
INVESTIGATION OF ASSOCIATION OF HETERORESISTANCE TO FLUCONAZOLE (FCZ) IN C, NEOFORMANS MENINGITIS (CM), DEVELOPMENT OF RESISTANCE (R) AND FAILURE OF THERAPY (RX)

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Introduction Failure to respond to FCZ in CM is a concern, and R development has been occasionally reported. In addition, hetero-R isolates (subpopulations heterogenous in susceptibility to FCZ) have been noted, including from patients (pts.) not treated with FCZ. Whether hetero-R explains Rx failures is unknown. A prior study (J. Clin. Micro. 41:267) indicated a prevalence of 4% hetero-R, using a definition of growth at 4xMIC on agar at 30°C. **Methods** We studied thusly isolates of 7 CM pts. deemed Rx failures; including failure to respond, relapse or persistent CSF cultures. The interval between Rx onset and failure isolates was 119-1352 d. in 6; unclear in 1 with relapse. **Results** PCR fingerprinting revealed identity of isolates from individual pts.. In 5 pts., FCZ was the sole or main Rx agent: initial isolate broth macrodilution MICs were 2-8 µg/ml, and all showed a 2-32 fold increase on Rx, with then 4 MIC 8-16 µg/ml and 1 R (32-64 µg/ml on 3 serial post-Rx isolates). In 2, amphotericin was main or sole Rx, and FCZ MIC decreased on Rx. Three of 5 developing, and 2/2 not developing, increased FCZ MIC showed hetero-R initial isolate (4xMIC agar 14-100% and 105-108% of control growth, respectively); 0/7 had highly R clones (growth on 64 µg/ml agar). One of 5 hetero-R on initial isolate lost hetero-R after FCZ Rx concurrent with 8-fold increased MIC. **Conclusion** Hetero-R is common (5/7) among pts. failing Rx, but correlation with increase in FCZ MIC on Rx is poor.