Reviewer's report

Title: Galactomannan testing of bronchoalveolar lavage fluid is highly reliable for diagnosis of invasive pulmonary aspergillosis in hematology patients

Version: 2 Date: 4 September 2009

Reviewer: Prasanna Khot

Reviewer's report:

General Comment: Hsu and colleagues test the potential of galactomannan antigen assay [Platelia Aspergillus seroassay (Bio-Rad Laboratories)] on BAL samples for the diagnosis of IPA in hematology patients. They report high diagnostic specificity and sensitivity.

MAJOR COMPULSORY REVISIONS

1) Was the study blinded?

2) Please estimate “Confidence Intervals” for the diagnostic sensitivity and specificity values. These will help gauge the magnitude of diagnostic performance in perspective of the number of cases tested.

3) Please consider estimating other diagnostic parameters like “likelihood or odds ratios, or predictive values”.

4) When a conclusion is reached that “BAL galactomannan testing is more effective than serum galactomannan testing”, then serum samples have to be tested for the entire cohort (cases and controls) and diagnostic performance values need to be reported for serum as well. This will promote objective comparison between the sample types. The larger shortcoming of this study is the lack of comparison with serum consistently applied to all samples.

5) Following are additional points that should be addressed in the Discussion section:

a) Why may BAL galactomannan testing be more sensitive than serum galactomannan testing? Is there evidence in the literature to support using either of the sample types?

b) What might be the potential of BAL galactomannan testing to distinguish between infection versus colonization? Does the data in this study offer any trends?

c) What maybe the pros and cons of using galactomannan testing when compared with other molecular diagnostic tests like PCR or detecting beta-glucans?
6) Please add to limitations of study:

a) Galactomannan antigen testing lacks analytical specificity for broad-range fungal detection and in addition, false positives due to non-Aspergillus fungi may also occur.

b) The controls have a significant fraction of non-hematological patients (n=35 out of 52). The title and conclusion mentions the utility of the galactomannan assay in hematology patients. Please explain how non-hematology patients would represent an appropriate control population to reach an overall conclusion about hematology patients? Please justify this aspect in the manuscript and/or mention as a limitation of the study-design. The diagnostic specificity could be high (98.1%) as a consequence of potential bias introduced by a significant pool of non-hematology patients used as controls.

7) What is the relationship between OD values and other diagnostics techniques, especially for the “cases” cohort? For example, do the highest OD values correspond to those cases that were positive by cytology? Another Table for the “cases” cohort with BAL galactomannan OD values and corresponding serum galactomannan OD values, culture, cytology, TLB data is necessary to better understand the results.

8) Figure 1: It is very useful to indicate the important cut-off data points on the ROC curve. For example: at OD 1.1, OD 0.5 and maybe a couple of other points. Please include these indicators in the figure. [E.g. see Fig 1 from Mushet et al, JCM, Dec. 2004, p. 5517–5522]

9) What supporting data can be provided to reach the conclusion on “Page 9, lines 11-14”?

MINOR ESSENTIAL REVISIONS

1) Page 3, line 6: change to, “results can be compared between centers”

2) Page 4, line 18: change to, “per BAL varied (40 ml to 150 ml) between studies”

3) Page 5, line 2 and elsewhere: change to, “EORTC/MSG”

4) Page 5, line 23: what volume was specifically used for BAL galactomannan testing? What volume was used for serum galactomannan testing?

5) Page 6, line 18: change to, “There were a total of 10 cases and 52 controls”

Level of interest: An article of limited interest

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a
statistician.

Declaration of competing interests:

I am co-inventor on two patent applications related to PCR-based diagnosis of invasive fungal infections (including diagnosis of IPA).
