Author's response to reviews

Title: Serum galactomannan index for early prediction of mortality in immunocompromised children with invasive pulmonary aspergillosis

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Author's response to reviews: see over
Editor’s Comment:

"Part of the conclusion paragraph is not directly derived from the observations reported in the manuscript, although the authors address the issues to improve antifungal therapy which is in itself an important message. It should probably say something like this may help to identify children at highest risk who would benefit from voriconazole as first line therapy and b) , c) as alternative therapy if refractory to first line agents (IDSA guidelines)."

→ In accordance with the editor’s advice, comments on inconclusive measures for intensive antifungal therapy were removed from the “Conclusions” section.

[ Line 298-299 ]
In addition, IPA patients at high risk for mortality, who show a persistently high level of serum GMI within 1 week of antifungal therapy, should receive more intensive antifungal therapy, such as antifungal combination therapy and early change of antifungal agents, and close TDM should be applied for these cases.

→ In addition, IPA patients at high risk for mortality, who show a persistently high level of serum GMI within 1 week of antifungal therapy, should receive more intensive antifungal therapy.
Reviewer’s report (1)

Reviewer: Adilia Warris

Reviewer’s report:
The authors have responded to my comments in great detail and the manuscript has improved a lot. I only wish to make a few comments on the revised version of the manuscript.

1. The authors have addressed the question about the use of antibiotics and its possible influence on false-positive GMI very well. For clarity I would suggest to add antibiotic usage (e.g. meropenem and pip-tazo) in table 2 and to mention the information as displayed in table 3 only in the text (as is done properly).

→ The comparison of administered antibiotic agents on the diagnosis of IPA between the survival and fatality groups was added in the Table 2. Table 3 was removed, and the following sentence was added in the “Results” section to explain the non-significant difference for frequencies of receiving piperacillin/tazobactam on the diagnosis of IPA between children with and without positive GMI.

[Line 195-197]
piperacillin/tazobactam was being administered to only seven (15.5%) children on the diagnosis of IPA and the frequency of receiving piperacillin/tazobactam on the diagnosis of IPA was not significantly different between cases with and without positive serum GMI (16.2% vs. 12.5%, p = 1.000).

2. I am content with the extra information about GM positivity in addition to the GMI in both the text and table 4. In particular for clinical argumentation it is important to show the duration and differences in positive GM results. I only noted a slight mistake in the text (line 203-205), I suppose the authors would like to state that the frequency of positive GM was also higher in the fatality group than in the survival group (and not the other way around).

→ Thank you, very much. The sentence was corrected.

[Line 204-206]
The frequency of positive GMI was also higher in the fatality group than in the survival group during the entire period of follow-up with significant differences at 1, 2, and 6 weeks after antifungal therapy.

3. Line 250-251; reason for persistent high GMI or positive GMI can also be related to underlying immunosuppression, is important to mention here.

→ The following sentence was added in the “Discussion section.”

[Line 252-254]
Persistently positive serum GMI despite antifungal therapy represents persisting fungal burden and continuous fungal infection. This could be caused by more suppressed immunity of the fatality group compared with the survival group, considering more children in the fatality group received palliative care for uncontrolled underlying malignancies and experienced prolonged neutropenia. Also, this may mean inadequacy of the administered antifungal therapy.
4. Line 260; please add the recent publication of Marr et al here, they performed a study to assess the value of combination therapy (anidula and voriconazole) and the conclusions of this study may suggest that combination treatment may have a benefit in the most severely ill patients (as may be reflected by persistent high GMI).

→The recommended article was additionally cited as reference No. 39, and the following sentence was added in the “Discussion” section.

[ Line 267-270 ]

However, a recently reported randomized trial showed a lower 6-week mortality in adults with IPA receiving voriconazole and anidulafungin compared with those receiving voriconazole monotherapy, although the difference was not statistically significant [39].

5. Figure 2 in my opinion doesn't add any information and could be omitted.

→ Figure 2 was removed from the manuscript according to your advice.
Reviewer's report (2)

Reviewer: Xuzhuang Shen

Reviewer's report:
I have read the manuscript and cover letter. It has answered all of our questions.
I have not any question and I suggest that this MS can be accepted.

→ Thank you, very much.