

Prevalence of Fluconazole Resistance in *Cryptococcus neoformans* Isolates from HIV⁺ Patients in Kampala, Uganda

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Background: Widespread use of fluconazole to treat or prevent fungal infections in HIV⁺ persons increases selective pressure for resistance. Fluconazole resistant *Cryptococcus neoformans* have been reported worldwide, including 16% of Ugandan *C. neoformans* isolates in the 1990s. In Sub-Saharan Africa, 10-week survival rates after cryptococcal meningitis are <50% in routine care. Whether increased fluconazole drug resistance contributes to this high mortality is currently unknown. We hypothesized that fluconazole resistance in *C. neoformans* isolates would be higher than previously reported due to more widespread fluconazole use.

Methods: Broth macro-dilution assays to determine fluconazole minimum inhibitory concentration (MIC) were prospectively performed on 80 initial cryptococcal isolates collected from Ugandans with AIDS and cryptococcal meningitis admitted to Mulago Hospital, Kampala, Uganda, who then received amphotericin B and fluconazole combination induction therapy.

Results: Only 21.3% of isolates (17/80) collected at the time of CM diagnosis had fluconazole MIC ≤ 8 $\mu\text{g/mL}$ (susceptible); whereas 68.8% of isolates (55/80) had MIC between 16-32 $\mu\text{g/mL}$ (susceptible dose-dependent), and 10% of isolates (8/80) had MIC ≥ 64 $\mu\text{g/mL}$ (resistant) at CM diagnosis. 3 of 8 persons with fluconazole resistant yeasts, died within 1 week. Thereafter, regardless of initial fluconazole MIC, CM relapse was uncommon in this population who received combination amphotericin + fluconazole induction therapy. Of 3 relapse events, 2 isolates had unchanged MIC being susceptible (8 $\mu\text{g/mL}$), susceptible dose-dependent (32 $\mu\text{g/mL}$), and 1 isolate developed 8-fold increase in MIC to become fluconazole resistant (256 $\mu\text{g/mL}$) within 3 weeks of initial diagnosis.

Conclusions: The majority of *Cryptococcus* isolates in Uganda had either dose-dependent susceptibility or resistance to fluconazole. In the setting of

amphotericin induction, relapse rates were very low. Initial consolidation therapy should likely routinely use higher dose fluconazole therapy (800-1200 mg/day) until cerebrospinal fluid (CSF) cultures are sterile. These data further support that induction fluconazole mono-therapy may intrinsically fail in a significant number of persons, yet fluconazole mono-therapy remains the most common CM treatment in Sub-Saharan Africa. Future studies are needed to determine the role of fluconazole susceptibility in relation to more detailed patient outcomes.