Risk Factors and Clinical Outcomes of Patients with Fluconazole Nonsusceptible *Candida tropicalis* Bloodstream Infections

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Objectives

Fluconazole non-susceptibility (FNS) rates have increased among *C. tropicalis* isolates in Asia. We aimed to explore the proportions and risk factors of candidemia caused by FNS *C. tropicalis* and the impact of FNS on patient outcomes.

Methods

There was a prospective *Candida* bloodstream infections (BSIs) cohort in a single medical center at Northern Taiwan. We retrospectively analyzed the first episode of *C. tropicalis* BSIs between 2011 and 2017. Antifungal susceptibility testing of the first isolate of each episode was performed by the microdilution colorimetric Sensititre YeastOne SYO-09 panel, and the results were interpreted according to Clinical and Laboratory Standards Institute (CLSI) species-specific breakpoints.

Results

During the study period, three hundred and forty-four episodes of *C. tropicalis* BSIs were identified. Of them, 58 (16.9%) first blood isolates were non-susceptible to fluconazole, including 10 isolates belonging to susceptible dose-dependent and 48 isolates belonging to resistance. The proportions of *C. tropicalis* BSIs and fluconazole resistant rates showed an increasing trend by years (both $P = 0.07$, **Figure 1**). There were no differences of patient outcomes, including 14-day and 30-day mortality, and persistence, between FNS BSIs and fluconazole susceptible (FS) BSIs (**Figure 2**). Compared to patients with FS BSIs, those with FNS BSIs were more likely to have moderate to severe liver disease, leukemia, receipt of steroid and antifungal exposure (AE), but less receipt of parental hyperalimentation compared to those infected by FS isolate (all $P < 0.05$). Of note, around 55% patients with FNS BSIs were azole naïve (**Table 1**).

Conclusion

Fluconazole resistance increased in *C. tropicalis* BSIs, but didn't worsen patient outcomes. Immunocompromised hosts and those with azole exposure were at risk for FNS *C. tropicalis* BSIs. Further investigations were warranted for azole naïve patients with FNS *C. tropicalis* BSIs.

Figure 1. Distributions of fluconazole susceptibility categories among 344 *Candida tropicalis* blood isolates (primary Y axis) and proportions of *C. tropicalis* in *Candida* bloodstream infections (secondary Y axis) by year. Primary Y axis: % of fluconazole resistance (red bar), susceptible dose dependent (yellow bar), and susceptible (grey bar); Secondary Y axis: % of *C. tropicalis* (black line); X axis: Year; Numbers below year: numbers of isolates in a given year

Figure 2. Comparisons of 14-day and 28-day mortality and persistent BSI patients grouped by fluconazole susceptibility categories. Y axis: % of patients with above outcomes. X axis: Three different outcomes. Fluconazole resistance (FR, red bar), susceptible dose dependent (FSDD, yellow bar), and susceptible (FS, grey bar); persistence defined as *C. tropicalis* isolated from blood at least 5 days after onset

Table 1. Comparisons of clinical characteristics between FS and FNS *C. tropicalis* BSIs.

Characteristics [#]	FS Group (n=286)	FNS Group (n=58)
Age, years	62.4 (53.0-74.4)	63.4 (55.1-72.1)
Male	165 (57.7)	36 (62.1)
Charlson comorbidity index	3.5 (2.0-6.0)	4.0 (2.0-7.0)
Congestive heart failure	25 (8.7)	4 (6.9)
Mild liver diseases	45 (15.7)	6 (10.3)
Moderate-to-severe liver diseases^{\$*}	13 (4.5)	6 (10.3)
Moderate-to-severe renal diseases	83 (29.0)	13 (28.3)
Diabetes mellitus	63 (22.0)	18 (31.0)
Solid tumor	151 (52.8)	27 (46.6)
Leukemia^{\$}	38 (13.3)	13 (22.4)
Lymphoma	18 (6.3)	3 (5.2)
Parental hyperalimentation^{\$}	39 (84.8)	29 (63.0)
Steroid use^{\$}	133 (46.5)	37 (63.8)
Chemotherapy	123 (43.0)	30 (51.7)
Neutropenia	155 (54.2)	34 (58.6)
Antifungal exposure^{\$*}	34 (11.9)	26 (44.8)
ICU onset	85 (29.9)	20 (34.5)
APACHE II score	20.0 (15.0-26.0)	19.0 (15.25-26.0)
Primary BSI	122 (42.7)	23 (39.7)
Catheter-related BSI	111 (38.8)	18 (31.0)
Urinary tract infection	51 (17.8)	13 (22.4)
Intra-abdomen infection	10 (3.5)	2 (3.4)
Appropriate antifungal agents w/in 48hr^{\$}	244 (85.3)	17 (29.3)
Removal of central venous catheters w/in 48hr	131 (55.0)	31 (64.6)

[#] Continuous variables: median (IQR); Categorical variables: numbers (%)

^{\$} Univariate analysis, $P < 0.05$

^{*} Multivariate logistic regression: **Antifungal exposure** (aOR, 6.00; 95% CI, 3.17-11.36); **Moderate-to-severe liver diseases** (aOR, 3.14; 95% CI, 1.05-9.33)