Cryptococcosis in AIDS: New Data but Questions Remain

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(See the Major Article by Longley et al on pages 581–7.)

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Cryptococcal meningitis (CM) is a common and often devastating disease in areas of high human immunodeficiency virus (HIV) prevalence. In sub-Saharan Africa, CM has become the leading cause of adult meningitis [1–3]. Without treatment, CM is fatal. Treatment mortality rates remain high, up to 70% at 3 months in low-resource settings, even when antiretroviral therapy (ART) is available [4].

Almost all HIV-associated CM could be prevented if HIV-infected patients were diagnosed and started on ART before their CD4+ cell counts fell to <100 cells/µL. Unfortunately, this is not the reality, with ongoing HIV transmission and late presentation commonplace [5]. The number of patients at high risk of developing CM is not decreasing, and other interventions must be considered. Azole prophylaxis for all patients is neither practical nor desirable.

Cryptococcal antigenemia has previously been shown to precede clinical cryptococcal disease and to be a sensitive predictor for impending CM without treatment [6]. In this issue of Clinical Infectious Diseases, Longley et al address early mortality among those presenting with advanced HIV by stratifying them into those with and those without detectable cryptococcal antigen (CrAg) using the latex agglutination assay (LA) and the more sensitive lateral flow assay (LFA) in blood, serum, and plasma [7]. In this prospective study, they used antifungals to treat those found to be CrAg positive. Those already found to have CM upon cerebrospinal fluid (CSF) examination were treated with amphotericin; those without proven CM but who were CrAg positive were treated with oral fluconazole. All patients were to be put on ART within 2–4 weeks after CrAg screening.

The authors and study team must be commended for running a prospective study and field testing the LFA. Although some of the numbers are small, the results are important. The authors found that LFA testing of blood, serum, or plasma yields equivalent results and is more sensitive, identifying 4-fold more than the traditional LA. Even with the more sensitive LFA, there was a lower incidence of cryptococcal antigenemia in this antiretroviral-naive, low-CD4 study population than expected (4.3%), which, as the authors state, may represent greater rollout of ART in South Africa and earlier diagnosis of HIV.

The authors show that all-cause mortality and cryptococcal-specific mortality were 2-fold higher at 1 year among those screening positive for cryptococcal antigen. Since the number of CM deaths was small, the observable difference in mortality is most likely due to the fact that CrAg positivity is a marker for severe immunocompromise. There were no other clinical or laboratory predictors for a positive serum LFA or for those with positive CSF assays, justifying the screening protocol and use of the more sensitive assay.

Upon further review, if those with proven CM are censored from the group that screened positive, mortality rates do not appear markedly different compared with rates for those who screened negative. The success of the study is demonstrated by the fact that the 12-month mortality for those screening positive for CrAg without proven CM was 17%. This approaches the rate for those who were CrAg negative, which was 12%. The inference here is that without antifungals, those screening positive for CrAg would have had higher rates of CM and death when compared with historical control groups.

Seven patients were found to be negative by LA but positive by LFA retrospectively and could be considered a very small quasi-control group, albeit a group that may have had lower CrAg titers. Initially they were treated as part of the antigen-negative group, receiving no antifungal therapy. A subsequent protocol amendment led to this group of patients being considered as antigen positive. It is interesting and somewhat unexpected that this group did extremely well, with the 6 patients who engaged with antiretroviral care surviving and the single patient who did not take antiretrovirals dying of CM. This raises the possibility that a randomized clinical trial with a control group that does not receive antifungals but where everyone receives antiretrovirals could be considered for future studies in this type of setting.
It is unfortunate that among those patients who tested positive for cryptococcal antigenemia, almost two thirds declined lumbar puncture. Since 4 of the 10 who agreed to have lumbar punctures had fit the criteria for CM with high mortality, clinicians need a more acceptable method for early diagnosis of CM. In this study, higher titers of LFA were associated with a diagnosis of meningitis. Although all patients screening positive for CrAg should have a lumbar puncture to investigate for possible CM, applying quantitative antigen titers may prove useful in clinical practice to guide stratify ongoing management of known cases, especially if it can be incorporated into an accurate point-of-care test.

The 4 cases of proven CM had a positive urinary antigen. However, the current version of the test does not seem useful as a screening tool given problems with false-positive tests. More research will be needed to determine if there could be any future role for the urinary test in screening or clinical practice.

Cryptococcal antigenemia is a promising target for a screening program: it is an important health problem, diagnosis is possible, there are no obviously better targets identified as predictors of cryptococcal disease, a latent phase of disease probably exists, and there are data about the natural history of the antigenemic state. What is not yet fully understood is what is the optimal therapy to use for those who screen positive, especially in the setting of ever-growing access to ART, improving health networks, and the increasingly sensitive LFA test, which presumably identifies cases earlier. Given its wide availability and low cost in areas of high HIV prevalence, fluconazole certainly seems to be the most reasonable first option to investigate, and it has performed well in this study. Although both the National Institutes of Health and US Agency for International Development have not been funding studies such as this, larger randomized clinical trials to compare dosing regimens, alternative antifungals, possible combination therapies, and possible incorporation of a control group that only receives ART could be useful to answer some of the questions raised by this study.

Note

Potential conflict of interest. Both authors: No reported conflicts. Both authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References