Author's response to reviews

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

Authors:

Claudio Viscoli (claudio.viscoli@unige.it)
Matteo Bassetti (mattha@tin.it)
Elio Castagnola (eliocastagnola@ospedale-gaslini.ge.it)
Simone Cesaro (simone.cesaro@ospedaleuniverona.it)
Francesco Menichetti (framenic@tin.it)
Sandra Ratto (sandra.ratto@unige.it)
Carlo Tascini (c.tascini@ao-pisa.toscana.it)
Daniele R Giacobbe (daniele.roberto.giacobbe@gmail.com)

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Author's response to reviews: see over
Dear Editor,

Please find enclosed the revised article “Micafungin for the treatment of proven and suspected invasive candidiasis in children and adults. Findings from a multicenter prospective observational study”.

We thank the reviewers for their valuable suggestions. The paper has been rewritten according to concerns. Listed below are specific responses to comments:

1) Referee 1:

<table>
<thead>
<tr>
<th>Major comments</th>
<th>Lines 1-259. The manuscript has been rewritten, reduced, and focused on safety data. Clinical responses are provided as descriptive results, without using neither the term efficacy nor effectiveness. In addition, limitations preventing from an appropriate evaluation of micafungin effectiveness have been added to the discussion.</th>
</tr>
</thead>
<tbody>
<tr>
<td>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.</td>
<td>We included suspected cases in line with the study major aim (post-marketing safety surveillance). However, we acknowledge that the first version of the manuscript did not clearly state this. In the revised version, responses in case of suspected IC have been retained as descriptive results, since we think the lack of difference of response according to certainty of IC diagnosis could be informative data. On the other hand, we recognize that inclusion of suspected cases is an important limitation when evaluating outcomes of success. This limitation has been added to the discussion.</td>
</tr>
<tr>
<td>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.</td>
<td></td>
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</table>
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).

The number of provided comparisons has been reduced in the manuscript revised version. In line with the study aims, comparisons have been reconsidered only as additional informative data, and limitations regarding any interpretation of micafungin effectiveness in the study have been added to the discussion.

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”.

The reduced follow-up is now accounted in the discussion as an important limitation in assessing both safety and survival rates, as possible toxicities and deaths occurring later than two weeks after EOMT were not reported in the study.

Minor comments

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.

The word “cluster/s” has been removed. We have only retained the description of the bimodal age distribution observed in the study population.

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.

This comparison has been removed, according to the goal of the paper. We have retained only the baseline presence of a CVC as descriptive data in Table 1.

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.

Lines 156. We changed the text accordingly. Median daily dose of micafungin was 2.2 mg/kg (IQR 2-4.1 mg/kg) and 100 mg (IQR 100-100 mg) in children and adults, respectively.

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.

The results in the abstract and in the paper have been re-written and focused primarily on safety results. Rates by subgroups are now reported as descriptive data in both text and tables.

5. Line 228—use of the word “fragile”—not sure that patients with IC enrolled in a

The term “fragile” has been removed.
clinical trial are any less or more fragile than the population presented here.

| 6. The discussion is repetitive in some parts and needs to be more to the point and more cohesive. |
| Lines 205-254. The discussion has been re-written, reduced, and focused on safety data. We have re-discussed clinical response only as descriptive data, and limitations preventing from an appropriate evaluation of micafungin effectiveness have been added. |

2) Referee 2:

<table>
<thead>
<tr>
<th>Major comments</th>
<th>If this comment refers to Table 3: although treatment period was longer in patients who respond to micafungin treatment than in those who did not, this comparison was not considered due to the inherent bias derived from the short duration of therapy in non survivors and in those with an early discontinuation of micafungin because of investigators’ assessment of treatment failure. Overall median treatment period with IQR is reported in the text (line 155).</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. The authors should detail the treatment period in the table.</td>
<td>Antifungal agents administered with micafungin are reported in the text throughout lines 158-160, and have also been added in Table 3. We also corrected a transcription error in numbers and percentage of combined regimes in the text. These results are now reported correctly.</td>
</tr>
<tr>
<td>2. As mentioned, some patients were on combined treatment. What other antifungal agents were given?</td>
<td>We included suspected cases in line with the study major aim (post-marketing safety surveillance). However, we acknowledge that the first version of the manuscript did not clearly state this. In the revised version responses in case of suspected IC have been retained as descriptive results, as we think the lack of difference of response according to certainty of IC could be informative data. On the other hand, we recognize that inclusion of suspected cases is an important limitation when evaluating outcomes of success. This limitation has been added to the discussion.</td>
</tr>
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<td>3. It is to my surprise that even as multi-center, the number of cases with invasive candidiasis was relatively small. Strictly speaking, suspected cases should not be included (as mentioned by the authors as one of the limitations). If the study period could be prolonged and suspected cases excluded, the outcome would be different.</td>
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3) Editorial requirement

| Please include the name of the specific ethics committees that approved the study. | A list of specific ethics committees has been added in the text after authors’ contributions. |

All the authors have seen and approved the manuscript. The manuscript has not been published and is not being considered for publication elsewhere.
Yours faithfully,

Daniele R Giacobbe

Corresponding author:

Daniele R. Giacobbe
Infectious Diseases Unit,
IRCCS San Martino Hospital,
University of Genoa,
IRCCS San Martino University Hospital – IST
L.go R. Benzi, 10 – 16132 Genoa, Italy
Telephone: +39 010 555 4667; Fax: +39 010 5556712

e-mail: daniele.roberto.giacobbe@gmail.com