ISSN: 2349-5197
Impact Factor: 3.765

INTERNATIONAL JOURNAL OF RESEARCH SCIENCE & MANAGEMENT

ASSOCIATION OF CD4 LEVELS WITH FLUCONAZOLE RESISTANCE IN HIV / AIDS PATIENTS WITH OROPHARYNGEAL CANDIDIASIS AT HAJI ADAM MALIK GENERAL HOSPITAL MEDAN

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DOI: 10.5281/zenodo.3734282

Keywords: AIDS/HIV, CD4, Oropharingeal candidiasis, Fluconazole, Sensitivity test.

Abstract

Oropharingeal candidiasis is clinically characterized by decline of CD4. The standard treatment for oropharingeal candidiasis by CDC 2009 recommendation is fluconazole. Treatment with fluconazole often develops failure of therapy, high relapse and incidence in HIV / AIDS patients.The aim of this study was toinvestigate the association of CD4 levels with fluconazole resistance in HIV / AIDS patients with oropharingeal candidiasis in RS.H. Adam Malik. The crosssectional approach on 36 HIV / AIDS patients with oropharingeal candidiasis in January-August 2017. Patients who fulfilled inclusion criteria were examined CD4 and candida sensitivity test. Data analysis using Fisher Exact Test and Mann-Whitney U test. The level of fluconazole resistance to CD4 was 19.4% and fluconazole resistance to C.albicans was 8%, while for C.non albicans the level of resistance to fluconazole was 45%. The candid a sensitivity test results on fluconazole did not have significant differences (p> 0.05) and there was a significant difference in CD4 levels with the type of candida species. There was no association of CD4 levels with sensitivity test results and there was association between the type of fungus with the sensitivity test results. There was a significant difference in CD4 levels with the type of candida species.

Introduction

Anti-fungal resistance can be a serious problem in the future, with widespread fungal infections and fewer available therapeutic options.Candidial fungi which are the normal flora, especially the digestive tract, the mucous membrane lining, the vagina, the urethra, the skin and under the fingernails hands and feet and live as a saprophyte in the human body which was previously thought to be contaminant proved resistant to all available antifungal drugs can even lead to invasive and life-threatening infections. This would be an emerging fungi or an emergency for AIDS patients and patients with immune system disorders [1,2].

Fluconazole resistance in candiasis in HIV/AIDS patients based on data from Centers for Disease Control and Prevention (CDC) United States in 2013 found about 7% bloodstream infection caused by candida resistant to fluconazole, most of which is Candida glabrata and increased prevalence of antifungal resistance class azole in candida isolate because of the type of strain of candida that resistant azole group [3,4] .

The earliest possible action of fluconazole in candidiasis has a significant impact on patient outcomes. The prophylaxis strategy of candididase with the administration of fluconazole in high-risk patients such as HIV / AIDS and patients with impaired immune system may initially benefit but in the treatment of oropharyngeal candidiasis patients HIV / failure of therapy, either in the form of high recurrence rate or incidence. Prolonged and repeated use of fluconazole in HIV / AIDS patients may cause resistance problems. Fluconazole resistance in HIV / AIDS patients with opportunistic infection of candidiasis is found with CD4 <50 cells / mm3 and opportunistic infections of oropharyngeal candidiasis in HIV / AIDS patients are common on CD4 <200 cells / mm3 [5,6]

Invasive candidiasis is one of the leading causes of nosocomial infections worldwide due to significant morbidity, mortality and healthcare rates. Patients with candidemia have a higher risk of death compared to

bacterial caused bloodstream infections. Several studies reported mortality rates as high as 47% in patients suffering from invasive candidiasis. Over 90% of life-threatening deep tissue diseases are caused by 5 of 15 fungal pathogens: C.albicans, C.glabrata, C.tropicalis, C.parapsilosis and C.krusei [7,8,9].

HIV / AIDS is one of the greatest public health threats today, according to the Durban International AIDS conference, South Africa's study found that the rate of HIV infection is increasing and the number of HIV / AIDS patients is likely to increase, the number of new HIV infections is high and increases time period. A substantial increase in the number of HIV / AIDS patients in the coming years and a tendency to increase incidence rates and the prevalence of fluconazole resistance in oropharyngeal patients HIV / AIDS patients around the world. antifungal resistance becomes a serious problem in the future. This problem of resistance needs to be addressed immediately by the search for new anti-fungal drugs. The discovery of new class of anti-fungal drugs is relatively slow, so the report needs to be watched, so it is important to develop effective prophylactic and treatment strategies in order to avoid problems caused by resistant fungi [10,11]

Methods

The purpose of this study is to find out the characteristics of HIV / AIDS patients with oropharyngeal candidiasis and analysis of the relationship of fluconazole resistance with CD4 levels in HIV / AIDS patients in hospitals. H. Adam Malik.

Patient Selection

This study uses analytical research methods with cross-sectional study design, conducted at the General Hospital Haji Adam Malik Medan in januari – August 2017. The samples were taken with total sampling technique. All sample patients is HIV / AIDS patients suffering from oropharyngeal Candidiasis. Ekclusion criteria wasPatients who had received fluconazole, pregnant and lactating mothers. This study was approved by Research Ethics Committee approval of the university medical faculty of North Sumatra and the hospital of Adam Malik.

Statistical Methods

Data analysis was performed through univariate and bivariate analyses using the SPSS 22nd version (SPSS Inc., Chicago) with a 95% confidence interval. Bivariate analysis was performed using Mann-Whitney U test with significance $p<0.05$.

Result

This study was followed by 36 subjects of HIV / AIDS patients suffering from oropharyngeal Candidiasis who have fulfilled the inclusion and exclusion criteria at RSUP H. Adam Malik Medan with the number of men 26 people (72.7%) and men 9 (11.1%) with the median age of 35 years. The most common marital status is unmarried 20 people (55.6%), The most common risk factor is sex and injection drug user (IDU) 26 people (72.7%), The most common of Candida sensitivity test results is sensitive 29 people (80.6%), The most common of type fungi is Candida albicans as much as 24 (66.7%), Candida tropicalis 3 (8.3%), Candida parapsilosis 1 (2.8%), Candida glabrata 4 (11.1%), Candida famata 2 (5.6%) and Candida lusitaniae 2 (5.6%).The median level of CD4 was 30.39 sel/mm^3 (6.1-1317).**(Tabel 1)**

In this study, a Mann-Whitney U test showed that there weren't significant relationship between CD4 level with Candida sensitivity test result ($p = 0.069$) in HIV/AIDS patients.**(Tabel 2)**

In this study, a Mann-Whitney U test showed that there were significant relationship between type of fungi with Candida sensitivity test result ($p = 0.069$) in HIV/AIDS patients.**(Tabel 3)**

Disscussion

This study obtained demographic data in the form of age, sex, marital status, risk factors and CD4. According to data from the Directorate General of PPM and PL of the Ministry of Health of the Republic of Indonesia in 2009, more than 50% of HIV / AIDS patients are young adults and productive age. Similarly, in the study of oropharyngeal candidiasis in HIV / AIDS patients in Lagos, Nigeria in 2008, 88.7% of the subjects were at a

young adult age of 213 samples of HIV / AIDS patients with oropharyngeal candidiasis by 18-28 19.70%, age 29-39 years as much as 42.20%, age 40-50 years as many as 26.80, age 51-61 years of 9.90% and> 62 years of 1.4%. [11] This study was followed by as many as 36 people of research subjects with the most age range at the age of young adult group of 70%.

The risk factor of HIV transmission in this research is mostly found is sex with injection drug as much 26 people (72.2%). Previous studies conducted by Yang H et al (2005) that the risk factors of HIV / AIDS transmission are the most are sexual risk factors, risky sexual behavior is a major factor related to HIV / AIDS transmission. [12]Transmission of HIV / AIDS in Indonesia based on risk factors occurred in sexual (heterosexual) in January - March 2016. Transmission of HIV from drug users by needle syringe is the greatest risk of rapid HIV transmission in Indonesia.[13]

Oropharyng candidiasis has been reported to occur 80-95% in HIV / AIDS patients [11]. According to reporting data from the Ministry of Health (2014) opportunistic infection in patients with HIV / AIDS caused by candidiasis (1,316 people) the highest after tuberculosis (1,085 people) and chronic diarrhea (1,036 people). [14] The results of Djauzi S et al. (2003) showed that the most frequent opportunistic infections in Cipto Mangunkusumo Hospital were oropharyngeal-esophageal (80.8%), tuberculosis (40.1%), cytomegalovirus (28.8%), among others are toxoplasma encephalitis, P. carinii pneumonia, herpes simplex, Mycobacterium Avium Complex (MAC).[15] Solomon et al (2008) study in India of opportunistic infections in HIV-positive patients injecting drug users gave the following results: hepatitis C 94.1%, oropharyngeal graft 43,2%, pulmonary tuberculosis 33,9%, lower respiratory tract infection 16 , 1% and others such as hepatitis B, herpes zoster / simplex From some of the above data it appears that the infection of candidiasis is an opportunistic infection disorder that most often attacks the gastrointestinal system.[16]

The use of fluconazole as a therapy and prophylaxis of oropharyngeal candidiasis in HIV / AIDS patients is extensive and inadequate resulting in resistance to fluconazole. Several studies have suggested that fluconazole resistance is associated with decreased CD4 cell count and an elevated viral load in HIV /AIDS patients. Failure of fluconazole therapy is due to the continued immunosuppression factor in patients with HIV / AIDS resulting in the emergence of high recurrence.[17] In other study by Wiliam et al (1997), The highest risk of fluconazole resistance in CD4 + HIV / AIDS patients is below 50 cells / mm3. In this study the sample population of 36 patients showed 30 patients (83.3%) with CD4 cell count <50 cells / mm3 and there were 6 patients (16.7%) with CD4 count> 50 cells / mm3.[18]

In this study identification of species of Candida and the sensitivity test of flukonazole ,'antifungal by using Vitek 2 tools. Sensitivity test result is grouped that is sensitive and resistant. In this study, there were 36 subjects in which 29 patients (80.6%) responded with fluconazole (sensitive) treatment with 7 patients (19.4%) who were insensitive or resistant to the treatment of fluconazole

Based on statistical test in this study showed the results of the correlation test is not significant (p> 0.001) and there is a difference between the amount of CD4 levels with fluconazole resistance in HIV / AIDS patients. The results of this study are similar to those of previous studies conducted by Zhang lulu et al.That fluconazole resistance has no relationship to CD4 cell count and viral load. [7]

In this research, most of the samples were 24 Candida albicans (63.7%), Candida glabrata, 4 samples (11.1%), Candida tropicalis, 3 samples (8.3%), Candida famata, 2 samples (5.6%), Candida lusitanie as much as 2 samples (5.6%) and Parapsilosis Candida as much as 1 sample (2.8%). The species responsible for oropharyngeal candidiasis in HIV / AIDS patients in this study were Candida albicans. This is in accordance with the AIDS Info guidelines data (October 2017) suggesting that the majority or most of the glorious species of oropharyngeal candidiasis in HIV / AIDS patients is Candida albicans. The results of this study were consistent with previous research that the incidence of the identification of Candida albikans in the oral cavity was reported to be 95% in HIV / AIDS patients [19] and oropharyngeal candidiasis can also be caused by non-albicidal Candida by glabrata Candida, krusei Candida, tropicalis Candida.[20]Candida albicans yeast is a commensal fungus in healthy individuals, although it can also be a pathogen in immunocompromised

disorders.[21]Candida albicans in normal circumstances can live in balance with various other microbes in the intestine. Individuals with suppressed immune systems, normal body fungi can cause disease.[22]

Based on the statistics in this study showed significant (category <0.01) categorical test results between species of candida species with fluconazole resistance in HIV / AIDS patients where non-albicidal Candida species were more likely to be resistant to fluconazole compared to albicans albicans species in HIV / AIDS patients . Resistance to the antifungals of fluconazole are grouped into two: intrinsic resistance and extrinsic resistance. In extrinsic resistance there is a sensitivity pattern of the previously sensitive species of candida to anti-fungal therapy and then becomes resistant, whereas in the intrinsic resistance of the candidiasis oropharyngeal candidate species has occurred early on against anti- In this research, there was an intrinsic resistance in the form of infection caused by Glabrata Candida / Kandida non albikans on 5 samples. Fluconazole resistance in Crustic Candida is caused by a disturbance of the 14α-demethylase enzyme causing failure in the function of fluconazole inhibition.

Resistance to fluconazole is common in patients with long-term use of fluconazole. In this study patients with a history of fluconazole were excluded and the study subjects were newly diagnosed HIV / AIDS patients and had never received fluconazole prophylaxis therapy. The results of this study indicate the presence of non-albican species that are resistant to fluconazole.

Recurrent oropharynx candidiasis and previous antifungal use were predictive factors that allegedly led to changes in species species of non-albicans. This may be due to recurrent oropharyngeal infarction patients exposed to antifungal use and on the further course of HIV / AIDS disease also found extensive fungal colonization.[11]

Rosana's research (2015) assessed the presence of mutations in albicans that infect HIV / AIDS patients. Research has reported the presence of resistance to the anti-fungal drug fluconazole. Resistance mechanisms are reported to occur genetically, mutation and gene overexpression.[23]

Conclusion

Fluconazole resistance rate at RSUP.H. Adam malik field is higher than other Asian countries. The type of candida fungus in HIV / AIDS patients at RSUP.H.Adam Malik Medan is albikans kandida (66.7%), glabrata Candida (11.1%), tropicalis Candida (8.3%) , Candida famata (5.6%), Candida lusitaniae (5.6%) and Candida parapsilosis (2.8%). There was no association of CD4 levels with fluconazole resistance levels in HIV / AIDS patients at Adam Malik hospital. Candida no albicans species were found in HIV / AIDS patients with lower CD4 levels.The use of fluconazoel antifungal can still be used on oropharyngeal candidiasis patients based on the right indication so as not to cause an increase in antifungal resistance.Need for further research, multicenter with more samples and studies linking fluconazole resistance to oropharyngeal candidiasis with CD4 in HIV / AIDS patients.

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