Performance of the Cryptococcal Antigen Lateral Flow Assay as a Diagnostic and Prognostic Tool for Cryptococcal Meningitis

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Background: The WHO now recommends the cryptococcal antigen (CRAG) lateral flow immunoassay (LFA) as an inexpensive, rapid diagnostic test for diagnosis of cryptococcal meningitis in resource limited settings. However, its accuracy compared to culture and utility in monitoring of treatment response is unknown.

Methods: We assessed the accuracy of CRAG LFA compared to CSF fungal culture, India ink and CRAG latex agglutination testing in archived cerebrospinal fluid (CSF) from a cohort of 142 HIV^+, ART-naïve patients in Mbarara, Uganda. We defined the reference (gold) standard for cryptococcal meningitis as cerebrospinal fluid (CSF) with >2 positive tests. We also compared baseline $\log_2$ LFA titers with baseline $\log_{10}$ cryptococcal colony-forming units (CFU)/mL for all positive tests. In a subgroup of 30 participants, CFU and LFA titers were measured at day 3, 7, and 14 of anti-fungal treatment to compare changes during the course of therapy.

Results: Of CSF samples, 54% (76/142) were classified as cryptococcal meningitis, based on 2 or more positive diagnostic tests. The LFA sensitivity was 100% and specificity 98.6%. The 1 putative false positive CSF CRAG LFA was positive in serum by CRAG testing. Log_2 LFA and quantitative culture $\log_{10}$ CFU were highly correlated at baseline ($R^2 = 0.7$, $p < 0.01$) (Table). In a sub-study of repeated testing (n = 30, median CD4 21.5 cells/μL, 53% with Glasgow coma scale <15), the correlation between $\log_{10}$ CFU/mL and $\log_2$ LFA titer decreased over time (day 3 $R_2 = 0.69$; day 7 $R_2 = 0.20$; day 14 $R_2 = 0.05$) as the burden of live organisms decreased yet antigen persisted. Early fungicidal activity and change in LFA titers did not correlate over 14 days ($p = 0.9$). In a multivariable logistic regression model, day 1 $\log_2$ LFA titers were predictive of mortality at 2 weeks (odds ratio [OR] = 2.0, 95% confidence interval [CI] 1.1-3.7, $p = 0.03$) and 10

weeks (OR = 2.1, 95%CI 1.1-3.9, $p = 0.02$) for each 2-fold dilution above an initial CRAG titer of 1:10.

Conclusions: The CRAG LFA on CSF is a highly sensitive and specific test compared to culture. Initial CRAG titers correlate well with the microbiologic burden and are predictive of mortality. However, change in LFA titers over time is not an accurate tool for assessing response to therapy, as antigen persists long-term. Consistent with other Ugandan data, cryptococcal meningitis accounts for the majority of meningitis in Mbarara, Uganda.