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Antifungal drug susceptibility and resistance

Echinocandin Mics Against Candida Species at Hospitals That Routinely Perform Susceptibility Testing of Bloodstream Isolates

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Objectives. Reference broth microdilution methods of *Candida* echinocandin susceptibility testing are limited by inter-laboratory variability in caspofungin minimum inhibitory concentrations (MICs). Recently revised Clinical Laboratory Standards Institute (CLSI) breakpoint MICs for echinocandin non-susceptibility may not be valid for commercial tests employed in hospital laboratories. Our objectives were to report echinocandin susceptibility data for *Candida* spp., as generated in real-time by hospital laboratories and reported to clinicians.

Methods. We conducted a multi-center, retrospective study of 9 U.S., Australian and New Zealand (N.Z.) hospitals that routinely tested *Candida* bloodstream isolates for echinocandin susceptibility from 2005-2013.

Results. In a survey of U.S. tertiary care teaching hospitals, 53% (8/15) reported that their clinical microbiology laboratory performed routine echinocandin susceptibility testing of *Candida* bloodstream isolates. Seven U.S., one Australian, and one N.Z. hospital participated in the study. Eight hospitals used Sensititre YeastOne assays. *Candida* spp. were *C. albicans* (n=1,067), *C. glabrata* (n=911), *C. parapsilosis* (n=476), *C. tropicalis* (n=185), *C. krusei* (n=104), and others (n=154). Resistance and intermediate rates were ≤1.4% and ≤3%, respectively, for each echinocandin against *C. albicans*, *C. parapsilosis* and *C. tropicalis*. Resistance rates among *C. glabrata* and *C. krusei* were ≤7.5% and ≤5.6%, respectively. Caspofungin intermediate rates among *C. glabrata* and *C. krusei* were 17.8% and 46.5%, respectively, compared to ≤4.3% and ≤4.4% for other echinocandins. Using CLSI breakpoints, 18% and 19% of *C. glabrata* were anidulafungin-susceptible/caspofungin-non-susceptible and micafungin-susceptible/caspofungin-non-susceptible, respectively; similar discrepancies were observed for 38% and 39% of *C. krusei*. Resistance rates for the three agents against *C. glabrata* were comparable across centers (range: 0 – 16%); however, intermediate rates between centers varied more for caspofungin (5-45%) than anidulafungin (0 – 3.1%) or micafungin (0 – 11.5%). If only YeastOne data were considered, inter-hospital

modal MIC variability was low (within 2-doubling dilutions for each agent). There were no significant trends in the emergence of resistance to each of the echinocandins over time.

Conclusions. YeastOne assays employed in hospitals may reduce the inter-laboratory variability in caspofungin MICs against *Candida* species that are observed between reference laboratories using CLSI broth microdilution methods. Echinocandin resistance was most common for *C. glabrata* and *C. krusei*, but rates were stable over the study period. Hospitals may overstate caspofungin-non-susceptibility rates among *C. glabrata* and *C. krusei* by using CLSI breakpoints to interpret YeastOne MICs. The significance of classifying isolates as caspofungin-intermediate and anidulafungin/micafungin susceptible will require clarification in future studies. Uncertainties surrounding echinocandin susceptibility testing of *Candida* spp. may dissuade centers from offering routine MIC measurements in-house.