinamide until the third week when anti-tuberculosis therapy was stopped due to elevated liver enzymes. He experienced adrenal crisis and was treated with hydrocortisone 100 mg intravenous (IV) push followed by 200 mg IV drip in 24 hours. He resumed anti-tuberculosis treatment (isoniazid, rifampicin and ethambutol) 11 days later.

He was admitted to the hospital again 2 months later for prolonged fever and low blood pressure (87/59 mmHg), complaining of nausea, vomiting and weight loss. He was treated with hydrocortisone 100 mg/day and meropenem 1g IV every 8 hours. Lung CT scan showed decreased mass in the RUL and diffuse centrilobular nodules at RUL and RML (Figure 11B). Abdominal CT scan showed enlarged bilateral adrenals (Figure 10B). Brain CT scan showed multiple ring enhancing hypodensity lesions at right occipital region, right temporal, left side pons and right cerebellum. Culture of the tissue biopsy at the right adrenal mass grew *Histoplasma capsulatum*. The patient was diagnosed with disseminated histoplasmosis. He was treated with amphotericin B at 0.7 mg/kg/day for 4 weeks then maintained with itraconazole (600 mg/day for 3 days followed by 400 mg/day for 12 months). The patient continued to receive IV hydrocortisone and fluid support throughout his antifungal treatment.

Figure 10. Abdominal CT scan showed increased bilateral adrenal mass. Taken on 26 July 2017 (A) and 13 October 2017 (B)

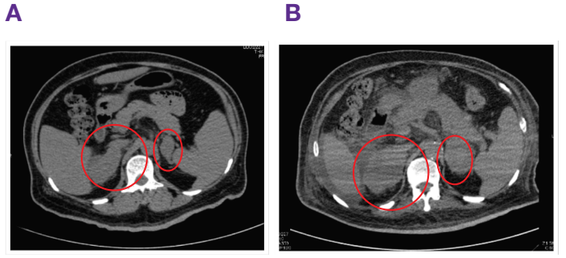
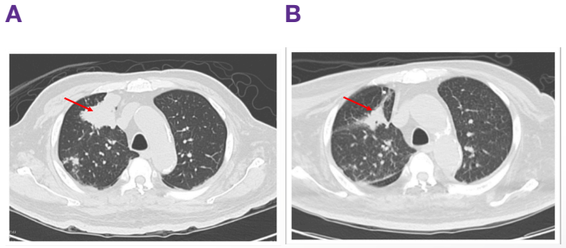



Figure 11. Lung CT scan showed RUL mass decreased after treatment. Taken on 26 July 2017 (A) and 13 October 2017 (B)




### Discussion

This case demonstrated the management of a patient with disseminated tuberculosis and histoplasmosis with adrenal insufficiency. Tuberculosis and histoplasmosis have similar symptoms.[1] Although these pathologies share certain similarities, there are clinical and laboratory differences. Differential diagnosis is important especially in Asian countries where both diseases are endemic. Disseminated forms of both diseases are rare but may occur in immunocompromised patients or patients with chronic medical conditions.[1]

Chest pain, cough and abnormal chest radiograph results are commonly associated with tuberculosis.[1] Conversely, abnormal imagery of the abdomen, in particular the enlargement of bilateral adrenal glands are more frequent in patients with histoplasmosis.[1,2] Differential diagnoses for both diseases can be further confirmed by culture results and PCR assays. They should be systematically tested without delay as a great number of patients with adrenal histoplasmosis may develop life-threatening adrenal insufficiency if untreated.[2]

### Clinical pearls

- Patients should be tested for tuberculosis and histoplasmosis in areas where both diseases are endemic
- Patient with adrenal crisis should be treated immediately with hydrocortisone while promptly investigating the etiology
- Patients with histoplasmosis are presented with bilateral adrenomegaly, which can be further confirmed by PCR and culture results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# Management of fungal infections in the ICU


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### The epidemiology of IFIs in Asia Pacific[1]

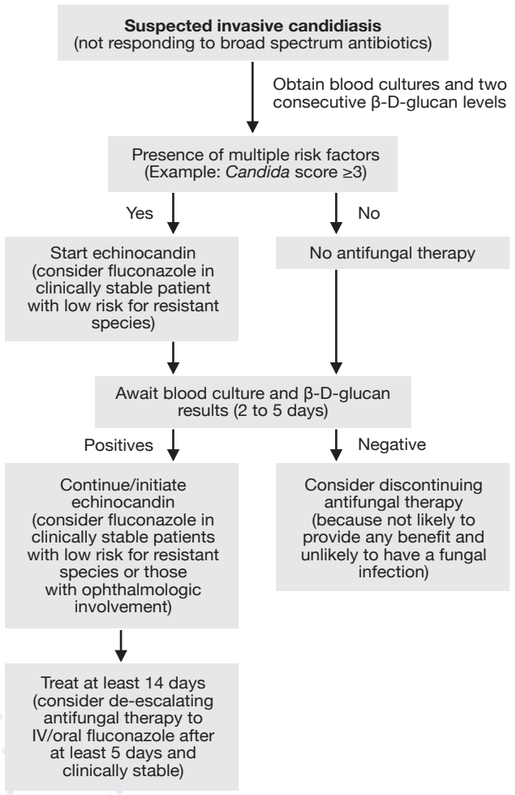
Invasive aspergillosis is the most frequently reported mold infection in immunocompromised individuals in Asia Pacific. Mucormycosis is rising in several countries, most notably in India. This opportunistic mold infection is associated with increase occurrence among patients with uncontrolled diabetes, and it is likely to continue given the rising prevalence of diabetes in the region. Hematologic malignancy, transplantation, trauma, burns, alcoholism, HIV infection and corticosteroid are also some of the predisposing factors for mucormycosis.

Candidiasis is the most common opportunistic yeast infection in Asia Pacific. Antifungal usage patterns, number of patients with catheters, age distribution and complex medical procedures are some factors that influence the incidence of the infection. Cryptococcosis occurs throughout Asia Pacific, predominantly affecting the respiratory tract and CNS in humans and animals after inhalation of the yeast. Eucalyptus, fig, and tamarind trees are natural habitat for the fungus. Cryptococcal infection is common in HIV-infected patients.

### Management of invasive candidiasis in the intensive care unit (ICU)

Candidiasis occurs in 50–70% of the critically ill patients.[2] Most patients who are admitted to the ICU are at risk of the fungal infection. There are scoring systems to assist decision making to treat fungal infections in the ICU.[3] However, certain scoring criteria may not be applicable to the local context and should be adjusted where possible. Understanding the incidence of candidiasis in the local healthcare setting and the availability of diagnostic methods in the facility are important factors to consider when adapting scoring systems. Diagnostic methods include blood culture and detection of fungal cell wall such as β-D-glucan via immunoassays, PCR and serology.[2,4] Blood cultures may detect 50–70% of *Candida* cases, missing patients with deep-seated candidiasis.[4] An easy-to-follow clinical pathway for invasive candidiasis can help to guide treatment (Figure 12).[3]

Figure 12. Treatment algorithm for invasive candidiasis.[3]




Patients should be assessed for their risk factors based on surrogate markers for invasive candidiasis and/or culture data.[5] Empirical antifungal treatment should be initiated immediately in critically ill patients with risk factors for invasive candidiasis with no other known cause of fever.[5,6] After 48–72 hours, patients should be re-evaluated to modify or discontinue antifungal treatment.[6] The IDSA recommends echinocandin treatment for non-neutropenic candidemia.[6] In addition to echinocandin, the Taiwan guideline recommends deoxycholate amphotericin B as a choice for primary antifungal treatment when other antifungal agents are not available (Table 3).[6] Amphotericin B is recommended for patients suspected with azole- and echinocandin-resistant *Candida* infections.[6] Fluconazole is an acceptable alternative for patients who are not critically ill and are unlikely to have fluconazole-resistant candidasis.[5]

Blood cultures should be performed after 48–72 hours of antifungal therapy and then every other day to establish the time point at which candidemia has been cleared.[6] Patients without obvious metastatic complications should continue treatment for 14 days after documented clearance of *Candidia* from the bloodstream and resolution of signs and symptoms attributable to candidemia.[6]

Patients with intra-abdominal candidiasis should receive the same treatment as non-neutropenic patients.[6] Central venous catheters suspected to harbor the source of candidiasis should be removed immediately in a safe manner in non-neutropenic patients.[5,6] This decision is considered on an individual basis for neutropenic patients.[5,6]

Disseminated candidiasis may cause endophthalmitis that can result in the loss of sight. Dilated ophthalmological examination is recommended within the first week of therapy in non-neutropenic patients to establish if endophthalmitis is present. Neutropenic patients should receive this examination on the first week after neutropenia recovery.[6]

**Table 3. Non-neutropenic empirical treatment for candidemia[5,6]**

| | Primary antifungal agents | Strength of recommendation |
|---|---|---|
| **IDSA guideline** | • Caspofungin<br>• Micafungin<br>• Anidulafungin | Strong recommendation; high-quality evidence |
| **Taiwan guideline** | • Deoxycholate amphotericin B | Strong recommendation; low-quality evidence |
| | • Echinocandin<br>• Fluconazole | Strong recommendation; high-quality evidence |

### Diagnostic and therapeutic options for mucormycosis and cryptococcosis

Mortality for mucormycosis is high.[7] This infection is diagnosed mainly using histopathology. Treatment includes amphotericin B and newer agents such as posaconazole and isavuconazole. Cryptococcosis treatment is tailored according to the immune status of the host, site of infection, access to healthcare facilities and availability of antifungal.[3] Patients with disseminated cryptococcosis and CNS disease should be given 2 weeks of induction therapy with amphotericin B and flucytosine. This is followed by 8 weeks of consolidation therapy with fluconazole and maintenance therapy to prevent recurrence in selected patients.[6]

#### Clinical pearls

- Most critically ill patients in ICU are prone to fungal infections, which are difficult to diagnose and treat
- Management of candidiasis should be individualized by assessing the risk factors of the patient and the response to current regimen
- Timely treatment with antifungal agents can reduce mortality rates

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# Genetic susceptibility of recalcitrant fungal infections

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Most fungal infections occur in the setting of the immunocompromised or immunosuppressive hosts. In the absence of these factors, fungal infections are normally mild, limited to the mucocutaneous surface.[1] However, when a fungal infection is recalcitrant and chronic, they may indicate genetic defects in fungal immunity.[1] Recalcitrant fungal infections are characterized by early onset of disease, commonly occurring in patients with no known immunocompromised conditions who are resistant to various systemic antifungal agents.[2]

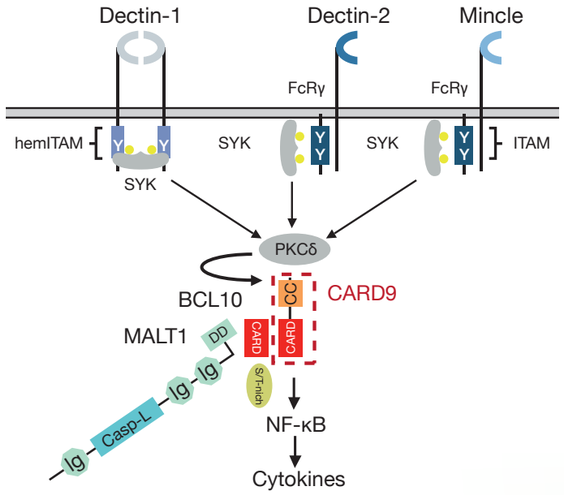
### *STAT1* gain-of-function mutations

Chronic mucocutaneous candidiasis (CMC) is characterized by susceptibility to *Candida* infections of the skin, nails and mucous membranes. Patients with Th17 deficiency are prone to CMC, suggesting a nonredundant role of the TH17 signaling pathway.[2] STAT1 is a major signaling molecule downstream of interferon receptor, which has a pivotal role in fungal immunity.[3] Gain-of-function mutations in the *STAT1* gene leads to defective Th17 response, which may explain the increased susceptibility to fungal infections.[4] Another fungal infection caused by *Fusarium solani* occurs early in patients who are recalcitrant to antifungal therapy.[5] Patients with this infection harbor a de novo missense mutation in the *STAT1* gene. Novel therapies for STAT1-related fungal infection include adding granulocyte macrophage colony-stimulating factor, hematopoietic stem cell transplantation or treatment with a JAK inhibitor such as ruxolitinib.[6,7]

### *CARD9* mutations

Clinical symptoms for phaeohyphomycosis caused by *Phialophora verrucosa* include persistent red plaques and nodules on the cheeks and faces.[8] *CARD9* is an adaptor protein that mediates the signaling pathway for NF-κB activation (Figure 14).[9] Distinct mutations in *CARD9* have been detected in patients with phaeohyphomycosis.[8] Genetic mutation in the *CARD9* gene may impair cytokine production in innate immune cells and the differentiation of Th17 cells.[8] Patients with *P. verrucosa* infection showed mark decreased in cytokines of Th17 cells and impaired immune response against the fungi. Animal studies have also demonstrated impaired Th17 responses associated with deficiency in CARD9, leading to susceptibility to multiple fungal infections. Specifically, *CARD9* knockout mice have impaired chemokines secretion and neutrophils recruitment against different dematiaceous fungi at the early stage of infection.[10]

Figure 13. CARD9 role in the NF-κB signaling pathway.[9]




#### Clinical pearls

- Clinical symptoms of CMC or cutaneous fusariosis may be explained by genetic defects in fungal immunity
- Mutation at the *STAT1* or *CARD9* genes may predispose to recalcitrant fungal infections indicative of diminished Th17 responses that are crucial for fungal immunity

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