Prevalence and clonality of Non Albicans Candida Species

Saba Memon[1], Najia Karim Ghanchi[2], Urooj Zafar[1]*, Joveria Farooqi[2], Kauser Jabeen[2]
[1]Department of Microbiology, University of Karachi, Pakistan
[2]Agha Khan University, Pakistan
*E-mail: sabamemon19@yahoo.com

ABSTRACT

Introduction: Invasive infections with Non Albicans Candida species are a global concern due to poor clinical outcomes and propensity to acquire resistance to antifungal agents. Non Albicans Candida species acquires antifungal resistance through mutation of drug target (*ERG11*), *FKS* 1and / or 2 gene and up regulation of ABC-transporter genes, etc. Multilocus sequence typing (MLST) is an efficient tool to study the molecular structural population of regional *C. glabrata* isolates and its comparison with global strains. The available data on antifungal resistance, molecular mechanisms of resistance and molecular epidemiology in clinical Non Albicans Candida species isolates is limited.

Objectives: This study evaluated antifungal resistance pattern, and minimum inhibitory concentrations (MICs) distribution, molecular determinants of drug resistance to azoles and echinocandins (*FKS1, FKS2* and *ERG11*) and clonality in invasive Non Albicans Candida species isolates from Pakistan. The results of this project will be critical for patient management, antifungal surveillance and control of invasive Non Albicans Candida species infections in the country.

Material and Method: Antifungal susceptibility data of 277 candidemia, deep organ and soft tissue (invasive) *C. glabrata*isolates against fluconazole, voriconazole, itraconazole, posaconazole, caspofungin, micafungin, anidulafungin and amphotericin B was retrieved. Susceptibility testing was performed using colorimetric broth microdilution and interpreted using CLSI criteria. Demographics, clinical history and outcome were also studied. Chi-square test was used to demonstrate association between antifungal resistance and clinical characteristics of the patients. Hence, 36 clinical invasive *C. glabrata* strains were analyzed for *FKS1* and *FKS2* gene mutations. Whereas 8 isolates were selected for *ERG11* gene mutation analysis.

Results: All 25 isolates were phenotypically identified as *C. auris (n=7), C. glabrata (n=8), C. parapsilosis(n=7)*and *C. tropicalis (n=3)*. The median (range) MICs for fluconazole was 128 (2-256) mg/L. Coding and non-coding region of *ERG11* from 25 isolates were sequenced and analyzed (Table 1).

In case of *C. auris*twonon-synonymous mutation at position Y132F and K143R wereobserved in5/7(72%) and 1/7(14%). One synonymous mutation L333 was also found in one non-can did emic*C. Auris* isolate.The *ERG11* nucleotide sequence analysis revealed synonymous mutation in *ERG11*coding region and non-synonymous mutation in non-coding region of *C.glabrata*. There was one non-synonymous mutation in fluconazole resistant *C. glabrata* isolate at position I166S in non-coding region. Novel synonymou smutations at position I100 and D278 were observed in 3/8 (38%) and 4/8 (50%) of the isolates, respectively. Where as previously reported D256, L341, P519 and R527 synonymous mutations in *ERG11* gene were observed in 8/8 (100%), 5/8 (63%) and 2/8 (25%) isolates respectively. In*C. Parapsilosis* non-synonymous mutation at position Y132F was observed in 6/7 (86%) isolates. In*C. tropicalis*, two non-synonymous mutation in coding region at position Y132F and S154F in *ERG11* gene were observed in all three fluconazole resistant isolates. Three novel non-synonymous mutations at position I277M, Y408N and I518V were observed in 1/3(34%), 2/3 (67%) and 1/3 (34%) of the isolates. Further more, synonymous mutations

were observed 3/3 (100%) at position C75 and L88, where as K454 was 2/3 (67%) and I518 was 1/3 (34%) respectively.

Conclusion: Emergence of fluconazole resistance in *C. tropicalis* and *C. Parapsilosis* from Pakistanis alarming. Phenotypi cresistance in *C. tropicalis*and*C. Parapsilosis* correlate with mutations in *ERG11* gene. Mutations in *ERG11* genein*C. Auris* corresponds to previously reported data fromPakistan. Ou rresults highlight the emergence of fluconazole resistance in previously susceptible *Candida* species, which is concerning due to toxicity o rlimited availability of altérnate treatment options.

Keywords: Antimicrobial drugs resistance, Candida, Non-Albicans candida species

ACKNOWLEDGMENT

Deans of science Research Grant, University of Karachi

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