Reviewer's report

Title: Micafungin for the treatment of proven and suspected invasive candidiasis in children and adults. Findings from a multicenter prospective observational study.

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Reviewer: Brian Fisher

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The following is a review of the article entitled “Micafungin for the treatment of proven and suspected invasive candidiasis in children and adults. Findings from a multicenter prospective observational study.” The authors stated goals for this manuscript are to provide a “post-marketing evaluation in the real life setting …to adequately validate efficacy and safety of this drug”. Listed below are some major and minor concerns for the paper.

Major:

1. The authors use the word “efficacy” throughout. This report is neither a report of efficacy or effectiveness. Both require a comparator group, which this study does not provide. Efficacy usually describes a comparison from a randomized controlled trial and effectiveness reports on a comparison from observational data. The presented manuscript is really a case series of patients that received micafungin for proven or suspected IC and thus only provides rates of success of treatment frequency of adverse events. It is fine to report such information but calling it efficacy data overstates the presented data.

2. They use the term “suspected IC”. This is an ambiguous term that is not consistent with the often used EORTC/MSG criteria (which they used for proven IC). Not sure why they chose to include suspected IC—may be useful to report on for safety issues associated to micafungin but should not be included in outcomes of success if the actual IC diagnosis is not well defined.

3. The authors state that patients signed an informed consent. However, there is no mention if any patients declined enrollment—I would be surprised if all consented and if some did not consent it may be that they had worse outcomes or more side effects, which could introduce bias.

4. In the methods section lines 141-146 they note a large number of comparisons (ie proven vs. suspected, monotherapy vs. combined, CVC removal etc.). A number of these comparisons are not pertinent to the stated goal of the paper and further simple comparisons using Chi-square and Fisher’s exact test are essentially meaningless in this setting as they do not account for confounders (especially confounding by indication which is a big issue with mono vs. combo and CVC yes vs. no questions).
5. The authors state that the limitation of reduced follow-up is okay because this is what happens in everyday clinical practice. This is not an appropriate excuse for this limitation. The idea that what happens in everyday practice is different than what happens to patients in a clinical trial is important to mention but this does not apply to poor follow-up. If lack of follow-up existed in the observed cohort it may have resulted in significant bias of the results. This cannot be explained away by “real world clinical practice”.

Minor:
1. They report age in “clusters”. < 18 is not really a cluster but rather represents the entire neonatal, pediatric and adolescent population. Furthermore they only had 36 patients in this age group all of which were less than 8.

2. Line 169/170 they note lines were removed in some at the “beginning” of therapy? Need to be more specific than this. As noted above I don’t think they should even bother with such comparisons anyway.

3. The median daily dose of mica for kids was provided but not indexed to weight. Not sure what 45mg median daily dose means for kids aged 1-8.

4. The results in the abstract and in the paper are filled with rates by subgroup that are not that useful. For instance they note that there was a higher rate of favorable response in patients in the non-ICU wards—this of course would be expected and does not add to the goal of the paper.

5. Line 228—use of the word “fragile”—not sure that patients with IC enrolled in a clinical trial are any less or more fragile then the population presented here.

6. The discussion is repetitive in some parts and needs to be more to the point and more cohesive.

In the end I think the authors missed highlighting what I would argue is an important if not the most important piece of knowledge to come from this report—that is the low risk of hepatic toxicity after micafungin exposure. Their sample size and time of followup is too small/short to answer the real question previously raised in animal studies about hepatic tumors. Nonetheless I think they could focus on the lack of hepatotoxicity seen in this case series as additional data to suggest this is not an issue in humans. They do address this but not until the end of the discussion. I would make this the focus and write this as a brief report.

**Level of interest:** An article of limited interest

**Quality of written English:** Not suitable for publication unless extensively edited

**Statistical review:** No, the manuscript does not need to be seen by a statistician.
Declaration of competing interests:

I have received research funding from both Merck and Pfizer Pharmaceuticals.