Author's response to reviews

Title: Low CD4 Count plus Coma Predicts Cryptococcal Meningitis in Tanzania

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Version: 3 Date: 15 February 2007

Author's response to reviews: see over
Dear Ms. Makri/BMC Infectious Diseases Editor,

Thank you for your thorough review of our manuscript# 5348833921173823 “Low CD4 Count plus Coma Predicts Cryptococcal Meningitis in Tanzania.” We have considered all reviewers’ comments carefully, have addressed all of them and modified the manuscript accordingly, and we feel this version is greatly improved. Please interpret the length of this rebuttal as a reflection of our commitment to BMC Infectious Diseases.

Sincerely Yours,

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First, we were pleased that 3 of the 4 reviewers generally approved the manuscript. Positive comments included:

Reviewer Corral: A well performed study on cryptococcal meningitis in Tanzania. An appropriate methodology, the number of patients, and fine statistical analysis make this report valuable. Accept after discretionary revisions.

Reviewer Mwaba: An article of importance in its field. Accept after minor revisions.

Reviewer Chang: An article whose findings are important to those with closely related research interests.

As for the concerns, we have sought to address them as fully as possible:

1. The editor mentions that one reviewer [Dr. Corral] expressed concerns about ethical aspects of the study and about the clarity of the introduction. We feel that these are important points to address in revising your manuscript.

Upon closely reading Dr. Corral’s comments, this reviewer does not imply that we breached any ethical conduct in performing this study. Rather, reviewer Corral requested that we clarify in the introduction (page 4 lines 9-12, page 7 lines 6-8) the reasons for examining clinical predictors for CM in the first place, since in developed countries “physicians cannot imagine the conditions of daily clinical practice” and “the possibility of empirical management of patients with clinical suspicion of meningitis based only on
clinical data would surely be rejected by hospital ethics committees.” Dr. Corral goes on to clarify that we “firmly reject this [empirical management] approach.” That is to say we do not advocate clinical diagnosis for CM over laboratory testing, which is completely accurate. We have fortified/modified the introduction accordingly, incorporating Dr. Corral’s own comments including “lack of resources for microbiological investigation or lumbar puncture.” Specifically, we have changed the introduction to read as follows:

“Cryptococcal meningitis (CM) is a leading cause of adult meningitis in studies from South Africa, Zambia, and Zimbabwe [1-3]. The scope of the problem is less clear in Tanzania, where the literature is limited to one retrospective study that found Cryptococcus in 7% of (175/1144) CSF specimens [4]. A major reason for the lack of reporting is the lack of diagnostic reagents. For instance the Medical Stores Department, the main distributor of medical reagents to Tanzania, does not procure either India ink or cryptococcal antigen tests [5]. The need for accurate CM diagnosis is newly heightened by the increased availability of fluconazole to many parts of Africa [6]. We therefore examined Tanzanian HIV patients with central nervous system presentations to determine the local rate of CM using CSF cryptococcal antigen testing as the gold standard. We also sought to determine whether particular clinical features could predict the diagnosis as a stopgap measure until diagnostic reagents for CM become more widely available.”

We also modified the discussion:

“Therefore while intuitively appealing to devise clinical management algorithms in settings with limited laboratory resources, we by no means advocate clinical diagnosis for this entity and would simply emphasize that the knowledge of CD4 < 100/µl plus coma in Tanzania should prompt strong consideration of CM.”

We would like to further elaborate on the ethical aspects of this study and how this work exceeded the “current standard of care” described by the most widely used ethical body (and the one BMC Infectious Diseases espouses) the Declaration of Helsinki Paragraph 29 (http://www.wma.net/e/policy/b3.htm). First, we did not manage meningitis by clinical criteria in this study: all patients received lumbar puncture with full microbiological investigation, results were made available to their physicians, and they directed therapy. The Declaration of Helsinki’s “current standard of care” in Tanzania is no cryptococcal testing and, frankly therefore, no treatment. We would emphasize that in this work we brought cryptococcal antigen detection to Kilimanjaro Christian Medical Centre, improving the current standard of care. The following statement is in the methods and is transparently true: “Informed consent was obtained from all participants, the University of Virginia Human Investigation Committee and the Kilimanjaro Christian Medical Centre Ethics Committee reviewed and approved the project, and all research was in compliance with the Helsinki Declaration.”

2. Reviewer Mwaba had no comments or concerns other than a grammar and spell-check, which has been performed.
3. Reviewer Chang recommended that the statements related to the use of fluconazole and therapeutic result be deleted since fluconazole 800mg/day is not a standard therapeutic regimen.

While we agree with the reviewer that the therapy/mortality findings are not relevant to the finding that “Low CD4 count plus coma predicts CM,” we feel this does not constitute a reason to remove all reference to them. Indeed, reviewer Corral recommends the contrary: “these are interesting results regarding outcome and response of CM to high dose oral fluconazole.” Of note, amphotericin B and flucytosine were not available in Tanzania at the time of this study, nor are they presently.” Clin Infect Dis. 1998 Jun; 26(6): 1362-6). In this context, we feel reporting the high mortality despite 800mg fluconazole, the maximal therapy we could possibly provide, is locally important and will be of interest to readers. However, if the editor request all such references are removed we can do so.

4. Reviewer Chetchotisakd remarked that “the general concept of the article is good,” and also appeared to have no concerns on the methodology or the results. Rather, the concern appeared to be the importance of the findings. The reviewer argued that the finding that low CD4 plus coma predicts cryptococcal meningitis is “not practical” since CD4 count measurements are not available at the time of presentation. As such, this reviewer advocates use of the serum cryptococcal antigen screening.

We completely agree with the reviewer that serum cryptococcal antigen screening would be a superior diagnostic in this setting (e.g., more sensitive and specific than CD4 < 100 and coma). As mentioned earlier in this rebuttal, we have clarified that we by no means advocate using CD4 < 100 and coma as a diagnostic test over cryptococcal antigen. It is important to add, however, that CD4 counts are more available in Tanzania than cryptococcal antigen. Therefore for the time being practitioners may find themselves with patients with CD4 < 100 and coma, yet without cryptococcal antigen results. In addition to having modified the introduction to emphasize that we do not advocate using CD4 plus coma to make the diagnosis, we clarified our position in the discussion.

“…we would advocate that improvements in therapeutics must be wed to improvements in diagnostics availability. During the time of study fluconazole was free (made available thanks to the Pfizer Diflucan Partnership Program), but this availability would have been aimless without cryptococcal antigen detection. Unfortunately, India ink exhibited a disappointing 60% sensitivity, worse than a clinical determination based on low CD4 count plus coma, therefore we are left advocating for increased availability of cryptococcal antigen tests (including use on serum [18]). As mentioned, the cryptococcal antigen test is presently not available through local dispensaries or Tanzania’s Medical Stores Department, the country’s main supplier of essential medicines and reagents.”

We then add in the discussion

“The finding that low CD4 count plus coma was a reasonably sensitive and specific feature for CM is unfortunate. First, clearly it requires CD4 quantitation, which although
is presently more available in our region of Tanzania, is also technically demanding and expensive. Secondly, the finding of coma may provide high specificity but will inherently miss earlier and better-prognosis presentations [20]. Therefore while intuitively appealing to devise clinical management algorithms in settings with limited laboratory resources, we by no means advocate clinical diagnosis for this entity and would simply emphasize that the knowledge of CD4 < 100/µl plus coma in Tanzania should prompt strong consideration of CM.”

Unlike Thailand, for example, where the disease is better recognized and detected, the only published work from Tanzania on cryptococcal meningitis was one retrospective study (reference [4]). We therefore hope, and think this reviewer would agree, that publication of this manuscript might be useful in raising awareness in Tanzania of the problem so that future discussion can be had on how to procure cryptococcal antigen detection (for use on serum as mentioned by the reviewer).