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Paper Poster Session
Antifungal drug treatment

Is fluconazole resistance (FLU-R) in Cryptococcus neoformans predictive of clinical outcome?

Antonio Vena*[1], Patricia Muñoz[2], Teresa Pelaez Garcia[3], Jesus Guinea[4], Francisco Braojos Sanchez[5], Carmen Martos Diaz[5], Maricela Valerio Minero[4], Emilio Bouza Santiago[6]

[1]*Hospital General Universitario Gregorio Marañon, Madrid , Spain*

[2]*Hospital General Gregorio Marañon , Madrid, Spain*

[3]*Instituto de Investigación Sanitaria Gregorio Marañón, Madrid, Spain*

[4]*Hospital General Universitario Gregorio Marañón, Clinical Microbiology and Infectious Diseases, Madrid, Spain*

[5]*Hospital General Gregorio Marañon, Madrid, Spain*

[6]*Hospital General Universitario Gregorio Marañón, Madrid, Spain*

Background: Systematic antifungal susceptibility testing is not considered routinely necessary in patients with cryptococcosis, purportedly due to the universal activity of standard drugs. However, documented clinical failures with 'FLU-resistant' strains and reports of resistance (R) rates ranging from 0.4-29% in the literature have set the alarm. Comparative studies among different susceptibility testing methodologies and the correlation of FLU R with clinical outcome are not available. Our aim was to analyze these two issues in a large tertiary care centre.

Material/methods: All cases of cryptococcosis diagnosed from 2000 to 2013 were evaluated. Susceptibility to FLU was tested by E-test and 3 broth microdilution methods (CLSI, EUCAST, Sensititre YEAST-ONE). Strains were considered as non-S to FLU when MIC was ≥16 µg/ml. Evolution of cultures specimens, cryptococcal antigen titers and clinical parameters were collected according to a pre-established protocol. Only the first pre-treatment isolate was included All patients received FLU as induction or maintenance therapy.

Results: Sixteen patients (10 HIV +, 75% male, mean age 45.5 ± 15 years) were included. Ten of the patients showed disseminated infection and 6 only CNS disease. The rates of non-susceptibility to FLU (range and geometric mean) were as follows: CLSI 6.3% (0.06-16, 2.538); EUCAST 50% (1-16, 6.375); Sensititre YEAST-ONE 62.5% (2-32, 10.750) and E-test 68.8 % (0.25-256, 29.906). Overall, 9 pts (56.3%) had a poor clinical outcome (4 died, 5 had persistent high Cryptococcal antigen in blood or CSF). The number of patients with poor outcome among the strains with MIC value < 8 vs ≥16 µg/ml was as follows: CLSI 8/15 (53%) vs 1/1 (100%); EUCAST 4/8 (50%) vs 5/8 (62.5%); Sensititre YEAST-ONE 3/6 (50%) vs 6/10 (60%) and E-test 3/5 (60%) vs 6/11 (54.5%). Risk factors associated

to poor outcome were: disseminated infection (28.6% vs 88.9, *p*=0.03), higher intracranial pressure at diagnosis (35.5 ± 20 cmH_20 vs 48 ± 6.2 cmH_20, *p*=0.02) and lower Glasgow Coma Scale (15 vs 14.4 ± 1.5 *p*=0.049). Resistance to FLU (by any method), was not associated with poor outcome.

Conclusions: Rates of *C. neoformans* non-S to FLU are very discrepant with the four studied methods (CLSI 6% - E test 69%). With the present methods, FLU resistance in *Cryptococcus* may be clinically misleading.