Reviewer's report

Title: Correlation of anti-fungal susceptibility with clinical outcomes in patients with cryptococcal meningitis

Version: 1 Date: 6 September 2012

Reviewer: Hien Nguyen

Reviewer's report:

Major compulsory revisions:

I appreciate the work of the authors on a very timely and pertinent issue in the management of patients with cryptococcal meningitis. Overall, the authors present some very interesting data that adds to the body of knowledge in this field.

As you are aware, the outcomes of patients with invasive fungal infections relate to a number of factors including treatment / management, toxin production, underlying host factors, drug delivery, possibly susceptibility (topic of this investigation), etc. As the investigation deals with outcomes, there should at least be some assurance that the treatment was in accordance to accepted standards of care as this is clearly known to have an impact on outcomes. Controlling (or at least mentioning that treatment was in accordance with accepted practice) for this variable would lend more credibility for interpretation of the correlation of susceptibility results and clinical outcome. For example, for patients with high intracranial pressure, progressive hydrocephalus, was the management in accordance with IDSA guidelines with serial lumbar punctures or shunt placement?

The methods section (line 98) suggests that follow up was conducted for all patients at 2 weeks. It is unclear what the results of the 2 week interim analysis were. Please include the interim analysis as a separate table or within the larger table as separate columns.

I have specific concern and need for clarification with line 97 (repeated on lines 428-9) of the manuscript stating, “After 2 weeks, patients in all groups received fluconazole 400-600mg daily for 8 weeks…” IDSA guidelines suggest maintaining induction therapy for 4 weeks in non-HIV, non-transplant patients (which were the majority of your patient population). While this could be debated, at the very least, known prognostic indicators of failure such as a persistent positive CSF culture would certainly guide the decision to continue induction therapy for another 2 weeks versus a switch to maintenance therapy. Most clinicians would at least repeat a CSF culture at 2 weeks to help determine if induction should be continued. Do the authors have this data to report?

Duration of induction therapy is concerning as a potential confounder since initial therapy did not have an association with 10 week outcome with respect to
susceptibility testing, but close of half of the failures had some kind of fluconazole resistance (and were switched to fluconazole likely earlier or at a lower dose than recommended for most cases). Therefore it would be helpful to know if the early (2 week) failures correlated with initial treatment regimens. In fact, the discussion (lines 258-270) seems to indicate that the initial treatment regimen MICs (higher values) correlated with failure at the early 2 week interim analysis but did not correlate with the 10 week outcome analysis. This also suggests that changing to fluconazole maintenance therapy at week 2 may be a bad idea for isolates with high fluconazole MICs.

The methods note that CSF results were collected (lines 86-87) but I did not see these values in the results section. The only possible mention of the CSF results were in the conclusion (lines 210-211). Please include the CSF results in table 2. If these CSF results were not associated with outcome (lines 210-211), the authors should explain why their findings are different than other studies.

Minor essential revisions:

Susceptibility testing is sometimes termed “resistance testing” as it is widely accepted that resistance generally dictates choice of antimicrobial, letting the clinician know what drug to avoid. In your manuscript and in table 2, there is mention of susceptibility (fluconazole MIC < 8 µg/mL) being associated with treatment success but the analysis may be better related to whether resistance is associated with failure. As you have decidedly more resistant isolates than most published studies, you can potentially report this analysis.

Line 269-270 (It suggested that MICs of fluconazole, determined by the CLSI method, is a potential predictor of therapeutic cure in patients with cryptococcal meningitis) refers to data suggesting that high fluconazole MIC resulted in failures. While I understand the intent, it is clearer to conclude that high fluconazole MIC is associated with 10 week treatment failure when fluconazole is used for maintenance therapy after induction therapy.

**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Needs some language corrections before being published

**Statistical review:** Yes, but I do not feel adequately qualified to assess the statistics.

**Declaration of competing interests:**

I declare that I have no competing interests