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Molecular mechanisms and clinical features of fluconazole-resistant Candida spp.

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Background: Azole resistance in *Candida spp.* is slowly emerging and has been associated with various different mechanisms. We aimed to investigate the resistance mechanisms and clinical features of fluconazole non-susceptible (FNS) *Candida spp.* recovered from a major regional tertiary referral hospital in Singapore.

Material/methods: All non-duplicate FNS *Candida* blood isolates collected during a candidemia surveillance study conducted from 2012 to 2015 were included for analyses. A fluconazole-susceptible (FS) control isolate (fluconazole MIC ≤2mg/L for *Candida albicans* and *Candida tropicalis*, MIC ≤32mg/L for *Candida glabrata*) was included for each FNS isolate. RTPCR was performed for the evaluation of *CDR1*/*CDR2*/*MDR1*/*ERG11* expression. Gene over-expression was defined as >3x the value of the wild-type ATCC strain. *ERG11* gene mutation analyses were performed using PCR and sequencing. Clinical information was collected retrospectively and included demographics, antifungal therapy, and outcomes.

Results: Forty-eight (24 FNS, 24 FS) isolates were included (8 *C. albicans*, 32 *C. tropicalis*, 8 *C. glabrata*). Cross-resistance to other azoles was detected in all FNS isolates except 2 *C. albicans*. In 7 out of 8 *C. albicans* isolates (3 FS and 4 FNS), amino acid substitutions in Erg11p were detected (FS – D116E, D153E, A383C, S536L; FNS – A114S, Y257H, V488I; both FS and FNS – E266D). A114S and Y257H were detected together in 3 FNS isolates. No amino acid substitutions were detected in FS *C. tropicalis*, while 3 amino acid substitutions (Y132F, F145L, S145F) were detected in 8 out of 16 FNS *C. tropicalis*. Y132F and S145F were detected together in the 8 FNS *C. tropicalis*. Two amino acid substitutions (I166S, L172P) were detected in 3 *C. glabrata* isolates (2 FS and 1 FNS). All Erg11p substitutions have been previously reported except S536L, I166S and L172P. **Figure 1** illustrates the mean relative expression levels of *ERG11*/*CDR1*/*CDR2*/*MDR*. The rates of overexpression of the various genes were similar among FS and FNS *Candida spp.*, with the exception of *CDR2* in *C. albicans* (0/4 FS vs. 3/4 in FNS). Eight FNS *C. tropicalis* did not exhibit any of the studied mechanisms. FNS isolates were more commonly isolated from patients with prior azole exposure

(40% vs. 8%, p=0.008). Echinocandins were the most common definitive treatment prescribed (88%). High mortality was observed in patients with both FNS and FS *Candida* infections (64% vs. 48%, p=0.25).

Conclusions: Different mechanisms of azole resistance are implicated in different *Candida spp*. A114S and Y257H Erg11p substitutions and *CDR2* overexpression were predominant mechanisms in FNS *C. albicans*, while the role of gene overexpression was less significant in *C. tropicalis* and *C. glabrata*. Azole resistance was more commonly observed in patients with prior antifungal exposure. Knowledge of these resistance mechanisms may allow rapid detection of these gene targets to guide antifungal therapy.

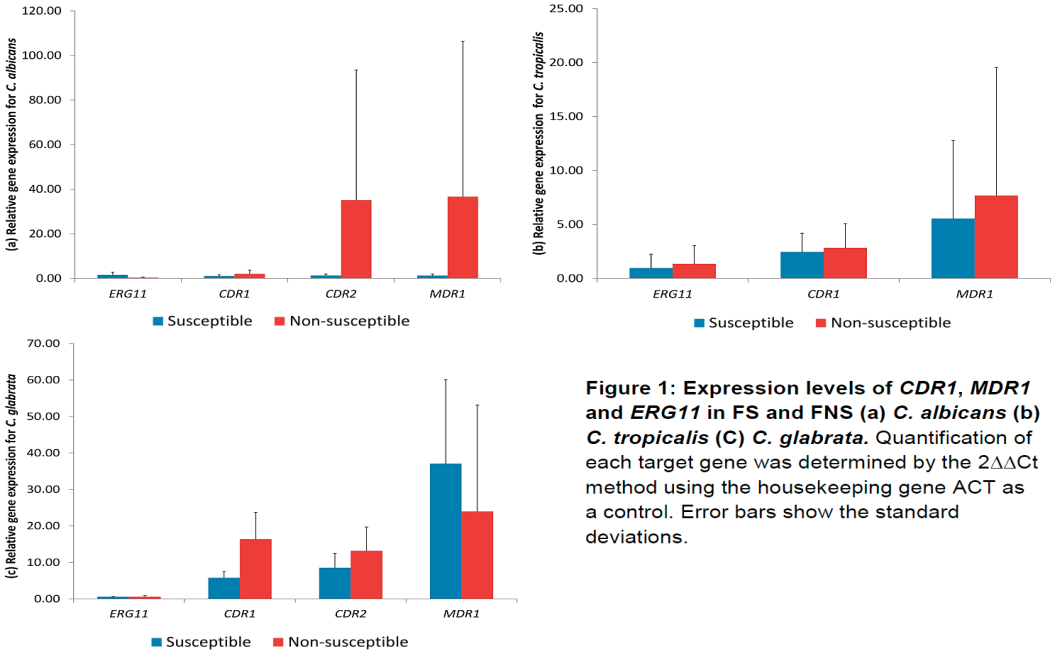

Figure 1: Expression levels of *CDR1*, *MDR1* and *ERG11* in FS and FNS (a) *C. albicans* (b) *C. tropicalis* (C) *C. glabrata.* Quantification of each target gene was determined by the 2ΔΔCt method using the housekeeping gene ACT as a control. Error bars show the standard deviations.