Fungal Infections Study Forum

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RECENT PAPERS IN MYCOLOGY

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Prosthetic Valve Candida species Endocarditis: New insights into Long-Term Prognosis- The ESCAPE study

Rivoisy C, Vena A, Schaeffer L et al. *Clinical Infectious Diseases*, Volume 66, Issue 6, 5 March 2018, Pages 825–832.

Prosthetic valve endocarditis caused by Candida species (PVE-C) is rare and devastating, with international guidelines based on expert recommendations supporting the combination of surgery and subsequent azole treatment. This was a retrospective study of PVE-C cases collected in Spain and France between 2001-2015, focusing on management-surgical/medical and outcome. It was found that 6-month mortality outcomes in patients in the medically treated cohort were similar to that in the surgical cohort. There was also no significant difference in the relapse rates between the two cohorts. Interestingly, L-amB based therapy was associated with a lower 6-month mortality as compared to echinocandin based therapy. Long-term fluconazole at a higher dosage (400 mg) was associated with lower risk of mortality at 6 months in susceptible Candida spp PVE. L-AmB induction treatment improved survival in patients with PVE-C. Medical treatment followed by long-term maintenance fluconazole may be the best treatment option for frail patients where surgical risks are high.

A Fungal Immunotherapeutic Vaccine (NDV-3A) for Treatment of Recurrent Vulvovaginal Candidiasis—A Phase 2 Randomized, Double-Blind, Placebo-Controlled Trial

John E. Edwards Jr, Michael M. Schwartz, Clint S. Schmidt, Jack D. Sobel et al *Clinical Infectious Diseases*, Volume 66, Issue 12, 1 June 2018, Pages 1928–1936.

Recurrent vulvovaginal candidiasis (RVVC) is a problematic form of mucosal Candida infection, characterized by repeated episodes per year. *Candida albicans* is the most common cause of RVVC. Currently, there are no immunotherapeutic treatments for RVVC. This exploratory randomized, double-blind, placebo-controlled trial evaluated an immunotherapeutic vaccine (NDV-3A) containing a recombinant *C. albicans* adhesin/invasin protein for prevention of RVVC.

In this unprecedented study of the effectiveness of a fungal vaccine in humans, NDV-3A administered to women with RVVC was safe and highly immunogenic and reduced the frequency of symptomatic episodes of vulvovaginal candidiasis for up to 12 months in women aged <40 years. These results support further development of NDV-3A vaccine and provide guidance for meaningful clinical endpoints for immunotherapeutic management of RVVC.

Dear Friends,

A warm welcome to the delegates of the 3rd Mycocon in New Delhi, India (21-23rd Sep, 2018).

In this newsletter we are reviewing some of the recent interesting publications in the field of mycology. Additionally we have a couple of interesting cases which illustrate the challenges in diagnosis and management of serious fungal infections. Aspergillus is spreading its tentacles and expanding its territories, one of the most recent being critically ill patients with influenza.

Recently Fungal Infection Study Forum (FISF) completed two multi-centre studies 'Invasive mould infections in Indian ICUs – descriptive epidemiology, management and outcome' and 'Multicenter observational study on epidemiology, treatment and outcome of Mucormycosis in India'. The results of the studies will be published soon. Both studies highlight the fact that 'India has very high incidence of invasive mould infections.

Another important achievement, FISF jointly with Society for Indian Human and Animal Mycologists (SIHAM) won the bid to host 21st Congress of International Society for Human and Animal Mycology (ISHAM) in 2021. The congress will be held at Delhi.

It also gives me great pleasure in announcing collaboration of the FISF with the Clinical Infectious Diseases Society of India. You can access the monthly newsletter of CIDS at http://www.cidsindia.org/publications.html. This newsletter shares information about fungal infections apart from other infectious diseases. CIDS hosts an annual conference which discusses the latest in the field of infectious disease relevant to our country; the forth coming conference is in Kochi between 23rd to 25th August 2019. Please visit www.cidsindia.org for more information.

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Changing Epidemiology of Invasive Mold Infections in Patients Receiving Azole Prophylaxis

Frederic Lamoth, Shimin J. Chung, Lauro Damonti, and Barbara D. Alexander *Clinical Infectious Diseases*, Volume 64, Issue 11, 1 June 2017, Pages 1619–1621

Breakthrough invasive mold infections (IMIs) that occur during posaconazole or voriconazole prophylaxis are rare complications for which epidemiological data are lacking. India appears to have a high burden of these infections but the exact incidence is not known.This retrospective analysis comparing 24 microbiologically documented breakthrough with 66 non breakthrough IMIs shows a shift towards non-Aspergillus molds with a significantly increased proportion of rare multidrug-resistant molds. Members of the *A. ustus* complex, which

exhibit relatively high voriconazole and posaconazole MICs (4–16 µg/mL in this study) and which have previously been reported in patients receiving azole prophylaxis, were the major cause of breakthrough invasive aspergillosis. Intrinsically azole resistant *Scopulariopsis* spp. were recovered in 12.5% of breakthrough IMIs. Other rare and notoriously multidrug-resistant molds, such as *Lomentospora prolificans* and *Rasamsonia* (previously *Geosmithia*) *argillaceae*, were also observed in this setting. Most of these infections required complicated therapeutic approaches, including use of potentially toxic drugs such as amphotericin B and/or regimens that included drug combinations; overall mortality was high. This study data supported use of amphotericin B as first-line empirical therapy of breakthrough IMI as this drug was the most and often only, active drug against the fungal species of this series. However, since the epidemiology of breakthrough IMIs may differ considerably between countries and/or hospitals, prophylactic strategies and therapeutic approaches for these severe and complicated infections should be tailored at each center according to the epidemiological context.

CD4 Cell Count Threshold for Cryptococcal Antigen Screening of HIV-Infected Individuals : A Systematic Review and Meta-analysis

Nathan Ford, Zara Shubber, Joseph N. Jarvis et al *Clinical Infectious Diseases*, Volume 66, Issue suppl_2, 4 March 2018, Pages S152–S159

In countries with a high incidence of cryptococcal infection & somewhat inadequate coverage of cART, screening all people living with human immunodeficiency virus (PLHIV) who have a CD4 count ≤100 cells/µL for cryptococcal antigen (CrAg) is needed to identify those patients who could benefit from preemptive fluconazole treatment prior to the onset of meningitis. The study found a high prevalence of CrAg positivity among people with advanced HIV disease consistent with expectations. This review further suggests that there may be additional benefit of screening individuals with CD4 cell count up to 200 cells/µL, depending on availability of resources and considering the practical advantage of providing the same package of care to all patients with advanced HIV disease within a public health approach.

Isavuconazole Treatment of Cryptococcosis and Dimorphic Mycoses

George R. Thompson III, Adrian Rendon, Rodrigo Ribeiro dos Santos et al *Clinical Infectious Diseases*, Volume 63, Issue 3, 1 August 2016, Pages 356–362.

Invasive fungal diseases (IFD) caused by *Cryptococcus* and dimorphic fungi are associated with significant morbidity and mortality. Isavuconazole (ISAV) is a novel, broad-spectrum, triazole antifungal agent (IV and PO) developed for the treatment of IFD. It displays potent activity in vitro against these pathogens.The VITAL study was an open-label non-randomized phase 3 trial conducted to evaluate the efficacy and safety of ISAV treatment in management of IFD (cryptococcosis and dimorphic fungi).This study demonstrated that ISAV had antifungal activity as both primary and salvage therapy in patients with cryptococcosis and dimorphic fungal infections. A successful response to therapy was seen in 24/38 (63%) of all patients at the end of therapy and an overall 89% (34/38) survival rate. The majority of patients treated in this study received ISAV as primary therapy and a successful response was observed in patients with pulmonary, non-CNS dissemination, and CNS infections. ISAV also offers potential advantages over other azoles in view of lower MICs, ease of administration, minimal inter-patient pharmacokinetic differences and fewer side-effects.

Detection of circulating Mucorales DNA in critically ill burn patients: preliminary report of a screening strategy for early diagnosis and treatment

Matthieu Legrand, Maud Gits-Muselli, Louis Boutin et al *Clinical Infectious Diseases*, Volume 63, Issue 10, 15 November 2016, Pages 1312–1317.

Invasive wound mucormycosis (IWM) is associated with an extremely poor outcome among critically ill burn patients. The purpose of this study was to describe the temporal relationship between the detection of circulating plasma Mucorales DNA and the diagnosis of invasive mucormycosis in patients with severe burns and to report the potential value of detecting circulating Mucorales DNA (cm DNA) for treatment guidance. Severely ill burn patients admitted to a tertiary referral center between October 2013 and February 2016 were included. Retrospective plasma samples were tested for the presence of cmDNA by PCR. Patients were then prospectively screened twice a week and liposomal amphotericin-B therapy initiated based on a positive PCR. The primary endpoint was the time between detection of cmDNA using qPCR and standard diagnosis. Secondary endpoints were the time from cmDNA detection and treatment initiation and mortality. This study suggests that the detection of cmDNA allows earlier diagnosis of IWM in severely ill burn patients and earlier initiation of treatment.

Assessment ofthe accuracy of histomorphologic diagnosis of aspergillosis and mucormycosis by immunohistochemical tests

Jiwon Jung, Young Soo Park, Heungsup Sung et al. *Clinical Infectious Diseases*, Volume 61, Issue 11, 1 December 2015, Pages 1664–1670

Distinguishing between IPA and pulmonary mucormycosis (PM) is clinically important but at times difficult. Although combining histomorphologic diagnosis with fungal culture results can make definite diagnoses, cultures are often negative, especially for mucormycosis. This study investigated the accuracy of histomorphologic diagnosis of mucormycosis and aspergillosis using immunohistochemical tests for mucormycosis and aspergillosis. Patients who met the modified criteria for proven and probable mucormycosis or invasive aspergillosis, for whom formalin-fixed, paraffin-embedded tissues were available, were enrolled. The diagnostic performance of immunohistochemistry was first tested in proven mucormycosis and aspergillosis cases. Thereafter its accuracy was determined in the probable cases. The sensitivity and specificity of mucormycosis immunohistochemistry were 100% (95% CI 65-100) and 100% (95% CI 68-100), and those of aspergillosis immunohistochemistry were 87% (95% CI 53-98) and 100% (95% CI 65-100), respectively in the proven cases. In probable mucormycosis cases, 87% were positive for mucormycosis IHC, 9% for aspergillosis IHC and 4% were negative for both. In probable aspergillosis cases, 63% were positive for aspergillosis IHC, 25% were positive for mucormycosis IHC and 13% negative for both. In the absence of fungal culture results, the immunohistochemistry tests seem helpful in differentiating between aspergillosis and mucormycosis.

SEVERE INFLUENZA AS AN EMERGING RISK FACTOR FOR INVASIVE PULMONARY ASPERGILLOSIS

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Case

A 57-year old male with uncontrolled diabetes mellitus (HbA1C 13.6%) was admitted with history of fever and runny nose followed by cough and dyspnea. He was admitted at a local hospital but because of worsening hypoxemia shifted to our ICU. Throat swab was sent for influenza PCR. He fulfilled the criteria for ARDS. He was managed initially with NIV but soon had to be intubated and mechanically ventilated for severe ARDS. Throat swab PCR was positive for H1N1. He was treated with broad spectrum antibiotics including piperacillin tazobactam and levofloxacin but no corticosteroids were given. The serial X rays showed developing nodular infiltrates along with changes of ARDS. CT chest could not be done due to respiratory dynamics. Tracheal aspirate showed growth of aspergillus spp. Galactomannan assay could not be performed due to cost issues. A diagnosis of probable Invasive pulmonary aspergillosis (IPA) early on (within 7 days of onset of influenza like illness) was made and treatment with voriconazole initiated. At the time of writing this paper, the patient is still on treatment.

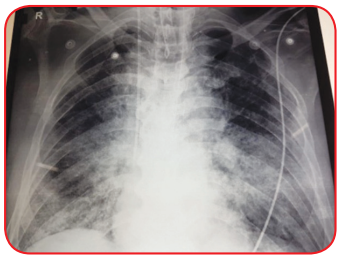

Figure 1: Patient's chest radiograph demonstrating nodular opacities in both lung fields

Discussion

IPA is a uniformly fatal disease, if untreated. Optimal management involves early diagnosis and early initiation of effective antifungal therapy. Classic risk factors for IPA include prolonged neutropenia, receipt of large doses of glucocorticoids, other immunocompromizing conditions such as immunosuppressive drugs used to treat autoimmune conditions and to prevent organ rejection and AIDS (acquired immunodeficiency syndrome) (Table 1). In recent times, certain emerging risk factors for IPA have been identified even in apparently immunocompetent individuals (Table 1) of which influenza is an important risk factor.

Table 1: Risk factors for IPA

Classical risk factors for IPA
Prolonged neutropenia (<500 cells/µl) for >10 days
Organ transplantation (highest risk with lung and stem-cell transplantation
High dose and prolonged (>3 weeks) corticosteroid therapy
Hematological malignancy (highest risk with leukemia)
Cancer chemotherapy
Advanced HIV/AIDS infection
Chronic granulomatous disease

Emerging risk factors for IPA
Severe asthma, chronic obstructive pulmonary disease with recent exacerbation
Critically ill patients on ventilator in ICU
Liver disease
Influenza

A retrospective analysis was done on patients with severe influenza admitted across 7 ICU's in Europe, between Jan 1, 2009, and June 30, 2016. IPA was diagnosed in 83 (19%) of 432 patients admitted with influenza (influenza cohort, either A or B), a median of 3 days after admission to the ICU. The incidence of IPA in the immunocompromised was as high as 32%, whereas in the non-immunocompromised the incidence was 14%. Conversely, only 16 (5%) of 315 patients in the control group developed IPA. The 90-day mortality was 51% in patients in the influenza cohort with IPA and 28% in the influenza cohort without IPA (p=0·0001). In this study, influenza was found to be an independent risk factor for IPA (adjusted odds ratio 5·19; 95% CI 2·63–10·26; p<0·0001), along with a higher APACHE II score, male sex, and use of corticosteroids.

The diagnosis of IPA in the setting of severe influenza is challenging. This is because the evolving pneumonia cannot be differentiated from bacterial infection or worsening of the primary illness. The CT findings in non neutropenic adults are also non specific; the characteristic halo sign/ crescent sign are rarely seen. A high index of suspicion is therefore essential. Isolation of aspergillus in the tracheal secretions should not be dismissed as colonization but should trigger the possibility of an IPA. A BAL galactomannan (cut off > 0.8) would greatly aid in the diagnosis but is not always possible because of severe respiratory compromise, slow turnaround time and cost in resource limited setting. Serum galactomannan (positive if > 0.5) has poor sensitivity unlike neutropenic patients. The specificity of serum galactomannan can also be confounded by prior administration of certain antibiotics such as piperacillin tazobactam. Blot et al have laid down criteria for diagnosis of IPA in non neutropenic adults in the ICU wherein a host with a risk factor such as influenza and compatible clinicoradiologic abnormalities with either a positive aspergillus culture from the tracheal aspirate or a positive serum/ BAL galactomannan suggests the diagnosis of probable IPA.

In summary critical care physicians, pulmonologists and infectious disease specialists should consider IPA as a possible cause for respiratory deterioration in a critically ill patient with severe influenza (either A or B) even if it is early in the course of the illness and initiate appropriate diagnostic and therapeutic strategies.

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CANDIDA AURIS VERTEBRAL OSTEOMYELITIS

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A 62-year-old gentleman with end-stage renal disease (ESRD) on maintenance haemodialysis (MHD) presented in June 2016 to our institute with features suggestive of subacute intestinal obstruction. He was admitted in the intensive care unit (ICU) and received meropenem, colistin and minocycline for various reasons. One and half months later, during hospitalization he developed weakness of the upper and lower limbs. MRI cervical spine revealed discitis and marrow edema at the level of C4-C5 with an epidural collection and compressive myelopathy.

He underwent surgical decompression with stabilization with implants (Figure 1). Pus culture grew *Candida auris* with resistance to both amphotericin B (MIC of 8 µg/ml) and fluconazole (>64 µg/ml) but sensitive to voriconazole (MIC 0.5 µg/ml) and echinocandins. He was initiated on micafungin 100 mg daily. Subsequently, Infectious diseases (ID) reference was sought. On reviewing the history, patient had developed persistent candidemia with repeated positive cultures of *candida auris* during the previous 2 months of ICU stay. Fundus examination did not reveal endophthalmitis. ECHO did not show any evidence of endocarditis. The micafungin was increased to 150mg/day and continued for 3 weeks. Subsequently, the antifungal therapy was de-escalated to oral voriconazole which is being continued as chronic suppressive therapy owning to the presence of prosthesis. The patient is doing well at 1 year of follow up.

Discussion

Among the spectrum of invasive candida infections, candida vertebral osteomyelitis (VO) is relatively rare syndrome. However, it should be suspected in the ICU setting especially in the presence of persistent candidemia. The axial skeleton, especially the spine, is the most common site of involvement in adults; in children, the long bones are more commonly involved. Early recognition and appropriate treatment of the candidemia in the index case could have prevented this debilitating complication.

Most common cause of *candida* VO is *candida albicans*. Other less common organisms include C. tropicalis, C. glabrata and C. parapsilosis. . Treatment includes surgical debridement in conjunction with prolonged antifungal therapy. Treatment recommendations for *Candida* VO are based on case reports and case series. Historically, an initial 2 weeks course with liposomal amphotericin B followed by fluconazole for 6-12 months was recommended. However the 2016 update by Infectious Diseases Society of America have recommended an echinocandin (caspofungin 50–70 mg daily, micafungin 100 mg daily, or anidulafungin 100 mg daily) for at least 2 weeks followed by susceptible azole for 6–12 months as preferred over an amphotericin B based regime.

Our patient had developed candida VO due to *Candida auris*, an emerging multidrug-resistant yeast in the Indian ICUs especially in Northern India. This fungus is often misclassified as other yeast, is highly drug resistant, colonizes the patient and hospital environment for prolonged periods and is also capable of causing outbreaks. Apart from causing candidemia, *C. auris* can also cause other locally invasive infections including shunt infections, meningitis, peritonitis, endocarditis etc.

In this index case with *Candida auris* VO, echinocandins are the preferred agents- the rationale being the fungicidal effect and low MICs of biofilm organisms for these agents. Like candida endocarditis, higher doses of echinocandins have been used in some cases of Candida VO; hence the reason for using higher doses. The challenge was oral maintainence therapy as fluconazole resistance in *C. auris* is universal and resistance to voriconazole is fairly common. Fortunately, the isolate in the index case had low voriconazole MIC's and hence the same could be used for continuation therapy. Whether the treatment can be stopped in future given the fact that the patient has an underlying implant is debatable. Prolonged therapy with voriconazole has issues related to cost and adverse effects.

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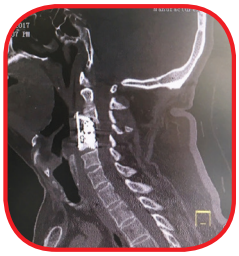

Figure 1: MRI cervical spine revealed hyperintensity involving C4-C5 discitis with vertebral osteomyelitis - surgical decompression with stabilization with implants

About FISF

The purpose of the Fungal Infections Study Forum is to conduct educational activities, undertake epidemiological and clinical studies and to promote research activities on invasive fungal infections. The results of such research would benefit the clinicians, mycologists and the general public. The trust was formed in view of emergence of Invasive fungal infections (IFIs) in India which is posing a serious challenge to the haematologists, critical care providers, ID specialists, pulmonologists, neurologists, medical mycologists and many other clinicians handling serious and immunocompromised patients.The trust is the independent working consisting of clinicians and mycologists and instituted on 3rd March 2012 at Mumbai, India. To know more about us visit www.fisftrust.org.