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EPIDEMIOLOGY AND DIAGNOSIS OF CRYPTOCOCCAL INFECTIONS

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Cryptococcosis is a serious and potentially fatal fungal disease caused by *Cryptococcus* species. Its main aetiologic agents are *Cryptococcus neoformans* and *C. gattii* species complex. *C. gattii* is more commonly found in Australia, British Columbia in Canada, The Pacific Northwest in the U.S. and Southeast Asia. Worldwide, it is estimated to kill over 180 000 annually, with 75% of deaths occurring in sub-Saharan Africa. A one-year mortality rate of about 70% has been reported for cryptococcal meningitis (CM) in low-income countries. After tuberculosis, cryptococcosis ranks second among the most common cause of AIDS-associated deaths in adults. *Cryptococcus* infection is a major concern in persons living with human immunodeficiency virus (HIV). In many developed countries, however, HIV-associated cryptococcosis has become uncommon due to the availability of highly effective antiretroviral therapy. In contrast, *Cryptococcus* infections in patients without HIV are increasingly appreciated, including in solid organ transplant recipients, other patients receiving immunosuppressive therapy, and patients who are otherwise considered immunocompetent. The diagnosis of cryptococcal infection can be done by direct microscopic examination of infected body fluids, histological examination of tissues samples, detection of cryptococcal polysaccharide antigen in body fluids and culture. Detection of cryptococcal polysaccharide capsular antigen (CRAG) is useful in both the diagnosis of infection and the prediction of prognosis and response to therapy. Several latex, enzyme-linked immunoassays and more recently immunochromatographic cryptococcal antigen tests are available. CRAG assays are based on detection of cryptococcal capsule polysaccharide glucuronoxylomannan. Sensitivityy and specificity in serum and CSF are excellent especially in AIDS patients (over 95%). Clinicians should be informed that CRAG in serum is positive in only 85% of non-HIV patients with disseminated and/or meningitis. The lateral flow assay (LFA) (semi-quantitative detection of polysaccharide antigen in serum or CSF) showed a high sensitivity and specificity for CSF (>99%) when compared to India Ink staining, cultures or CRAG.

HOW DO WE TREAT CRYPTOCOCCAL SYNDROMES?

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The most frequent cryptococcal syndromes are meningitis, fungaemia, antigenaemia, pneumonia and osteomyelitis. Echinocandins are inactive and should not be used. Most cases are treated with a mixture or sequence of amphotericin B (AmB), flucytosine and fluconazole. Itraconazole and voriconazole are also active and may substitute for fluconazole if another fungal infection also needs treatment, such as co-incident histoplasmosis, or pulmonary aspergillosis.

Initial therapy of cryptococcal with AmB yields much higher response rates than fluconazole alone. The daily dose of deoxycholate AmB should be 1mg/kg, or 3mg/kg liposomal/lipid-associated AmB and given for at least 7 days. Alternatively 10mg/kg as a single dose can be used. Dose rounding to the nearest 50mg

Message from the Editor

Dear Friends

A very warm welcome to the delegates of Mycocon 2023. We hope that this carefully curated conference will be able to augment your knowledge of invasive fungal infections and help you in your day to day practice. We begin with key take aways of talks from our renowned international Faculty viz Dr David Denning, Dr Cornelia Lass-Flörl, Dr Martin Hoenigl and Dr Paschalis Vergidis. Next we have a review of selected papers in Mycology relevant to our day to day practice. This is followed by an article which describes serious adverse effects and drug-drug interactions of azole antifungals. thus reminding us to be extremely cautious while using these drugs. Then we have three cases, one each of hepatosplenic candidiasis, influenza associated pulmonary aspergillosis and histoplasmosis. All these cases have important messages for clinical practice.

Finally a reminder to all readers to contribute cases of invasive fungal infections (aspergillosis, mucormycosis and rare/ endemic fungi) to the fungal registry at www.fungireg.in. Contributors are free to publish their submitted cases elsewhere and will receive reimbursement of Rs 2000 per case. They will also have the opportunity to submit the samples to PGI Chandigarh for accurate identification and susceptibility testing.

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The Mycocon 2023 conference abstracts have been published in Journal of CIDS Issue 1, Volume 2. You can access them at https://journals.lww.com/cids/pages/currenttoc.aspx

is acceptable. The addition of flucytosine (100mg/kg daily adjusted for renal dysfunction) improves survival by about 25%. It is usually given for 2 weeks. High dose fluconazole (800-1200mg) can be given in addition, or started after AmB has been stopped. In HIV infected patients, high dose fluconazole is continued for ~10 weeks and then 200mg daily is given, unless rifampicin is also prescribed when at least 400mg should be used. In HIV infected patients antiretroviral initiation (or re-initiation) is usually deferred for 4 weeks to reduce the risk of IRIS, but this is controversial. At least one second lumbar puncture reduces mortality in HIV positive patients.

In HIV negative patients, especially non-immunocompromised patients, a similar regimen is appropriate, with greater attention to raised intracranial pressure. Repeat lumbar punctures, use of a lumbar drain or a ventriculo-peritoneal shunt may be required.

In patients with either cryptococcal fungaemia or antigenaemia, it is critical to exclude meningitis with a lumbar puncture and antigen testing on the CSF. If excluded, fluconazole monotherapy is usually sufficient, using a dose of at least 400mg daily, preferably higher initially. Cryptococcal pneumonia and osteomyelitis also respond to fluconazole monotherapy. Some isolates of *Cryptococcus* spp. are resistant to fluconazole or develop resistance on therapy, but the accuracy of susceptibility testing is poor.

Treatment failure is relatively common in meningitis, and after excluding IRIS, should be managed with re-induction therapy, treating raised intracranial pressure and possibly adding gamma interferon.

Resources

https://en.fungaleducation.org/

INTERPRETING MICS AND BREAKPOINTS FOR FUNGI

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Antifungal susceptibility testing (AFST) provides an *in vitro* measure by determining the concentration of drug required to inhibit an organism to a specified degree, termed the minimum inhibitory concentration (MIC). Many factors influence the outcome of *in vitro* susceptibility testing, including endpoint definition, inoculum size of the organism, time of incubation, temperature of incubation, and medium used for testing. The goal of AFST is to reliably produce MIC values that may be used to guide patient therapy, inform epidemiological studies, and track rates of antifungal drug resistance. There are various methods that have been standardized by standards development organizations such as broth dilution and disk diffusion. Other commonly used methods include gradient diffusion and the use of rapid automated instruments. There are *in vitro* phenomena which complicate the endpoint determination, independent of the standard being followed, and may cause a determination of false resistance. Breakpoints are used to predict whether an antifungal agent will be clinically effective against a particular fungal isolate. They are based on a combination of MIC values, pharmacokinetic/pharmacodynamic values, and clinical outcome data. For many fungus-antifungal combinations, these data might never be available. For these combinations, epidemiological cutoff values (ECVs) provide a methodology for categorizing isolates as either wild type (WT) or non-WT. The European Society of Clinical Microbiology and Infectious Diseases (ESCMID) recommended AFST of all *Candida* isolates from blood and other deep sites. In addition, they stated the usefulness of AFST for isolates from patients who were failing therapy, isolates from rare species, and isolates from species that are known to develop resistance. The Infectious Diseases Society of America (IDSA) also recommended antifungal susceptibility testing, at least for azoles, for all bloodstream and clinically relevant *Candida* isolates. They also suggested that echinocandin testing be considered for patients with either *C. glabrata* or *C. parapsilosis* infection. IDSA guidelines for the management of aspergillosis recommend against routine AFST of *Aspergillus* isolates. They recommend testing for patients who are unresponsive to antifungal agents or who are suspected to have a resistant isolate. ESCMID provided the first strong recommendation for susceptibility testing of *Aspergillus* in 2017.

MANAGEMENT OF INVASIVE CANDIDIASIS – RESULTS OF THE ECMM CANDIDA III STUDY

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Objectives

The European Confederation of Medical Mycology (ECMM) collected data on epidemiology, risk factors, treatment, and outcomes of culture proven candidemia across Europe in order to assess how adherence to guideline recommendations correlate with outcomes.

Methods

Each participating hospital (number of eligible hospitals per country determined by population size) included the first ~10 culture proven IC cases after 01-Jul-18 and entered data into the ECMM Candida III database on the FungiScope™ platform. EQUAL Candida Scores (10.1111/myc.12746) reflecting adherence to recommendations of IDSA and ESCMID Guidelines were assessed.

Results

A total of 632 Candidemia cases were included from 64 institutions in 20 European countries. Patient's characteristics are displayed in Table 1. Overall mortality was 45% (286/632), and hospital stay was prolonged (median 2 days) for completion of parenteral therapy only in 16% (100/621) of patients. EQUAL Candida Score was evaluable for 589 cases with candidemia (Figure 1). Candida scores correlated significantly with duration of hospitalization ($r= 0.442$; $p<0.001$) and - after exclusion of patients hospitalized <7 days (n=119) - were significantly higher in patients who survived versus those who died ($p<0.001$). Duration of hospitalization was in median 16 days after diagnosis of candidemia. Initial echinocandin treatment was associated a.) with lower overall mortality (42%, 148/353) versus those without initial echinocandin therapy (53%, 126/236; $p=0.007$), and b.) with longer duration of hospitalization among survivors (median 24 days, IQR 15-40 days vs. median 16 days, IQR 7-33 days; $p<0.001$). In those where candidemia was treated for at least 14 days, 78% (239/306) survived, compared to 66% (67/102) in those treated for less than 14 days, but who survived beyond day 14 after diagnosis.

Conclusions

Initial echinocandin treatment was associated with increased overall survival, but also longer duration of hospitalization (hospitalization was prolonged only for completing treatment in 16%). Overall mortality of IC was 45%. EQUAL Candida scores were significantly higher on those who survived, indicating that adherence to clinical guidelines may increase survival.

MANAGEMENT OF INVASIVE ASPERGILLOSIS

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Despite improvements in treatment over the last two decades, invasive aspergillosis (IA) is still a devastating fungal disease. Since the number of immunocompromised patients and vulnerable people increases, subsequently rising numbers of IA are observed. Furthermore, emergence of azole- resistant strains are reported on six continents, presenting a new challenge in the treatment of IA. Therapeutic options for IA currently consist of three different classes of antifungals (triazoles, polyenes, echinocandins), each of them with their advantages and shortcomings. Especially in settings of difficult to treat IA comprising drug tolerance/ resistance,

limiting drug- drug interactions, and/or severe underlying organ dysfunction, new agents are needed. There are promising new options for potential treatment for IA in late- stage clinical development, including olorofim (a dihydroorotate dehydrogenase enzyme inhibitor), fosmanogepix (a Gwt1 enzyme inhibitor), ibrexafungerp (a triterpenoid), opelconazole (a triazole for inhalation use) and rezafungin (an echinocandin with long half- life time). Also, with new insights in the pathophysiology of IA, immunotherapy as add- on therapy is currently researched, showing encouraging results, although mostly in preclinical settings. In this review we intend to discuss the current treatment strategies of IA. Then we give an outlook on the possible new pharmaceutical therapeutic options and their potential role in the treatment of IA. Lastly, we want to give an overview in the research of immunotherapy regarding IA.

ANTIFUNGAL STEWARDSHIP & WHAT'S NEW IN THE ANTIFUNGAL PIPELINE?

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Appropriate antifungal use has been recognized as a significant component of any antimicrobial stewardship program. The objective of the lecture is to review successful antifungal stewardship interventions and provide guidance on how to improve antifungal use. We will review the 5 Ds of antifungal stewardship (correct Diagnosis, right Drug, correct Dose, appropriate Duration, timely de-escalation). Engagement of high-prescribing specialists, access to fungal diagnostics, screening for drug-drug interactions and therapeutic drug monitoring are key components of a successful antifungal stewardship program.

Several novel antifungal agents have entered late-stage clinical development. The objective of the lecture is to review their potential role in clinical practice. The mechanism of action, spectrum of activity and distinct pharmacokinetic properties of these agents will be discussed. We will review the role of rezafungin (long-acting echinocandin), ibrexafungerp (oral glucan synthase inhibitor), olorofim (DHODH inhibitor) and fosmanogepix (*Gwt1* inhibitor) through a series of challenging clinical cases. We will also summarize the design and endpoints of actively enrolling clinical trials.

SELECTED PAPERS IN MYCOLOGY 2022-2023

Rajeev Soman
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Simon SP, Li R, Silver M, et al. Comparative Outcomes of Candida auris Bloodstream Infections: A Multicenter Retrospective Case-Control Study. *Clin Infect Dis*. 2023; 76(3):e1436-e1443.

Background

C. auris has intermediate virulence between *C. albicans & C. glabrata*, but higher ability to spread, higher resistance & appears to have a higher mortality compared to other C. spp, but direct comparative studies are lacking

Hypothesis

A comparative study may better elucidate the rates of recurrence & mortality

Results

In this study involving Candida blood stream isolates, from 3 Brooklyn hospitals, *C. auris* BSI was not associated with an increased 30-day mortality (AOR 1.014) as compared to non*Candida auris* BSI. However, a higher risk (AOR 4.461) for microbiologic recurrence within 60 days was observed with *C. auris*. This was possibly because persistence on the skin is the predisposing factor for *C. auris* rather than GI surgery, parenteral nutrition, (neutropenia) as with other C. spp

Applicability in my practice

The persistence on the skin despite treatment, is of great importance in a hot, humid, tropical climate such as India. Hence there is higher need for decolonization, infection measures & vigilance.

Aldejohann AM, Wiese-Posselt M, Gastmeier P, Kurzai O. Expert recommendations for prevention and management of Candida auris transmission. *Mycoses*. 2022; 65(6):590-598.

Background

C. auris poses an important risk to hospitalized patients. It is both difficult to diagnose & treat. Once introduced into a unit, persistence in the patient, environment & transmission to others are challenging

Hypothesis

Recommendations can be based on epidemiology, biology & interventions that prevent transmission in real-life to enable optimal containment

Recommendations and Applicability to my practice

Accurate identification is needed with up to date MALDI TOF MS data base. Antifungal susceptibility testing is needed, but only CDC tentative break points are available and echinocandin resistance needs confirmation by FKS sequencing. Testing of follow-up isolates is also needed. Personal protective equipment, 1:1 care, alcohol based hand sanitizers, chlorhexidine wipes/ bath are recommended for colonized/ infected patients. Per acetic acid instead of quarternary ammonium compounds for surfaces, H_2O_2 wipes for USG transducers are recommended. Treatment initiation only if clinically relevant (not for skin, TA, urine from indwelling catheter). Echinocandin, LAmB, combination. In the event of a case, all patients in the unit should be tested, separate areas in the unit created and admissions to the unit stopped. Staff testing is not necessary. Follow-up with 2 swab-series 1 week apart with treatment stopped 7 days before testing, de-isolation typically after 3 months & testing needed prior to re-admission are also recommended. Patients in the unit should be screened once a week for 3 months after the last patient is discharged. All these recommendations seems very difficult in practice in resource limited settings.

Jarvis JN, Lawrence DS, Meya DB, et al. Single-Dose Liposomal Amphotericin B Treatment for Cryptococcal Meningitis. *N Engl J Med*. 2022; 386(12):1109-1120.

Background

CM is a leading OI in HIV patients especially in resource limited settings like Africa. Shorter & easier treatment is an unmet clinical need. ACTA study showed better performance of 1 week treatment compared to the current standard of at least 2 weeks & has thus informed the WHO guidelines 2018.

Hypothesis

Single dose L AmB 10 mg/kg could have better penetration, long T1/2, be easier to administer, safer & equally effective.

Methods and Results

844 HIV-positive adults with cryptococcal meningitis were randomized in a 1:1 ratio to receive either a single high dose of liposomal amphotericin B (10 mg per kilogram of body weight) on day 1 plus 14 days of flucytosine (100 mg per kilogram per day) and fluconazole (1200 mg per day) or the current World Health Organization-recommended treatment, which includes amphotericin B deoxycholate (1 mg per kilogram per day) plus flucytosine (100 mg per kilogram per day) for 7 days, followed by fluconazole (1200 mg per day) for 7 days (control. The 10 weeks all-cause mortality was 24.8 vs 28.7% in the trial and control groups respectively. Fungal clearance cfu/d was similar in both groups. The incidence of significant ADR was lower in the trial group (50.0 vs 62.3%)

Applicability in my practice

The results are indeed relevant for resource limited setting since single dose therapy reduces risk of ADR and nosocomial sepsis. However in the private setting such as mine where ADR can be monitored, managed & nosocomial sepsis can be

avoided, is the 'theoretical' benefit of at least 2 week AmB + 5FC induction worth it? This has given a <5% mortality rate in my practice. The patients anyway need inpatient stay for >1-2 w for repeated CSF drainage. The cost of LAmB and missing erosion of efficacy in sequential NI trials should also be considered. Neither the WHO, nor the AMBITION regimen can be applied to patients with parenchymal disease, relapsed disease, those who do not improve, remain culture positive and to non-HIV patients

Shi C, Shan Q, Xia J, et al. Incidence, risk factors and mortality of invasive pulmonary aspergillosis in patients with influenza: A systematic review and meta-analysis. *Mycoses*. 2022; 65(2):152-163.

Background

It is estimated that there are 291000 deaths every year due to influenza globally. Secondary infection is common due to muco-ciliary and immune dysfunction & microbiome alteration. IAPA (influenza associated pulmonary aspergillosis) is increasingly recognized, yet awareness among intensivists & ID physicians is low

Hypothesis

Knowledge about incidence & risk factors will help devise strategies for prevention & treatment

Results

The incidence ranged from 4% overall to 12% in ICU. If >30% patients had BAL GM test, incidence rose to 18%. The pooled mortality was 52% which is 2.4 fold if no IAPA. Risk factors include male, smoking, influenza A (subtype H1N1 1.44x) chronic lung disease, severe condition requiring supportive therapy, steroids before admission, solid organ transplant and hematologic malignancy.

Applicability in my practice

Influenza needs close monitoring and testing, especially if in ICU & multiple risk factors are present. One may consider prophylaxis for IA, although need more data. Emphasis on flu vaccination & mitigation of risk factors like smoking, steroid use are needed

Soman R, Chakraborty S, Joe G. Posaconazole or isavuconazole as sole or predominant antifungal therapy for COVID-19-associated mucormycosis. A retrospective observational case series. *Int J Infect Dis*. 2022; 120:177-178.

Background

AmB has been the mainstay of treatment for invasive mucormycosis and the new azoles have been recommended as step-down or step-up. Unavailability of AmB during the epidemic of CAM in India required the use of azoles as primary therapy based on non-inferiority results of VITAL, SECURE & MoveOn studies.

Hypothesis

Unavailability or failure of AmB (±PCZ) needs new options. PCZ & ISVCZ with doses optimized for attaining the required PK PD indices by TDM or by extrapolative considerations could fill this therapeutic gap

Methods

PCZ or ISVCZ were given based on availability, affordability, site of infection rather than on pre-set criteria. Some had disease progression elsewhere while on AmB & were initiated on PCZ or ISVCZ. Some with prominent skull base or cerebral involvement had a switch from PCZ to ISVCZ due to lack of response. TDM was used for PCZ in all cases & for ISVCZ for some cases when it became available

Results

16/28 patients were cured, 5 improved, 6 died, of which 2 were directly attributable to IM & 1 was lost to follow-up These outcomes compare favourably with those among patients treated with AmB in other studies.

Applicability in my practice

Treatment used in this study during pandemic conditions was by compulsion rather than by intention. Hence wider applicability of these findings cannot be assumed. Can use PCZ or ISVCZ in future instead of AmB with greater confidence if the latter cannot be given due to various reasons.

Lamoth F, Lewis RE, Kontoyiannis DP. Investigational Antifungal Agents for Invasive Mycoses: A Clinical Perspective. *Clin Infect Dis*. 2022; 75(3):534-544.

Background

Fungi have fewer distinct metabolic pathways that can be selectively inhibited. AF resistance, adverse drug reactions, drug-drug interactions mean that there is an unmet clinical need for better therapy.

Hypothesis

New agents with novel chemistries, better PD, PK could be useful for difficult to treat IFI

Results

See Figure Below

Applicability in my practice

Rezafungin (given once weekly) for continuation of treatment and prophylaxis. Ibrexafungerp highlights include PO, bone penetration, synergy with Ech, AmB. Olorofim for Scedosporium, Lomentospora, *F. oxysporum*. Fosmanogepix is oral and broad spectrum. These new agents need thoughtful integration into practice. IM still remains a challenge

Antifungal drug	*Candida* spp.		*Aspergillus* spp.		*Mucorales*	*Fusarium* spp.	*Scedosporium / Lomentospora* spp.
	Wild-type[1]	Echinocandin-resistant[2]	Wild-type[3]	Azole-resistant[4]			
Rezafungin	Except *C. parapsilosis* (higher MIC)						
Ibrexafungerp							
Olorofim						Activity against *F. oxysporum* >> *F. solani*	
Manogepix	Except *C. krusei* (higher MIC)					Some resistant isolates (*F. oxysporum*, *F. verticilloides*)	Few resistant isolates (*S. apiospermum*)

Activity against most isolates; Variable activity (species-specific or isolate-specific); Marginal activity (few susceptible isolates or relatively high MIC); No significant activity

INTRODUCTION TO CLINICALLY RELEVANT CARDIAC TOXICITY AND DRUG INTERACTIONS WITH AZOLES

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Invasive fungal infections (IFIs) are difficult to treat for a variety of reasons and have a high mortality rate. Challenges associated with a diagnosis of (IFIs) and host factors such as neutropenia, continuous immunosuppressive medication, malignancies, and comorbidities significantly affect survival. Antifungal drug toxicity and pharmacological drug-drug interactions with co-administered medicines are a small and often neglected but also important factor affecting patient outcomes. In this article, we are describing important toxicities and common drug interactions with azoles in clinical practice.

Case 1: A 10 year female Ms. KP, 28 kg weight was admitted with fever with chills off and on up to 101.8° F for last 45 days for which she has received multiple courses of broad-spectrum antibiotics. Reason for current hospitalization was diffuse abdominal pain for last 7 days and watery coffee brown colored diarrhea since last 4 days. Her CT scan examination of abdomen & pelvis showed evidence of proctitis. CT scan thorax was unremarkable except bilateral pleural effusions. Sigmoidoscopic examination revealed pseudomembranous colitis and stool examination for C. difficile GDH and toxin was positive.

She was tachycardic with pulse rate 100/min and BP: 100/60 mm of Hg. Her other laboratory reports were grossly deranged; Hb: 6.2 gm/dl, WBC: 34,200/cmm, DC: 91% Polys, 7% Lymphos, platelet counts: 52,000/cmm , Na: 130 mmol/L, K : 2.57mmol/L, total protein: 4.76 gm/dL, Alb: 2.02 gm/dL, CRP 33 times ULN, Procalcitonin: 33.61 ng/ml. She was treated with metronidazole, oral vancomycin and correction of hypokalemia. Histopathology reports of biopsy from descending colon and sigmoid reported focally eroded mucosa, infiltrated by neutrophils, ulcer slough reveals presence of budding yeast forms of candida species with edematous lamina propria. Intravenous fluconazole 200mg was added to current antimicrobials.

Follow up on 6th hospitalization day, patient showed marked clinical improvement following antimicrobials, with no abdominal pain. She started eating and tolerating oral feed, passing formed stool and no fever in last 72 hours. Her further testing revealed normal serum beta d glucan (11.71 pg/ml), and hypokalemia was corrected with K: 3.81 mmol/L. Her baseline ECG on admission was normal with QTc: 486 ms. Repeat ECG on 3rd day of fluconazole showed prolongation of QTc 541 ms. (Figure 1) Repeat electrolytes, serum calcium and magnesium advised with daily ECG. Patient suddenly died same day during sleep likely to be related to cardiac arrhythmia/Sudden cardiac death.

QTc and Azoles

A QTc of more than 500 msec or a QTc rise of more than 60 msec after treatment raises serious concerns about the potential risk of sudden cardiac death from Torsade de Pointes (TdP).[1]

All triazole antifungal medications, with the exception of isavuconazole, have been linked to QTc prolongation. Fluconazole was shown to be associated with the largest number of TdP/QT prolongation records (61.61%). Patients between the ages of 45 and 65 had the highest prevalence (31%) of triazole-related TdP/QT prolongation. According to one study, the adverse effects of TdP/QT prolongation can appear anywhere from 0-14 days after taking any of the four triazoles.

Proactive prevention and therapy of Torsade de Pointes (TdP)/QT prolongation is strongly recommended due to the severity of the condition and the potential mortality it can cause. Because of the combined mechanism of increased exposure of the co-administered medication and sharing the same cardiac toxicity, the risk is increased when azoles are used concurrently with other medications implicated in QTc prolongation and metabolized by the CYP3A4 system, such as amiodarone, astemizole, terfenadine, and cisapride. ECG and serum electrolyte monitoring—especially potassium, calcium, and magnesium—are crucial in preventing fatal cardiac arrhythmias. Clinicians should also be careful while combining azole with other agents with QTc prolongations like hydroxychloroquine, quinolones, azithromycin, clarithromycin and other agents.[2]

Case 2: A 30-year-old female was receiving stable immunosuppressive therapy (MMF, Tac, and prednisolone 5mg) for living-related renal Tx for the past two years, with normal renal function. She developed diabetes following the transplant and is currently receiving oral hypoglycemic agents. During a routine medical checkup, the nephrologist identified oral candidiasis and prescribed fluconazole 200 mg orally, once per day, for two weeks. After 12 days since her last routine consultation, the patient was hospitalized with headache, hypertension, insomnia, irritability, and hallucinations of two days duration. The patient exhibited no fever, respiratory, or urinary symptoms. She was responsive to verbal commands, irritable, and her systemic evaluation revealed no neck rigidity. Her blood pressure was 170/110 mmHg, her pulse rate was 88 beats per minute, and her temperature was normal. Laboratory results revealed S. creatinine levels of 2.4 mg/dL, complete blood count of 5200/cmm, and normal levels of electrolytes, urine, and liver function. Prior to 12 days, she was healthy with normal renal function. Her current symptoms of headache, irritability, insomnia, and hypertension, accompanied by an acute renal injury, raised the possibility of tacrolimus toxicity. Her serum tacrolimus concentration was 24 mg/L, which were very high. A renal biopsy confirmed the toxicity of tacrolimus.

She fully recovered by reducing her tacrolimus dosage. Fluconazole was discontinued after two weeks, and the patient resumed her original tacrolimus dosage over the next two weeks.

Why did she develop tacrolimus toxicity?

There are significant pharmacological interactions between fluconazole and tacrolimus. Clinicians should be aware of these drug interactions with azole antifungals, as they can result in loss of therapeutic effect or toxicity of the co-administered medication by altering its hepatic metabolism, as seen in the case described above.

Azoles are substrates for and inhibitors of cytochrome P450 (CYP450) enzymes, particularly CYP3A4, as well as membrane transporter inhibitors, including P-glycoprotein (P-gP). Most of the medications are metabolized by the enzyme CYP3A4, which is found in the liver and gastrointestinal tract. Due to the inhibitory effect of azoles, coadministration of drugs metabolized by CYP3A4 and/or P-gP can result in increased exposure and toxicity, necessitating dose reduction and therapeutic drug monitoring to maintain efficacy. Among azoles, itraconazole and posaconazole are more potent inhibitors of CYP3A4 as compared to fluconazole or voriconazole.[3]

Other drugs with the potential to affect the hepatic microsomal system by inducing or inhibiting CYP3A4 can also impact azole levels and therapeutic efficacy. (Table 1) Itraconazole and voriconazole are metabolized by the liver while fluconazole is mainly excreted unchanged into the urine, and hepatic metabolism via CYP3A4 accounts for only 11% of the total drug excreted. So, fluconazole is less affected by other drugs with potentials to induce or inhibits hepatic microsomal enzyme system. While voriconazole is a substrate for CYP2C19 and, to a lesser extent, for CYP2C9 and CYP3A4. Itraconazole is predominantly metabolized by CYP3A4 and is the only azole antifungal drug with an active metabolite hydroxy-itraconazole. Posaconazole metabolism involves glucuronidation of the drug. These agents are susceptible for drug interactions from the other drugs with potentials to induce or inhibits hepatic microsomal enzyme system. Explanation for understanding the interpretation of table 1. Carbamazepine is a substrate for CYP3A4, so inhibiting this enzyme with azoles increases carbamazepine exposure, necessitating

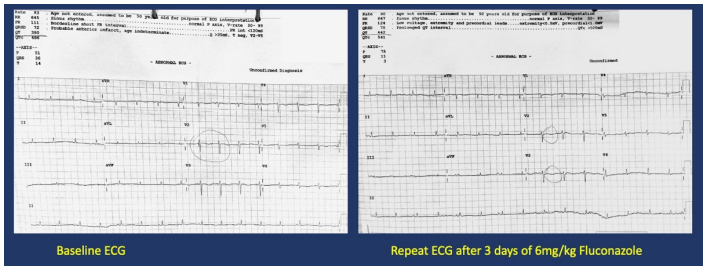

Figure 1: ECG of case # 1

Table 1: Metabolic pathways of commonly used drugs relevant to azoles

Anticonvulsants	Substrate	Induce
Carbamazepine	CYP3A4	CYP3A, CYP 2C19, UGT
Phenobarbital Pnehytoin	CYP2C9, CYP2C19	CYP3A4,2C9,2C19
Gabapentin, Pregabalin, Topiramate and Levetiracetam	excreted unchanged	-
Lipid Lowering		
Atorvastatin Rosuvastatin	CYP3A4	-
Pitavastatin	UGT, OATP1B1	-
Antimicrobials		
Azithromycin	CYP3A4 minor	-
Clarithromycin	CYP3A4	CYP3A4
Erythromycin		CYP3A4
Rifampicin		CYP3A4
Rifabutin	CYP3A4	CYP3A4
Sedatives		
Benzodiazepines Alprazolam Diazepam Zolpidem Nitrazepam Clonazepam Midazolam	CYP3A4 & Mix CYP enzymes	-

monitoring of plasma levels. It also induces CYP3A and 2C19 and can decrease voriconazole levels, whereas voriconazole increases carbamazepine exposure.

Take home messages

Toxicities, particularly QTc prolongations, must be closely monitored while prescribing an azole antifungal. Many other drugs have substantial drug-drug interactions with azoles and a formal drug interaction check should be done before prescribing azoles. Patients may need frequent therapeutic drug monitoring and dose adjustments for concomitantly given medicines such as tacrolimus, cyclosporine, and others.

References

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HEPATOSPLENIC CANDIDIASIS IN PEDIATRIC ACUTE LYMPHOBLASTIC LEUKEMIA

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Case report

A 6-year-old boy, recently diagnosed with B-Acute lymphoblastic leukaemia (ALL) and initiated on induction chemotherapy (prednisolone, vincristine, pegaspargase), presented on day 9 of chemotherapy with complaints of fever and bilateral leg pain. On examination, his hemodynamics were stable, and the systemic exam was unremarkable. He was neutropenic with ANC <500. Blood cultures were sent, and meropenem was given. While in hospital, he developed a papular rash over the trunk and limbs (Figure 1). He was started on amphotericin B in view of persistent neutropenia (ANC 100) and high-grade temperature. Ultrasound abdomen and 2D echo showed normal study. He had mild worsening of leg pain, which he had since admission. On examination, there was tenderness and swelling of the knee joint, and the fluctuation test was positive. USG knee joint revealed 3-5ml fluid collection in the left knee joint and a normal right knee joint.

Blood cultures showed yeast, finally reported as pan sensitive Candida tropicalis (Box 1). Serum BDG was 509 pg/ml. Amphotericin was changed to micafungin. He had prolonged febrile neutropenia and persistent candidemia on repeat cultures after 72 hours of therapy. His fever gradually settled on micafungin, and knee joint tenderness improved. His WBC improved to >1000 on day 22 of induction. His steroid dose was reduced due to candidemia. He was afebrile for two days, further blood cultures cleared, and he was discharged in a stable condition on micafungin 50mg once daily as an outpatient.

One week after discharge, he continued his chemotherapy at day care (vincristine and oral prednisolone). He again had a low grade of fever and lack of wellbeing. A PET-CT scan revealed multiple lesions in the liver, spleen, kidney, small lesions in gastrocnemius, soleus, sartorius, gracilis, right plantar fascia (Figure 2,3).

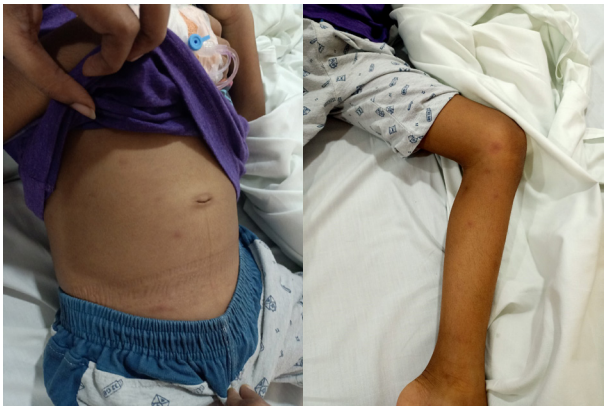

Figure 1: Papular rash on the trunk and lower limb.

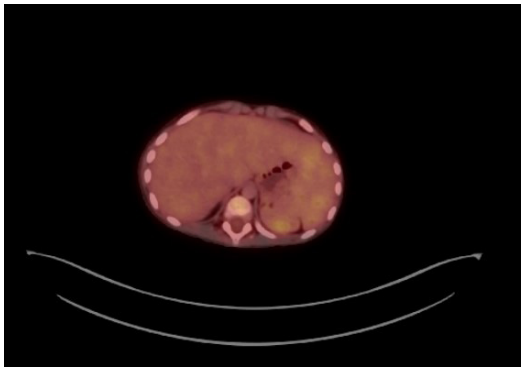

Figure 2: Multiple FDG avid lesions in the liver and spleen.

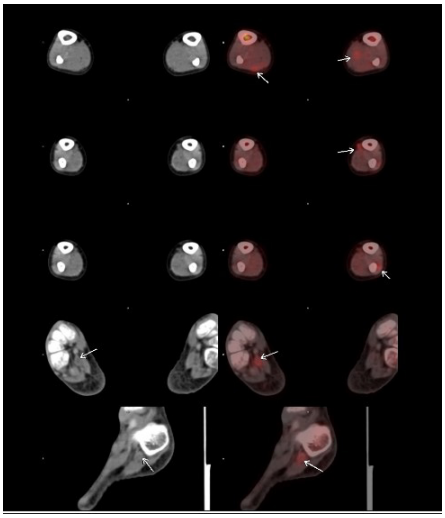

Figure 3: Multiple small lesions in the leg muscles and foot.

Micafungin was continued for four weeks and then switched to fluconazole 12 mg/kg, i.e., 150 mg orally once a day, which was planned to continue until his chemotherapy sessions are completed and remission achieved. He improved clinically from an infection perspective and continued therapy for his leukaemia.

Discussion

Hepatosplenic candidiasis, also known as chronic disseminated candidiasis[1], is an uncommon syndrome seen almost entirely in patients with hematologic malignancies and who have just recovered from neutropenia[2]. ALL is the most common underlying malignancy in patients with HSC, and most of them develop HSC during the induction phase of chemotherapy[3]. Our patient with recently diagnosed ALL was initiated on induction chemotherapy and presented on Day 9 with fever and leg pain. Organ involvement in chronic disseminated candidiasis includes liver, spleen, kidneys, skin and retina: our patient had involvement liver, spleen, kidneys, skin, and lower limb muscles. Ultrasonography is a helpful screening imaging modality; however, a CT scan is more sensitive. The role of PET-CT in diagnosis and subsequent assessment of treatment response is well studied[4]. IDSA recommendations are

1. Initial therapy with lipid formulation AmB, 3–5 mg/kg daily or an echinocandin for several weeks, followed by oral fluconazole, 400 mg (6 mg/kg) daily
2. Therapy should continue until lesions resolve on repeat imaging, premature discontinuation of antifungal therapy can lead to relapse
3. Chemotherapy or hematopoietic cell transplantation if required, should not be delayed because of the presence of chronic disseminated candidiasis, and antifungal therapy should be continued throughout the high-risk period to prevent relapse[5].

Conclusion

A high index of suspicion is needed for the diagnosis of hepatosplenic candidiasis. Species identification and drug susceptibilities should be obtained whenever possible. Intravenous amphotericin or echinocandin for the initial four weeks followed by oral fluconazole is recommended management. Treatment should continue till all lesions are resolved on follow-up imaging. If further chemotherapy or other immunosuppression is planned, treatment should continue until such immunosuppression lasts to prevent relapse.

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A CASE OF INFLUENZA ASSOCIATED INVASIVE PULMONARY ASPERGILLOSIS

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An eighty year old female patient with diabetes, hypertension, chronic Atrial fibrillation (AF) and COPD was admitted to ICU with complaints of fever, cough and breathlessness for 3 days. She was mildly tachypneic and hypoxic at admission. Chest X-ray (Figure 1) on admission was normal. Treatment with oxygen by nasal prongs, ceftriaxone, azithromycin and steroids by the primary unit was initiated. Six days later, the patient had respiratory deterioration and ID opinion was taken. The HRCT (Figure 2) showed multiple nodules with surrounding ground glass opacities (halo sign).

With the clinical deterioration and radiological findings, the possibility of invasive pulmonary aspergillosis (IPA) was considered. Serum galactomannan was positive. So the patient had clinico-radiological and mycological features of IPA but no host factor was found so far. The onset of illness with respiratory symptoms and normal chest X ray suggested the possibility of respiratory viral infection. Hence, URTI Biofire (Multiplex PCR) was advised which was positive for Influenza A H3 and Parainfluenza Virus 3. Thus the entry criterion of a preceding viral illness, with ICU admission was added giving a diagnosis of probable Influenza-associated pulmonary aspergillosis (IAPA).[1] Patient was started on Oseltamivir 75 mg twice daily and Isavuconazole 200 mg thrice daily for initial 2 days followed by 200 mg once daily. Isavuconazole was preferred over voriconazole and posaconazole in view of AF since both these drugs cause QT prolongation while isavuconazole produces QT shortening. Serum galactomannan after 7 days showed a reduction to 1.08. Patient improved symptomatically and radiologically, hence was discharged.

Influenza infection is identified as a risk factor for IPA in immunocompromised and immunocompetent hosts including normal individuals, and is therefore described as entry criterion rather than host factor.[1] This also increases the positive predictive value of S. galactomannan in such a patient. IAPA has been described following multiples subtypes of influenza A and influenza B infections. IPA can also complicate other viral infections such as SARS-CoV-2, respiratory syncytial virus, parainfluenza, and adenovirus.[2] Pathogenesis involves damage to epithelium, defective fungal host responses and sporulation followed by invasive growth. The median time between influenza diagnosis and IAPA is reported to be 2 days (range 0–4 days).[1] These data suggest that IAPA typically presents early in the course of influenza infection among patients admitted to ICU. It has high mortality of approximately 50 %. Corticosteroids and interestingly neuraminidase inhibitors are also implicated to be risk factors for the development of influenza-associated IPA, and are associated with poor prognosis.[1]

Measures to prevent IAPA include cessation of smoking, emphasizing influenza vaccination in high risk patients. Patients with influenza needs close monitoring

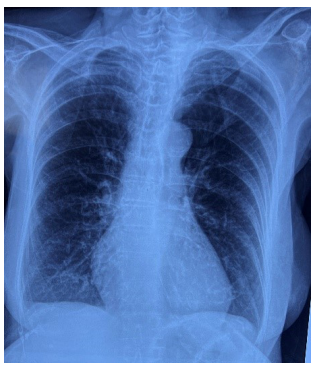

Figure 1: Normal chest x ray on initial presentation

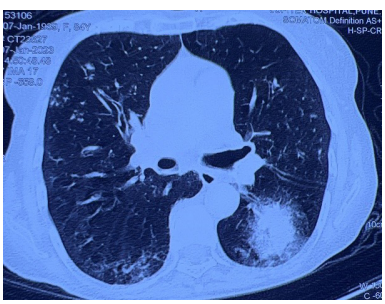

Figure 2: Nodular opacities with GGO- halo sign.

and testing for IAPA especially if critically ill with multiple risk factors. It is uncertain at present whether prophylaxis for IA in selected patients is warranted and calls for further studies.

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TRIPLE TROUBLE: MYELOMA, TUBERCULOSIS AND HISTOPLASMOSIS

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Introduction

This case with triple problems of multiple myeloma, tuberculosis and histoplasmosis has several diagnostic and management issues and hence is discussed here.

Case report

This 61 year old non diabetic male and resident of Mumbai presented with pain and swelling in the right chest wall in Jan 2020. He was investigated for myeloma and M band was positive with bone marrow aspiration showing 10% plasma cells. CT showed rib lesion with bilateral adrenal enlargement. The swelling was aspirated and it showed necrotizing granulomas with AFB. The Xpert MTB/ Rif was positive with no rifampicin resistance. He was HIV negative. Treatment with HRZE was initiated following which he developed drug induced hepatitis and treatment was modified. Therapy for myeloma was deferred at that time. After around 6 months of anti TB therapy and myeloma diagnosis in June 2020, he developed oral and facial lesions (Figure). A biopsy of the oral lesion showed intracellular yeast suggestive of histoplasmosis. No cultures had been sent. A diagnosis of disseminated histoplasmosis was made and treatment with itraconazole was initiated @ 200 mg thrice daily for 3 days and then 200 mg twice daily. The anti TB therapy was modified to a non-rifampicin based regime including isoniazid, levofloxacin, pyrazinamide and ethambutol. Itraconazole drug levels were performed after 2 weeks and were sub therapeutic. The dose was increased to 200 mg thrice daily with which therapeutic levels were achieved. There was gradual healing of the skin and oral lesions. The patient tolerated itraconazole well but had significant joint pains which resolved only after stopping pyrazinamide and levofloxacin. Hence anti TB treatment was modified to include isoniazid, ethambutol and cycloserine. Repeat PET scan, 3 months after initiating anti histoplasma therapy showed increase in bone lesions, increase in plasma cells in bone marrow to 29% and increase in light chains and hence chemotherapy for myeloma was advised. It was however again deferred by the relatives. Anti TB treatment was stopped after 1 year and itraconazole was continued. The repeat imaging showed persistent enlargement of the adrenal glands but no other feature of histoplasmosis. Finally after 15 months of anti histoplasma therapy and 21 months of myeloma diagnosis, chemotherapy for myeloma was started. Itraconazole was continued during the initial part of chemotherapy but then stopped later due to gastrointestinal adverse effects. The patient is currently on chemotherapy for myeloma and is free of histoplasmosis and tuberculosis

Discussion

This case raises several issues worth discussion. The first is the accuracy of diagnosis. Here, diagnosis was made only by histology and no microbiologic tests could be performed. The other intracellular yeast like organisms which should be differentiated from histoplasmosis in the Indian setting include talaromycosis, cryptococcosis and Candida glabrata (1). Second issue is the source of infection.

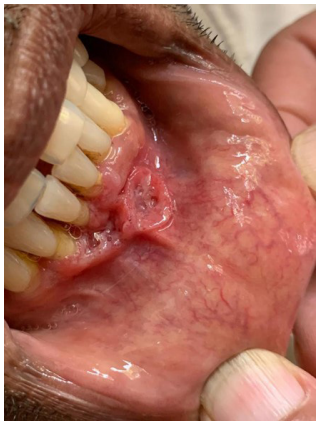

Figure: Oral lesions in the index patient

Histoplasmosis is now being reported from most states of India and not just the Gangetic belt (2). This patient however probably acquired infection from caves near Dehradun (Uttarkhand) which he visited a few months before he fell sick. The next issue is what led to disseminated histoplasmosis since he did not have the traditional risk factors for the disease? We hypothesize that the myeloma caused subtle immune disturbances which probably lead to both tuberculosis and histoplasmosis. The fourth issue is co administration of anti tubercular and antifungal therapy. Since rifampicin significantly reduces levels of all azoles including itraconazole, there was no option but to eliminate rifampicin from the regimen (3). Fortunately since the patient had already received 6 months of rifampicin based therapy, sacrificing the drug was not as difficult as it would be in a patient with newly diagnosed extensive tuberculosis. Fifthly, the importance of therapeutic drug monitoring with itraconazole cannot be over emphasized (4). This patient achieved therapeutic levels only with increased doses. Patients should be counselled to take the capsules with fatty meal. The syrup formulation which is taken empty stomach or with acidic beverages such as colas is now available in India but has poor oral tolerability. Finally should antifungal therapy be continued during periods of immunosuppression as secondary prophylaxis? While there are no guidance documents for HSCT and chemotherapy patients, recommendations for solid organ transplant recipients have been published. They report relapse rates of less than 5% if adequate initial therapy has been given and discourage continuation of azole therapy. Screening by repeated urine histoplasma antigen tests may be done if available to detect relapse (5).

To conclude, histoplasmosis poses challenges related to diagnosis and treatment especially in the setting of coinfections and immunosuppressive therapy.

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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 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 haematologists, critical care providers, ID specialists, pulmonologists, neurologists, medical mycologists and many other clinicians handling serious and immunocompromised patients.The trust consists of clinicians and mycologists and was instituted on 3rd March 2012 at Mumbai, India.