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THERAPEUTIC DRUG MONITORING (TDM) OF ANTIFUNGALS IN CLINICAL PRACTICE: A QUICK GUIDE FOR CLINICIANS

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Invasive fungal infections are associated with high mortality. Several factors affect antifungal drug pharmacokinetics including age, weight, food/drug interactions, metabolism (genetic polymorphism), and liver disease. Hence the need for monitoring drug levels in patients receiving antifungals. Therapeutic drug monitoring (TDM) is generally required for drugs with narrow therapeutic index (Flucytosine), variable or unpredictable pharmacokinetics (Voriconazole, Itraconazole), and drugs which have established relationship between plasma drug concentrations with efficacy or toxicity (Voriconazole, Itraconazole, Posaconazole). TDM is not required for monitoring amphotericin B and Echinocandin therapy and is also not well determined for the newer azole-isavuconazole.

Timings for blood collection for determining drug level

Drug levels are generally checked for peak level (toxicity) and trough level (effectiveness). For peak level sample need to be collected at 2 hours after consuming drug while for trough level, blood should be draw before administration of next dose. Clinicians should be aware about PK parameters of the drug to decide timing as the drug may take several days to weeks before it achieves steady state level in plasma after initiating therapy. e.g. voriconazole takes 3-5 days while posaconazole take 7 days to achieve steady state levels. Loading dosage of drug is given to achieve early steady state levels.

Fluconazole

After oral administration, fluconazole is rapidly and fully (bioavailability >90%) absorbed, with a time to maximum absorption of 0.5–1.5 h after intake of medication. Fluconazole has linear and predictable PK parameters and hence TDM is not required except when patient is receiving renal replacement therapy (CVVHD), malabsorption, drug interactions with concomitant medications and to check compliance. Important PK parameters of Fluconazole are shown in Box 1.

- Linear & predictable PK over dose range 50 -800 mg/day with normal renal function
- Wide tissue distribution
- $t_{½}$ = 25 -40 hours
- AUC = administered dose, i.e. 800mg produce AUC of 800ml/L
- Predictable blood levels: every 100 mg results in level of 5µg/ml, 800mg = 40µg/ml in healthy volunteers

Voriconazole

Voriconazole (VCZ) has high (96%) oral bioavailability in adults. It exhibits saturable metabolism and demonstrates nonlinear kinetics, irrespective of the route of administration. Increasing doses result in supra proportional increases in drug levels. A dosage increase from 3 to 4 mg/kg intravenously every 12 hours results in a 2.3-fold increase in area under the curve. While in pediatric patients, VCZ oral bioavailability is 44.6 – 66% and elimination appears to be faster compared with adults, requiring higher weight-based doses. While higher VCZ concentrations 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 4 times higher exposure to VCZ compared with extensive metabolizers. VCZ pharmacokinetics has high interpatient variability. Current literature suggests that trough concentrations at steady state should be used to evaluate plasma VCZ concentrations. Initial trough concentrations should be obtained 5 days after the start of therapy to ensure that steady state concentrations have been achieved. Desirable VCZ trough level for therapeutic range is 1–5.5 µg/mL. Multiple studies suggest better clinical outcomes in patients whose VCZ trough level is > 1mcg/ml.[1,2] Higher VCZ level is associated with higher incidence of visual disturbances, heaptotoxicity and neurologic toxicity (eg, confusion, hallucinations, extrapyramidal effects).[3]

Dear Friends,

It gives me great pleasure in presenting you the 2nd issue of this newsletter. This issue discusses an interesting case of fungal endocarditis, the role of drug monitoring in fungal infections and what is the latest in the fungal world. Feedback is welcome.

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Posaconazole

Posaconazole displays linear PK with dosages of 50-800mg/day. It has saturation of absorption above 800mg/day and takes ~7-10 days to achieve steady state concentrations. Studies conducted in hematological patients found that breakthrough infections are higher in patients whom posaconazole level is < 700ng/ml.[4,5]

Itraconazole

Oral bioavailability is variable and dependent on the type of formulation. Oral suspension has 30% higher bioavailability then the capsule formulation. Bioavailability of capsule is increased by food (Coca Cola) and gastric acidity while solution is better absorbed with empty stomach. The recommended therapeutic levels are 1 µg/ml.

Flucytosine

Oral flucytosine absorption is rapid with 80-90% sbsorption efficiency is and excreted mainly by the kidney (90%). It has a narrow therapeutic index (30-80 mg/L) with concentration dependent drug toxicity (blood dyscrasias, hepatic injury, or GI disturbances with Peak >100 mg/L). For TDM, obtain 2 hr post-dose concentrations after 3-5 doses and repeat levels 1-2 times weekly if fluctuating renal function.[6]

Conclusions

TDM helps clinicians in individualizing drug therapy to maximize treatment benefit, reduce the risk of failure and drug toxicity in patients with invasive fungal infections. They can also be used to monitor compliance. Unfortunately, in India we have limited numbers of specialized labs that perform these assays. Another limitation is the high cost of these assays.

Table: Summary recommendation of TDM of antifungals

Drug	Timing for sample	Target level
Voriconazole	Trough level at 3-5 days	1.5 -5.5 µg/ml
Posaconazole	Trough level, at 5 -7 days	Prophylaxis; > 0.7 µg/ml Treatment: > 1.0 µg/ml
Itraconazole	Trough Level, at 7 days	0.5 – 4.0 µg/ml
Flucytosine	Trough level & 2h after dose within three days of starting treatment	Pre-dose: 20-40 µg/ml Post-dose: 50 -100 µg/ml

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AN UNCANDID ENCOUNTER

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A 25-year-old lady presented in January 2014 in Medanta-The Medicity with history of fever since 1 month (Dec 2013). The fever was persistent despite on ceftriaxone, gentamicin and meropenem (administered in various other institutes). On enquiry she was found to have severe aortic stenosis (AS) with bicuspid aortic valve for which she had undergone aortic valve balloon dilatation (ABVD) elsewhere in October 2012. On examination she was found to have petechial haemorrhage over the conjunctiva (Figure 1), anaemia and absent left dorsalis pedis artery. Limb Investigations revealed neutrophilic leuocytosis (WBC- 11,600 & Neutrophils- 90%). Transthoracic echocardiography (TTE) revealed a large vegetation measuring 2.2 X 1.8 cm at aortic valve; a small cavity (?? Abscess) at root coronary cusp with protrusion of small part of vegetation into right ventricular cavity with no aortic regurgitation (AR). Blood cultures were positive for *candida tropicalis* (Figure 2, 3 and 4). She was also found to have bilateral candida endophthalmitis. She was started on L-AmB (4 mg/Kg/day) along with 5-FC (100 mg/kg/day). Two days on treatment, she developed an episode of syncope. Cardiopulmonary resuscitation (CPR) was done and the patient was revived. Color Doppler of the lower limbs showed left lower limb ischemia with emboli in the left femoral artery. She was immediately operated – vegetation excised (Figure 5), aortic valve replacement (AVR) was done using a bioprosthetic valve and a dacron patch was used for covering VSD. Left femoro-popliteal embolectomy was done. Post surgery, she developed complete heart block for which permanent pacemaker implantation (PPI) was placed.

Fig. 4: Blood cultures positive for *candida tropicalis*

Investigation	Result
Aerobic C&S Blood	Positive
Organism	Comment
0161 Candida tropicalis	
Antibiotic	**Sensitivity**
Amphotericin B	S
Fluconazole	S
Caspofungin	S
Voriconazole	S
Flucytosine	S

Post op Day 10, patient developed leucocytosis. On examination, there was tenderness at CVC site and repeat peripheral blood cultures- ¼ were positive. CVC was removed and caspofungin 150 mg added. Repeat blood cultures after 72 hrs were negative. 3 weeks later, patient developed fever, oral ulcers & eosinophilia. The blood cultures were negative. L-AMB and 5FC was stopped in view of drug fever. IV Caspofungin 150 mg OD was continued for 6 weeks followed by oral fluconazole which is being continued as chronic suppressive therapy.

The patient is doing well at 3 years of follow up.

Fig. 1: Petechial Haemorrhage over the conjunctiva in the patient with IE

Fig. 2: Gram stain showing budding yeast

Fig. 3: Blood culture growing smooth colonies of candida

Fig. 5: Vegetation form the infected aortic valve

Discussion

Candida infective endocarditis is an emerging problem. Diagnosis is difficult and delayed. Risk factors include cardiac valvular surgery in most cases, cancer chemotherapy, prolonged presence of CVCs, IV drug use, & prior bacterial endocarditis.

Optimum therapy for Candida IE (native valve and prosthetic valve) is a combination of valve replacement and a long course of antifungal therapy. The IDSA guidelines recommend liposomal amphotericin B 3-5 mg/ kg/day with/ without flucytosine as initial therapy. However, AmB and azoles have decreased activity when compared with echinocandins against biofilms and penetrate poorly into vegetations. Because of the alarming mortality rate associated with fungal IE and the availability of newer antifungal drugs, in particular fungicidal drugs like the Echinocandins, recommendations have evolved. The current IDSA guidelines therefore recommend high dose echinocandins (caspofungin 150 mg/day/ anidulafungin 200 mg/ day or micafungin 150 mg/day) as acceptable alternatives. The index case also showed a satisfactory response to the echinocandins. In case the isolate is fluconazole susceptible, de escalation to fluconazole 400-800 mg/day is possible once the patient is stable, the candidemia has cleared. The duration of therapy is 6 weeks post replacement or even longer. The current guidelines recommend life long suppressive therapy in case of prosthetic valve endocarditis.

This case illustrates the challenges and resources involved in managing a case of candida endocarditis. In this patient, temporal association suggest AVBD as the possible risk factor and thus the importance of infection control measures cannot be overemphasized

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WHAT IS NEW IN THE FUNGAL WORLD?

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Candida auris candidaemia in Indian ICUs: analysis of risk factors

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Objectives: To identify the risk factors associated with Candida auris candidaemia, as this fungus now poses a global threat.

Methods: We performed a subgroup analysis of a previously reported study of 27 Indian ICUs. The clinical data of candidaemia cases due to C. auris and other Candida species were compared to determine significant risk factors associated with C. auris infection.

Results: Of the 1400 candidaemia cases reported earlier, 74 (5.3%) from 19 of 27 ICUs were due to C. auris. The duration of ICU stay prior to candidaemia diagnosis was significantly longer in patients with C. auris candidaemia (median 25, IQR 12–45 days) compared with the non-auris group (median 15, IQR 9–28, p<0.001). Based on logistic regression modelling, admission to north Indian ICUs [OR 2.1 (1.2–3.8); p= 012], public-sector hospital [OR 2.2 (1.2–3.9); p =0.006], underlying respiratory illness [OR 2.1 (1.3–3.6); p =0.002], vascular surgery [OR 2.3 (1.00–5.36); p=0.048], prior antifungal exposure [OR 2.8 (1.6–4.8);p<0.001] and low APACHE II score [OR 0.8 (0.8–0.9); p= 0.007] were significantly associated with C. auris candidaemia. The majority (45/51, 88.2%) of the isolates were clonal. A considerable number of isolates were resistant to fluconazole (n=43, 58.1%), amphotericin B (n=10, 13.5%) and caspofungin (n=7, 9.5%).

Conclusions: Although C. auris infection has been observed across India, the number of cases is higher in public-sector hospitals in the north of the country. Longer stay in ICU, underlying respiratory illness, vascular surgery, medical intervention and antifungal exposure are the major risk factors for acquiring C. auris infection even among patients showing lower levels of morbidity.

Comments

Candida auris has emerged as a challenge due to its nosocomial transmission, outbreak potential, multidrug resistance and associated high morbidity & mortality.

C. auris has the biologic & epidemiologic potential for extensive emergence & dissemination. Although isolates in each region of the world are similar & different from those in others, recent inter-continental clonal spread has been documented. C. auris has the ability to produce prolonged outbreaks & occupy unidentified niches in the hospital environment by its thermo-tolerence & ability to form large clusters. The intensivist in the Indian ICU should be vigilant for C. auris infection in patients with prolonged ICU stay and prior antifungal exposure.

There are difficulties in timely & definitive identification of C. auris by many commercial tests. The optimal treatment is unknown but may involve using multiple classes of AF agents in the highest doses. Overall the emergence of this pathogen is a grim reminder of the emergence of Carbapenem-resistant-Enterobacteriaceae.

Invasive Pulmonary Aspergillosis-mimicking Tuberculosis

Sung-Han Kim, Mi Young Kim, Sun In Hong, Jiwon Jung, Hyun Joo Lee. *Clin Infect Dis* 2015; 61:9-17.

Background: Pulmonary tuberculosis is occasionally confused with invasive pulmonary aspergillosis (IPA) in transplant recipients, since clinical suspicion and early diagnosis of pulmonary tuberculosis and IPA rely heavily on imaging modes such as computed tomography (CT).

Methods: All adult transplant recipients who developed tuberculosis or IPA at a tertiary hospital in an intermediate tuberculosis-burden country during a 6-year period were enrolled. First, we tested whether experienced radiologists could differentiate pulmonary tuberculosis from IPA. Second, we determined which radiologic findingscould help us differentiate them.

Results: The CT findings of the 28 patients with tuberculosis and 80 patients with IPA were compared. Infarct-shaped consolidations and smooth bronchial wall thickening were more frequent in IPA and mass-shaped consolidations and centrilobular nodules (<10 mm, clustered) were more frequent in tuberculosis. Besides, findings of post primary pulmonary tuberculosis such as centrilobular nodules, branching linear and nodular opacities, patchy or lobular areas of consolidation, and cavities, are helpful in distinguishing TB from other pulmonary infectious diseases.

Conclusions: Certain CT findings appear to be helpful in differentiating between IPA and tuberculosis. Nevertheless, the CTfindings of about one-third

of pulmonary tuberculosis cases in transplant recipients are very close to those of IPA.

Comments: CT findings of Invasive Pulmonary Aspergillosis can be confused with those of post-primary TB in high TB endemicity countries. However a timely diagnosis of either condition is important for the immunocompromised patient as well as for public health.

The time of diagnosis from the onset of immunocompromise appears to be earlier for IPA than for TB, although there is some overlap. Ser Galactomannan also shows positivity in TB in a proportion of cases. Thus epidemiologic, radiologic & microbiological tests are all need to be factored in for making these diagnoses & should be extensively studied in regions such as India, where both diseases occur commonly.

Fluconazole Prophylaxis for the Prevention of Candidiasis in Premature Infants: A Meta-analysis Using Patient-level Data
Clin Infect Dis 2016; 63:604-610.DOI:https://doi.org/10.1093/cid/ciw363

Background: Invasive candidiasis (IC) is an important cause of sepsis in premature infants and is associated with a high risk of death and neurodevelopmental impairment. Prevention of IC has become a major focus in very low birth weight infants, with fluconazole increasingly used as prophylaxis.

Methods: We identified all randomized, placebo-controlled trials evaluating fluconazole prophylaxis in premature infants conducted in the United States. We obtained patient-level data from the study investigators and performed an aggregated analysis. The occurrence of each endpoint in infants who received prophylaxis with fluconazole vs placebo was compared. Endpoints evaluated were IC or death, IC, death, Candida colonization, and fluconazole resistance among tested isolates. Safety endpoints evaluated included clinical and laboratory parameters.

Results: Fluconazole prophylaxis reduced the odds of IC or death, IC, and Candida colonization during the drug exposure period compared with infants given placebo: odds ratios of 0.48 (95% confidence interval [CI], .30–.78), 0.20 (95% CI, .08–.51), and 0.28 (95% CI, .18–.41), respectively. The incidence of clinical and laboratory adverse events was similar for infants who received fluconazole compared with placebo. There was no statistically significant difference in the proportion of tested isolates that were resistant to fluconazole between the fluconazole and placebo groups.

Conclusions: Fluconazole prophylaxis is effective and safe in reducing IC and Candida colonization in premature infants, and has no impact on resistance.

Comments: Prophylaxis for Invasive Candidiasis (IC) in at risk patients is a subject of great interest. Invasive Candidiasis is very consequential for infants with <1500 gm weight. Infants with IC are at risk of developing shock, meningitis, renal failure, retinopathy of prematurity, periventricular leaukomalacia and chronic lung disease.

Fluconazole prophylaxis reduces IC and candida colonization. Despite reduction in IC there was no effect on mortality during period of exposure. However, reduction in IC is clinically significant as complications associated with IC can be prevented. Adverse drug reactions with fluconazole & emergence of resistance were not significant. As with all preventive interventions questions about the numbers needed to treat & prophylactic versus pre-emptive & empiric strategies will remain. Fluconazole is a relatively "friendly" drug to use. If infections with Fluconazole resistant Candida need to be prevented, is there a suitable agent available for extensive use ?