Asia Fungal Working Group
NEWSLETTER | May 2016

Editors' Welcome

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We warmly welcome you all to the May 2016 issue of the Asia Fungal Working Group (AFWG) newsletter. This edition focuses on an ever-important mold infection, aspergillosis. Two cases complicating initial viral infections with unusual clinical backgrounds are shared with learning points emphasizing on risk factors and prompt recognition. An interesting article on fungal asthma is likewise presented. Finally, a drug summary on voriconazole, the recommended drug for invasive aspergillosis, is hereby conveyed, which will certainly be very helpful for the prescribing physicians.

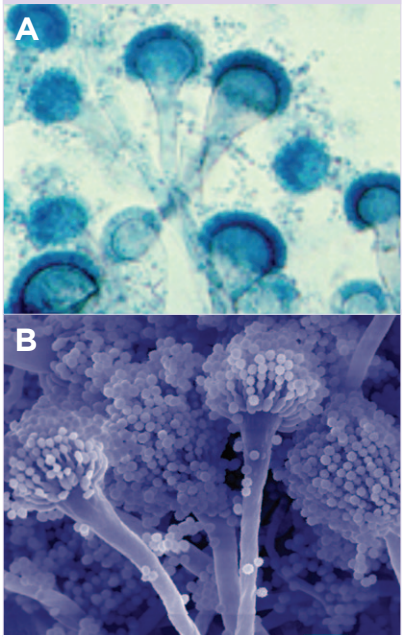
IN-FOCUS:

Aspergillus

Aspergillus, of which *A. fumigatus* is the most commonly isolated species, is an important etiology of life-threatening fungal infections in the immunocompromised population, including those with prolonged neutropenia, transplant recipients and HIV-afflicted patients with advanced disease. As cited in the 2008 Infectious Diseases Society of America (IDSA) treatment guidelines, aspergillosis causes patient afflictions that are classically defined as invasive (respiratory, central nervous system and other organs), saprophytic (otomycosis and pulmonary aspergilloma) or allergic (sinusitis and allergic bronchopulmonary aspergillosis [ABPA]).[1]

Diagnosis: Proven aspergillosis requires histopathological evidence of infection and a positive culture of a specimen from a normally sterile site. Probable aspergillosis requires fulfillment of criteria within 3 categories: host factors, clinical manifestations (symptoms, signs and radiological features), and microbiological evidence. Therefore, proven or probable infection requires the recovery of *Aspergillus*. However, there are 2 exceptions cited in the IDSA guidelines.[1] The first exception includes the fairly frequent occurrence of histopathological demonstration of hyphae consistent with *Aspergillus* species in patients with negative culture results. The other exception is the use of a surrogate non–culture-based method (ie, a positive galactomannan assay or (1-3)-β-D-glucan assay result and radiologically compatible CT findings) in an immunocompromised host with clinical findings of infection that constitute the definition of probable invasive aspergillosis.

***Aspergillus fumigatus* under (A) brightfield microscopy, with lactophenol cotton blue staining, and (B) scanning electron microscopy (x1,000)**



Images courtesy of Dr Ariya Chindamporn

Reference:
1. Walsh TJ, et al. *Clin Infect Dis* 2008;46:327-360.

Laboratory Diagnosis of Invasive Pulmonary Aspergillosis (IPA)

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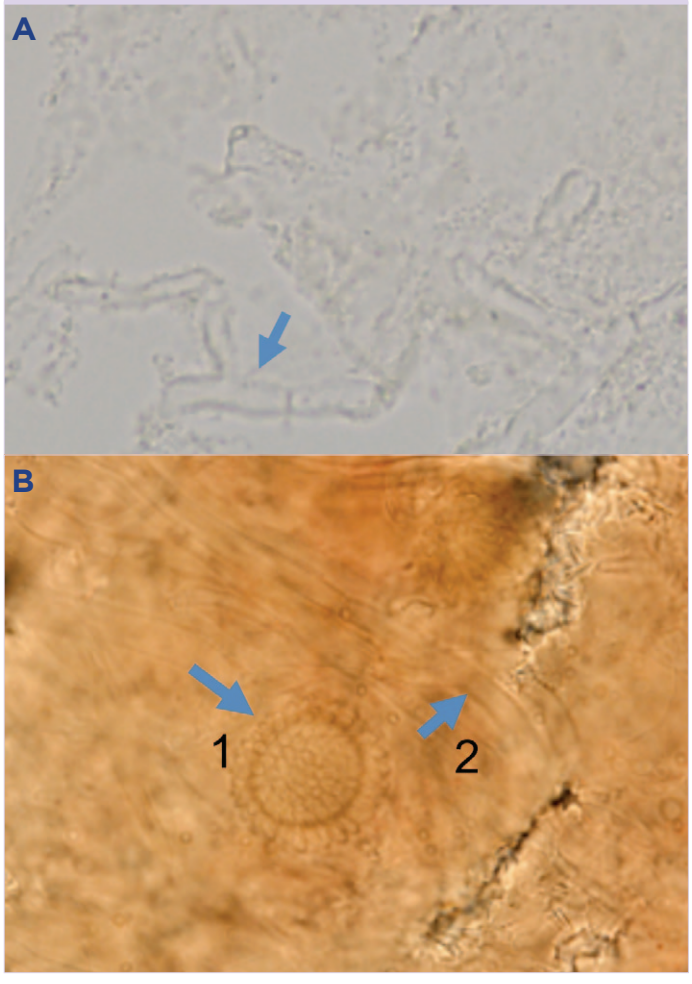
Like other fungal infections, direct examination, culture and non–culture-based methods including histopathology, serology and polymerase chain reaction (PCR) are the general protocols for laboratory diagnosis of aspergillosis. The recommended specimens are sputum, bronchoalveolar lavage (BAL), blood and tissue from biopsy.

Direct examination of any specimen by potassium hydroxide (KOH) preparation (Figure) and Gram stain are the priority for prompt information. However considering its natural distribution being practically everywhere, the presence of septate hyphae of *Aspergillus fumigatus*, is not significant for diagnosis. To obtain a strong documentation of infection, thorough investigation by collecting multiple specimens is recommended to increase the yield of positive cultures from multiple samples, especially from BAL.

Recently, aspergillosis has been found in both immunocompromised and immunocompetent hosts. Based on the 2016 European Respiratory Society (ERS) and the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) guidelines for the management of chronic pulmonary aspergillosis,[1] the key laboratory tests for respiratory specimens are direct examination, histopathology and fungal culture, with the last being the best diagnostic procedure. Furthermore, BAL specimen is recommended for patients with cavity or nodular pulmonary infiltration. PCR is another choice for laboratory diagnosis.

Galactomannan assay from paired samples of BAL or serum is a non–culture-based diagnostic test. The sensitivity and specificity of galactomannan testing in BAL sample is 77.2% and 77.0%, respectively, with the cut-off level of 0.4; and 85.7% and 76.3%, respectively, with cut-off level of >0.5. For serum galactomannan testing for the diagnosis of chronic pulmonary aspergillosis, the sensitivity and specificity rates are 66.7% and 63.5%, respectively (cut off level 0.7). Aside from the detection of galactomannan from the fungal cell wall, (1-3)-β-D-glucan is another component that can be examined as well. Even though positive results from these two assays are not definite indications of the fungus, negative results from these tests can provide strong evidence that the sample/specimen does not have non-septate hyphae.

Figure. Potassium hydroxide (KOH)-preparation of bronchoalveolar lavage sample showing (A) septate hyphae, and (B) phialide from the top view (1) and septate hyphae (2) (x400)



Images courtesy of Dr Ariya Chindamporn

Reference:
1. Denning DW, et al. *Eur Respir J* 2016:47:45-68.

Two-Hot-to-Handle: A Case of Severe Dengue Fever and Invasive Aspergillosis

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A 36-year-old Thai male, previously in good state of health, was admitted in a local hospital for diagnosis of dengue infection, based on a positive IgM serology. He initially presented with low-grade fever and malaise for 2 days. Three days later, he developed respiratory distress requiring intubation and he was subsequently transferred to Ramathibodi Hospital. Initial work up revealed massive left hemothorax, for which chest tube drainage was done. Dengue PCR was positive for dengue virus type 2 with a viral load of 7,000,000 copies/mL, 7 times higher than the level seen among the average infected population.

On the first hospital day, hemophagocytic syndrome was diagnosed, given the evidence of bicytopenia (anemia and thrombocytopenia), elevated ferritin >10,000 ng/mL and confirmatory bone marrow study findings. He received intravenous immunoglobulin but no corticosteroids or other immunosuppressive drugs.

On the fourth hospital day, screening for serum galactomannan by ELISA was positive (2.67; reference range 0-0.49 Ag Index). Micafungin was started as prophylaxis.

On the eighth day of the illness, a small faint round nodule was observed over the right upper lung field on chest radiograph and a repeat galactomannan test showed 2.50. A diagnosis of probable IPA was made. Antifungal therapy was switched from micafungin to amphotericin B deoxycholate. However, the pulmonary lesion continued to grow larger over time. Chest CT exhibited multiple pulmonary nodules with the largest measuring 3 cm in diameter, located in the right upper lobe. Bronchoscopy was performed and BAL galactomannan was 4.63 (reference range 0-0.49 Ag Index). Eighteen days later, BAL culture reported *Aspergillus terreus* with a minimum inhibitory concentration (MIC) of 0.075 to posaconazole. At this point, antifungal therapy was switched to voriconazole temporarily, and then to intravenous posaconazole once available, because of hepatotoxicity concern. Aside from a prolonged course of antifungal treatment, patient had likewise been adequately covered with courses of antibiotics for bacterial pneumonia and bacteremia.

Throughout the hospital course, the patient had persistent lymphopenia with peak CD4 count of 8 cells/mL (1%). His condition continued to deteriorate until he required left pneumonectomy for infection control. Apart from intravenous posaconazole, micafungin and flucytosine were added, aiming for synergistic effect. Despite therapeutic posaconazole levels in the plasma, pleural fluid and lung tissue, serum galactomannan continued to rise and peaked at 8.97 prior to his death.

Key learning points

In addition to prolonged neutropenia, treatment with chemotherapy and corticosteroid use, severe dengue infection has been reported to be an associated cause of invasive aspergillosis in some case series.[1] The potential explanation is the strong inhibition of nuclear factor-kB that is important for lymphocyte and neutrophil proliferation,[2] causing eventual reversal in the CD4/CD8 ratio.[3] Th2- type response with elevated IL-10 and IL-4 levels in severe dengue infection might enhance susceptibility to invasive aspergillosis as well.[4,5] With these possibilities, severe dengue infection can potentially create an immunocompromised status in a previously healthy individual, predisposing the patient to opportunistic infections.[1,3] This is consistent with a case series study from our hospital that described four patients who initially had severe dengue infection but later succumbed due to severe invasive aspergillosis within 14 days of onset of dengue infection.[1]

References:
1. Larbcharoensub N, et al. Southeast Asian *J Trop Med Public Health* 2011;42:1106-1112.
2. Wati S, et al. *J Gen Virol* 2011;92:807-818.
3. Liu CC, et al. *J Med Virol* 2002;68:241-252.
4. Chaturvedi UC, et al. *Curr Sci* 1999;76:63-69.
5. Schmid MA, et al. *Front Immunol* 2014;5:647.

Asia Fungal Working Group
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Influencing *Aspergillus*: A Case Report of IPA Complicating Influenza B Pneumonia

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Invasive pulmonary aspergillosis (IPA), a well-known cause of life-threatening infection in immunocompromised patients, has been reported to complicate a viral infection in immunocompetent hosts.[1-3]

A 42-year-old man presented with a 4-day history of fever, productive cough, rhinorrhea and pharyngeal pain. He was a chronic smoker (10 pack-years) and a social drinker, with minor coronary heart disease and asthma on inhaled salbutamol. He was not diabetic and an HIV screen was negative. He was not on systemic steroids or traditional medications.

On admission, he was febrile but hemodynamically stable and was saturating well on room air. The chest was clear to auscultation and a chest X-ray (CXR) was normal. The procalcitonin was 0.26 µg/L (normal value <0.50 µg/L), white blood cell count (WBC) was 5.29 x 10^9/L and the absolute lymphocyte count (ALC) was 0.99 x 10^9/L (reference range 1.0-3.0 x 10^9/L). He was diagnosed with upper respiratory infection and treated symptomatically. A throat swab was positive for influenza B.

He remained febrile on days 1 to 3 of admission and reported increasing breathlessness. On day 3 of admission, he developed respiratory failure and hypotension requiring vasopressor support. A repeat CXR (Figure A) showed new extensive consolidation bilaterally. Repeat procalcitonin was now 9.0 µg/L, WBC now 8.96 x 10^9/L and ALC was 0.29 x 10^9/L. A bronchoscopy (BAL) was performed, which showed purulent secretions with erythematous airway mucosa. He was given broad-spectrum antibiotics and oseltamivir. As his respiratory status continued to deteriorate, he was intubated. Investigations from the BAL were negative except for a galactomannan level of 1.33 (reference range 0-0.49 Ag Index). The serum galactomannan was 0.15 (reference range 0-0.49 Ag Index). Serial CXRs continued to show improvement (Figure B) and he was extubated on day 6 of admission.

He continued to improve but on day 15 of admission, he turned febrile and hypotensive. Investigations revealed a normal procalcitonin level but a WBC of 22.16 x 10^9/L (96% neutrophils). A repeat CXR (Figure C) showed right upper lobe consolidation. A CT scan of the thorax revealed a mass-like consolidation in the right upper lobe with cavitation.

He underwent transthoracic needle biopsy of the mass. Microbiological tests for tuberculosis and bacterial cultures were negative. Histology showed fungal elements with morphology that was enhanced with Gomori methenamine silver (GMS) staining. These were filamentous, uniform in diameter and had acute angle branching, consistent with *Aspergillus* species. Fungal cultures from his initial BAL grew *Aspergillus niger*. He was commenced on voriconazole and completed a 12-week course with complete resolution of symptoms and CXR findings.

Discussion

The first report linking IPA with influenza was in 1952.[4] Since then, there have been several reports of IPA complicating influenza.[5-8] In these reports, the diagnosis of IPA was usually proven or probable by contemporary criteria, but that of influenza was usually made either by serology or on clinical grounds only. Nevertheless the H1N1 pandemic of 2009 seems to have led to an increase in the number of reports, suggesting that the association cannot be ignored.[5,8]

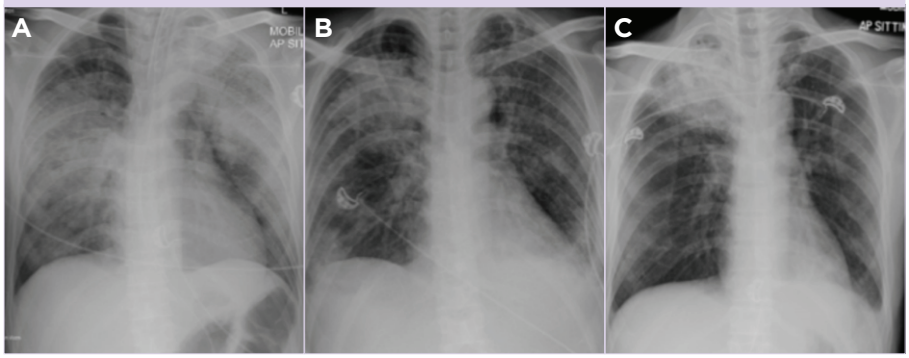
Several issues still need clarification. In some reports, aspergillosis and influenza appear to have been co-infections, as in our patient, while in others, IPA appears to have followed influenza. The time of onset may have implications for pathogenesis.

As for reasons for the association, several hypotheses have been put forward, including exposure to several antibiotics (for a non-resolving pneumonia)[4] and lymphopenia[8]. Garcia-Vidal et al suggested that the virus might induce alterations in the bronchial mucosa, hence permitting fungal invasion. The increase in IL-10 in H1N1 infection could also play a role.[5]

Clancy et al offer some clues that might aid the early diagnosis of this potentially lethal complication.[7] From their literature review, they suggest that persistently negative bacterial and viral studies, coupled with the isolation of *Aspergillus* from respiratory samples in a person with a diffuse and/or cavitary pneumonia should prompt a lung biopsy. In the modern era, how much a role serum and BAL galactomannan could play has not yet been defined.

We suggest that IPA complicating influenza infection is an emerging clinical entity. A high index of suspicion is required to make the diagnosis and an increase in general awareness amongst medical personnel will aid the diagnosis and prompt treatment of such patients.

Figure. CXR images taken on (A) Day 4 post-intubation showing bilateral confluent consolidation; (B) Day 7 post-extubation showing improvement in bilateral infiltrates; and (C) Day 15 showing persistent right upper lobe consolidation



References:
1. Fischer JJ, et al. *JAMA* 1979;241:1493-1494.
2. Alshabani K, et al. *Expert Rev Respir Med* 2015;9,89-96.
3. Lat A, et al. *Emerg Infect Dis* 2010;16:971-973.
4. Abbott JD, et al. *Br Med J* 1952;1:523-525.
5. Garcia-Vidal C, et al. *Clin Infect Dis* 2011;53:e16-e19.
6. McLeod DT, et al. *Br Med J* 1982;285:1166-1167.
7. Clancy CJ, Nguyen MH. *Chest* 1998;114:629-634.
8. Adalja AA, et al. *Influenza Other Respi Viruses* 2011;5:225-229.

Fungal Asthma

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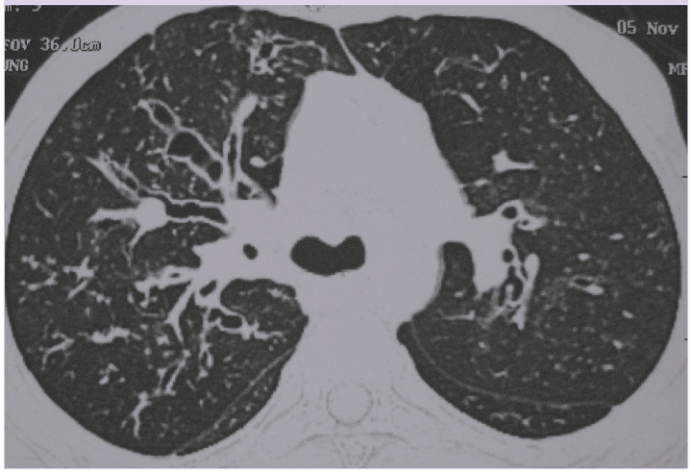
Asthma is a chronic inflammatory disease of the airways characterized by bronchial hyperresponsiveness and variable airflow obstruction. It manifests clinically as recurrent episodes of wheezing, breathlessness, chest tightness and cough.[1] There is current evidence to demonstrate a close association between fungi and asthma, the so-called fungal asthma or allergic fungal airway disease.[2,3] Fungi can colonize the tracheobronchial tree of asthmatic patients with subsequent release of fungal antigens, which can trigger or worsen asthma. Several small studies have identified certain genetic factors linking the risk of fungal asthma with individual mutations in mediators of innate and adaptive immunity.[4,5] Fungal asthma can manifest itself as fungal sensitization or fungal allergy. Fungal sensitization is an immune-mediated response to a fungus, without evidence of inflammation or tissue damage, clinically documented by an elevated fungal-specific IgE. Fungal allergy is an immune-mediated inflammatory response to a fungus causing tissue damage.

Table. Clinical manifestations of fungal asthma (in increasing order of severity)

Aspergillus fumigatus-associated asthma (AFAA)
Controlled asthma Elevated *A. fumigatus* (or other fungus) specific IgE (>0.35 kUA/L) Total IgE <500 IU/mL
Severe asthma with fungal sensitization (SAFS)
Severe asthma Elevated *A. fumigatus* (or other fungus) specific IgE (>0.35 kUA/L) Total IgE 500-1000 IU/mL Normal *A. fumigatus* specific IgG (<27 mg_A/L)
Serologic allergic bronchopulmonary ABPA (ABPA-S)
Asthma *A. fumigatus* specific IgE >0.35 kUA/L Total IgE >1000 IU/mL Elevated A. fumigatus specific IgG (>27 mg_A/L) Transient or fixed pulmonary opacities Total eosinophil count >500 cells/µL Normal high-resolution CT of the chest
ABPA with bronchiectasis (ABPA-B)
Asthma *A. fumigatus* specific IgE >0.35 kUA/L Total IgE > 1000 IU/mL Elevated *A. fumigatus* specific IgG (>27 mg_A/L) Transient or fixed pulmonary opacities Total eosinophil count >500 cells/µL High-resolution CT of the chest showing bronchiectasis

Although several fungi can cause fungal sensitization, fungal allergy is caused only by a small number of thermotolerant fungi, the most common being *Aspergillus fumigatus*.[6-8] The clinical presentation of fungal asthma can vary from fungal sensitization at one end, manifesting as *Aspergillus fumigatus*-associated asthma (AFAA) to ABPA at the most extreme end of the spectrum (Table). Severe asthma with fungal sensitization (SAFS) defines a phenotype of severe asthma characterized by severe asthma and fungal sensitization but exclusion of ABPA.[2,7] ABPA is the most well-characterized form of fungal asthma that manifests clinically as difficult-to-control asthma, recurrent pulmonary opacities and bronchiectasis (Figure).[9] The interest in ABPA stems from the fact that if the disorder is recognized and treated adequately, the onset and/or progression of the irreversible manifestations of ABPA including bronchiectasis and pulmonary fibrosis can be halted.

Figure. High-resolution CT image of the chest showing bronchiectasis in a patient with allergic bronchopulmonary aspergillosis



The diagnosis of fungal asthma is made on a combination of clinical, radiological and immunological findings (Table). The most useful investigations in differentiating between various entities of fungal asthma include total IgE and *A. fumigatus* specific IgG levels. It is important to differentiate between these various entities as the treatment options are different. The

treatment principles in fungal asthma include avoidance of fungal exposure, control of the underlying inflammatory process with glucocorticoids and attenuating fungal burden with the use of antifungal therapies. While patients with AFAA do not require any particular treatment, patients with SAFS may benefit from itraconazole therapy (400 mg/day for six months).[10] On the other hand, the initial treatment of choice for ABPA is glucocorticoids.[11] Unfortunately, the natural history of ABPA is characterized by recurrent episodes of exacerbation requiring repeated treatment with glucocorticoids.[12] In such situations, antifungal treatment with itraconazole can serve as steroid-sparing agent.[13,14] In those with recurrent exacerbations, the use of nebulized amphotericin B has been shown to reduce the frequency of exacerbations.[15,16] Other treatment options include newer azoles such as voriconazole and posaconazole, omalizumab and methylprednisolone pulses.

Before initiating glucocorticoids, physicians should carefully evaluate the potential risk and benefit of the use of glucocorticoids in an individual patient due to the following concerns. First, glucocorticoids enhance the growth rate of *A. fumigatus* and *A. flavus* in vitro.[17] Hypercortisolemic patients, such as those with endogenous Cushing's syndrome, and much more frequently, those receiving exogenous glucocorticoids, are especially at risk of invasive fungal diseases. This vulnerability is attributed to the complex dysregulation of immunity caused by glucocorticoids.[18]

Finally, several issues remain unsolved. There is still no clear consensus or guideline to suggest when and in whom should an antifungal agent be given in addition to glucocorticoids. Also, there is still uncertainty regarding the fungi that are relevant in fungal asthma, the natural history of fungal sensitization and its relationship with fungal allergy, and the pathogenesis and treatment of fungal asthma. Clearly, more data is required in asthmatic patients to determine the relationship between fungal sensitization and the development or progression of lung damage, as well as the clinical and immunological criteria needed for the definition of AFAA, SAFS and ABPA.

References:
1. Agarwal R, et al. *Lung India* 2015;32(Suppl 1):S3-S42.
2. Denning DW, et al. *Eur Respir J* 2006;27:615-626.
3. Denning DW, et al. *Clin Transl Allergy* 2014;4:14.
4. Agarwal R. *Indian J Chest Dis Allied Sci* 2011;53:137-140.
5. Agarwal R, et al. *Mycoses* 2012;55:357-365.
6. Woolnough K, et al. *Curr Opin Pulm Med* 2015;21:39-47.
7. Agarwal R. *Curr Allergy Asthma Rep* 2011;11:403-413.
8. Agarwal R, Gupta D. *Med Mycol* 2011;49(Suppl 1):S150-S157.
9. Agarwal R, et al. *Clin Exp Allergy* 2013;43:850-873.
10. Denning DW, et al. *Am J Respir Crit Care Med* 2009;179:11-18.
11. Agarwal R, et al. *Eur Respir J* 2016;47:490-498.
12. Agarwal R, et al. *Chest* 2006;130:442-448.
13. Stevens DA, et al. *N Engl J Med* 2000;342:756-762.
14. Wark PA, et al. *J Allergy Clin Immunol* 2003;111:952-957.
15. Chishimba L, et al. *J Asthma* 2015;52:289-295.
16. Ram B, et al. *J Asthma* 2016 Jan 22:1-8. [Epub ahead of print]
17. Ng TT, et al. *Microbiology* 1994;140:2475-2479.
18. Lionakis MS, Kontoyiannis DP. *Lancet* 2003;362:1828-1838.

VORICONAZOLE:

A Quick Reference for Practicing Clinicians

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Voriconazole (VCZ) is a second-generation, broad-spectrum triazole antifungal agent. Its spectrum of activity includes *Aspergillus, Candida, Fusarium* and *Scedosporium* species. It has no activity against Mucorales and reports suggest that VCZ exposure could be a potential risk factor for infection with Mucorales. VCZ is also not effective for urinary candidiasis as it does not achieve sufficient urinary concentration.

Approved indications of VCZ include treatment of invasive aspergillosis, candidemia, disseminated candidiasis (skin, abdomen, kidney, bladder wall, wounds), esophageal candidiasis, and other serious infections caused by *Scedosporium Apiospermum* and *Fusarium* spp. in patients intolerant or refractory to other therapy.

Pharmacokinetic parameters

VCZ has high (96%) oral bioavailability.[1] When administered with food, its absorption is reduced and this results in a 22% reduction in exposure at steady state level. It exhibits saturable metabolism and demonstrates nonlinear kinetics, irrespective of the route of administration, with increasing doses resulting in supra-proportional increases in drug exposure. A dosage increase from 3 to 4 mg/kg intravenously every 12 hours results in a 2.3-fold increase in the area under the curve (AUC).[2,3]

In pediatric patients, VCZ oral bioavailability is 44.6-66% and its elimination appears to be faster compared with adults, requiring higher weight-based doses. Higher VCZ concen-

trations have been reported in patients aged ≥65 years with standard dosage.

VCZ is extensively metabolized by CYP2C19 and, to a lesser degree, by CYP2C9 and CYP3A4. CYP2C19 exhibits genetic polymorphisms among various ethnic populations. Approximately 15-20% of Asians are poor CYP2C19 metabolizers, which may result in four times the exposure to VCZ compared with extensive metabolizers.[2,4] VCZ pharmacokinetics has high interpatient variability due to CYP2C19 genetic polymorphism and drug-drug interactions.

Dosage recommendations

Adult patients: Two loading doses of VCZ 6 mg/kg given 12 hours apart, followed by 4 mg/kg every 12 hours, is the recommended dosage.

Pediatric patients: Aged 2 to <12 years and 12-14 years with a body weight <50 kg: Two loading doses of 9 mg/kg given 12 hours apart, followed by 8mg/kg every 12 hours.

Obese patients: Standard VCZ dosing using actual body weight in obese and overweight patients resulted in higher associated serum concentrations. Dosing using adjusted body weight may be necessary in this population in order to achieve optimal concentrations while preventing the potential for increased toxicity.[5]

Patients with renal insufficiency: Oral VCZ can be used as standard recommendation. Intravenous VCZ is not recommended due to potential nephrotoxicity of sulfobutylether-beta-cyclodextrin (SBECD), which is a solubilizing excipient used for intravenous VCZ formulation. However, a recent study showed that SBECD, does not increase risk of renal damage in patients with compromised renal functions.[6]

Drug-drug Interactions

VCZ is metabolized extensively by the liver microsomal enzyme system and at the same time, it is also a potent inhibitor of CYP3A4, CYP2C19, CYP2C9 and CYP2B6 enzymes. Co-administration of VCZ with enzyme inducers (eg, efavirenz, rifampicin, phenytoin, St John's worts) reduces VCZ exposure while VCZ increases the exposure of substrates for cytochrome enzymes such as midazolam, tacrolimus, phenytoin, sirolimus, omeprazole and rifabutin by inhibiting substrate metabolism. Similarly, concomitant use of enzyme inhibitors, such as fluconazole and erythromycin, increases the VCZ AUC by 150% and 67%, respectively. Concomitant use of enzyme inducers, inhibitors or substrates for hepatic microsomal enzymes requires close monitoring with therapeutic drug monitoring.

Therapeutic drug monitoring

Current literature suggests that trough concentrations at steady-state should be used to evaluate plasma VCZ concentrations.[3] Initial trough concentrations should be obtained 5 days after the start of therapy to ensure steady-state concentrations are measured. Target VCZ trough therapeutic range is 1-5.5 µg/mL.

Adverse drug reactions

Common adverse drug reactions are transient visual disturbances, typically occur within 30 minutes after dosing. Other less common adverse drug reactions include increase transaminases, rash, photosensitivity, hallucinations, jaundice and encephalopathy. Higher VCZ level is associated with higher incidence of visual disturbances, hepatotoxicity and neurologic toxicity (eg, confusion, hallucinations, extrapyramidal effects).[3,7]

As VCZ is a trifluorinated antifungal, long-term use of VCZ is a risk factor for the development of fluoride excess and subsequent painful periostitis and exostoses in post-transplant patients.[8] A trough concentration of >3.0 µg/mL is associated with increased hepatotoxicity, particularly for the Asian population, and >4.0 µg/mL is associated with increased neurotoxicity.[9] Routine therapeutic drug monitoring of VCZ may reduce drug discontinuation due to adverse events and improve the treatment response in patients with invasive fungal infections.[10]

VCZ: Clinical pearls

- **VCZ has high oral bioavailability in adults.**
- **Pediatric patients requires higher weight-based dosage.**
- **VCZ therapeutic drug monitoring is recommended due to CYP2C19 genetic polymorphism and drug-drug interactions.**
- **Trough level should be obtained 5 days after initiation of therapy.**
- **Clinicians should be careful for significant drug interactions associated with VCZ usage.**
- **Visual disturbances are transient and typically seen within 30 minutes after starting therapy.**

References:
1. Scott LR, Simpson D. *Clin Infect Dis* 2003;36:630-637.
2. Smith J, et al. *Antimicrob Agents Chemother* 2006;50:1570-1572.
3. Pascual A, et al. *Clin Infect Dis* 2008;46:201-211.
4. Goodwin ML, Drew RH. *J Antimicrob Chemother* 2008;61:17-25.
5. Davies-Vorbrodt S, et al. *Pharmacotherapy*. 2013;33:22-30.
6. Lilly CM, et al. *BMC Infect Dis* 2013;13:14.
7. Tan K, et al. *J Clin Pharmacol* 2006;46:235-243.
8. Wermers RA, et al. *Clin Infect Dis* 2011;52:604-611.
9. Jin H, et al. *J Antimicrob Chemother* 2016 Mar 10. pii: dkw045. [Epub ahead of print]
10. Park WB, et al. *Clin Infect Dis* 2012;55:1080-1087.

AFWG Update

The AFWG, a working group of the International Society for Human and Animal Mycology (ISHAM), is governed and run by a group of mycologists and infectious disease specialists in Asia. The aims of the AFWG are to improve the diagnosis and management of invasive fungal infections, as well as to augment fungal surveillance data to support best practices in the region.

On February 2016, the original group welcomed two new executive committee members: Professor Retno Wahyuningsih of Indonesia and Dr Mitzi Chua from the Philippines, thereby increasing country representation to a total of seven.

The AFWG has been conducting educational and training workshops throughout Asia and has ongoing multicenter research studies on the epidemiology and management of invasive fungal infections. This newsletter officially welcomes you to the first country-based Medical Mycology Training Network (MMTN) for 2016, which is taking place on 13-14 May 2016 in Cebu City, Philippines.

Furthermore, the AFWG is currently conducting two regional surveys to understand the status of mycology laboratory services and the clinical management of invasive fungal infections, respectively, in China, India, Indonesia, Philippines, Singapore, Taiwan and Thailand. The aims of these surveys are to identify real-life gaps and needs, and thereby help advance mycology services and clinical practices across Asia.

Soon, the official AFWG website will be launched and will definitely provide a very accessible framework for networking and getting updated mycology information tailored to Asia researchers and healthcare professionals.

How can you contribute?

Are you from China, India, Indonesia, Philippines, Singapore, Taiwan or Thailand? We would love your help by completing the following online surveys :

Survey on diagnostic mycology laboratory services

To be completed by the person in charge of the mycology laboratory or his/her assigned personnel from China, India, Indonesia, Philippines, Singapore, Taiwan or Thailand

One survey per mycology lab

Go to:

www.surveymonkey.com/r/AFWGMycologySurvey

Survey on clinical management of fungal infections

To be completed by any infectious disease physician, hematologist/oncologist, transplant physician/surgeon or critical care specialist who manages patients with invasive fungal infections from China, India, Indonesia, Philippines, Singapore, Taiwan or Thailand

One survey per physician

Go to:

www.surveymonkey.com/r/AFWGClinicianSurvey

Meet the AFWG Executive Committee Members

Front row (L to R):
Professor Retno Wahyuningsih, Professor Ruoyo Li

Second row (L to R):
Dr Pei-Lun Sun, Professor Yee-Chun Chen, Dr Ariya Chindamporn, Dr Mitzi Chua

Back row (L to R):
Dr Porpon Rotjanapan, Dr Tan Ban Hock (Co-chair), Professor Arunaloke Chakrabarti (Co-chair), Dr Atul Patel, Professor Zhengyin Liu