Reviewer's report

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

Version: 1 Date: 24 March 2015

Reviewer: Adilia Warris

Reviewer's report:

I have noticed with great interest the manuscript of Han and his colleagues in which they have made an attempt to describe the value of galactomannan index (GMI) as an early predictor of mortality in paediatric patients with IPA. To address specifically the paediatric patients group is of great value in the field of paediatric mycology. Only one study has been studied GMI as an early predictor (Rohrlich et al) but only included 10 patients of which only 3 patients had enough data to be analysed for this purpose. A couple other studies have included both adult and a few paediatric patients, but always very small numbers. So this study does contribute to our knowledge of paediatric aspergillosis but I want to address a few issues which in my opinion need to be dealt with before the manuscript is suitable for publication.

Major comments for compulsory revisions:

1. The authors should refer to the paper of Rohrlich in Ped Infect Dis Journals, as well the meta-analysis published by Miceli et al in CID 2008 should be mentioned due to the fact that this meta-analysis covers all the published studies before 2008 and summarizes as well which studies included children in their analyses (although no subgroup analyses could be made). This should be mentioned in the discussion paragraph, and the statement in line 74 on page 4 should be changed.

2. First sentence of the background paragraph; I am not sure if the authors want to state that invasive aspergillosis is the most common fungal infection in hem-onc paediatric patients, Candidemia is more common (unless prophylaxis is used without activity against moulds), but invasive aspergillosis is most common mould infection. Please rephrase accordingly.

3. It would be good to include the management strategy and/or common practice in persistent febrile neutropenia and the use of GM/antifungal prophylaxis/diagnostic driven approach/empirical approach/etc. When was a CT-chest performed. Is it standard of care to follow-up the GM as stated in line 93-94 on page 5?

4. Was the duration of the neutropenia after diagnosis of IA/start of antifungal treatment associated with outcome and/or GMI?

5. Due to the fact that the study is based on proven and probably invasive aspergillosis, table 2 does not seem to add anything to table 1 and can be deleted (as well as line 151-153). The survival and fatality group can’t be
differentiated on the criteria they were diagnosed, only a differentiation between
the number of cases of proven and probable and how they relate to the outcome
can be made. Should be added to table 1. It would also be good to inform the
reader how the proven diagnosis were made (doesn’t follow from table 2, no
biopsies are mentioned).

6. The indications (and definitions) for second line and targeted antifungal
therapy are not clear. What was the percentages of patients progressing to
second line and the so-called targeted antifungal therapy?

7. Duration of neutropenia is different in table 1 and table 3. Please explain.

8. Discussion paragraph; to use the GMI as a measure to intensify treatment as
stated by the authors should be discussed more properly, antifungal combination
therapies have not shown to increase the survival rate. Any other thoughts? Use
of TDM to monitor closely voriconazole treatment?

9. Discussion about false-positive GMI is relevant if the authors think that this
may have influenced their results, but in that case the authors should show in the
tables the use of particular antibiotics in the 2 groups.

Minor comments for minor essential revisions:

10. Why did the authors chose for an age cut-off of 20 years of age, normally
paediatric patients are referred to as either < 16 or < 18 years of age.

11. Line 115 on page 6: ‘or was predicted to be lower than 500/mm3 after 2 or 3
days’. Please explain.

12. Line 120 on page 6: ‘positive GMI’s tested within 4 weeks of antifungal
therapy were regarded as true positive’, this is not clear to the reader, please
explain.

13. I would consider to add to table 4 the number of the positive GM ratios
defined as > 0.5, any differences here?

**Level of interest:** An article of importance in its field

**Quality of written English:** Acceptable

**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