Author’s response to reviews

Title: Invasive fungal sinusitis in patients with hematological malignancy: 15 years experience in a single university hospital in Taiwan

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Author’s response to reviews: see over
Dear Dr. Rajabi:

Thank you very much for your kind attention to our paper entitled “Invasive fungal sinusitis in patients with hematological malignancy: 15 years experience in a single university hospital in Taiwan.” by CY Chen et al. We also sincerely appreciate your agreement for delay to respond to you about our manuscript. During the period, we have revised our manuscript according to the comments and suggestions of the editor and the reviewers and the manuscript also had been sent to an English editor to revise the spelling and grammars of this manuscript. What we have done are listed and explained in the following:

Reviewer 1: Dr. Ray Hachem

1. The authors mentioned that there were 25 patients with proven or probable invasive fungal sinusitis the majority of them caused by aspergillus flavus 12 and only two patients with IFS due to aspergillus fumigatus. This finding is surprising because aspergillus fumigatus is the most commonly reported organism causing mold infections. It is important that the authors should clarify that they are not dealing with an outbreak.

Response: The Aspergillus flavus has been reported more common of invasive fungal sinusitis in Asia, Africa (ref. 24, 25). We think the epidemiology of invasive fungal sinusitis might be varied among different geographic distribution. There was no outbreak of invasive fungal sinusitis in this study. (Page 11, Line 5-6, underlined).
2. Do we have compliance data on the infection control measures for these periods? It would be interesting to know if there is any difference between the study group and the control group enrolled and how why 64 patients for the control was chosen why not double the cases 92 patients?

Response: The infection control measures are no difference between these periods, except hand hygiene promotion has been emphasized since 2003 after SARS at this hospital. All the control patients with sinusitis were checked by ENT doctors and excluded the possibility of invasive fungal sinusitis. (Page 7, Line 13-14, underlined). The study group and the control group enrolled were chosen from the same time cohort of patients with hematological malignancy. Therefore, there was no enough case number to reach 1:2 case collections.

3. Since patients have not been investigated via a prospective randomized clinical trial. I am not sure we can say that the intensity of chemotherapy and allogeneic stem cell transplantation had no impact on the prognosis of IFS.

Response: We agree the reviewer’s opinion, and revised the sentence as” The intensity of chemotherapy and allogeneic stem cell transplantation were not independent prognosis of invasive fungal infection.” (Page 14, Line 11-12, underlined). And, we also add to the discussion “Whether the intensity of chemotherapy and allogeneic stem cell transplantation were the independent prognosis of invasive fungal infection need further investigated.” (Page 17, Line 18-19, underlined).

4. The attributable mortality of patients with AML was also much greater than non-AML patients. Was this attributable mortality to IFS?

Response: Yes, the attributable mortality of patients with AML was higher than
non-AML. All the patients died rapidly due to IFS (median survival, 15 days; 25th and 75th percentile, 10 and 34 days, respectively). (Page 13, Line 11-13, underlined).

5. In this study, there were four patients with mucormycoses they *did* receive high dose antifungal therapy and aggressive surgical debridement, but three died (mortality, 75%). What was the antifungal agent given to those patients, and did the one who survived recover from neutropenia?
Response: Two patients received amphotericin B, and two patients received both amphotericin B and amphotericin B liposomal. All four patients had surgical debridement. The survival patient is a case of T-CLL who received anti-CD52 therapy. Although her neutropenia is not completely recovered, she was relatively stable immunity and she did not receive intensive chemotherapy during the course.

6. The authors mentioned that in this study, we showed earlier diagnosis by using serial Aspergillus galactomannan antigen test in the modern medical era to detect IFS, which may lead to decreased morbidity and mortality in high risk patients. I did not see enough evidence for such statement in this study.
Response: We agreed the reviewer’s opinion. We revised as “Aspergillus galactomannan antigen test in the modern medical era to detect IFS, which may lead to early introduce anti-fungal agent and aggressive surgical debridement, and potentially decreased morbidity and mortality in high risk patients.” (Page 17, Line 4-6, underlined).

7. Need to include limitations of the study.
Response: This study is a retrospective single institution experience. We add the limitations in the discussion. (Page 17, Line 7-12, underlined) Thank you very much!
Reviewer 2: Dr. Michel Wolff

A. Methods section

1. The non IFS group (64 patients) should be better defined: how were these patients chosen? Do the authors perform systematic sinus imaging in patients with haematological malignancy? How was defined non-IFS? How many patients had sinus samples taken with subsequent cultures?

Response: The non-IFS group was selected as the same time cohort of patients with hematological malignancy. In our institution, if the sinusitis suspected in hematological patients, we routinely take Water’s view and consult otolaryngist for local evaluation and culture. CT and MRI sinus study were performed according clinical decision. (Page 8, Line 1-5, underlined). The results for fungus culture of the 64 non-IFS patients were all negative. Fourteen patients (22%) had tissue biopsy and none had evidence of invasive fungal sinusitis.

2. What was the cut-off for positive Aspergillus galactomannan test?

Response: In our institution, an optical density (OD) index of 0.5 or higher is considered positive for aspergillus galactomannan test. (Page 8, Line 16-17, underlined).

3. Concerning statistics, could the authors indicate how they chose variables which were introduced in the multivariate analysis?

Response: Factors which p level is below 0.2 in the univariate analysis were selected for multivariate Cox regression analysis. (Page 10, Line 7-8, underlined).

B. Results section

- Among the 25 patients with proven IFS, how many had a positive biopsy specimen
and how many had positive culture results?

Response: of the 25 patients with proven IFS, 15 patients had positive biopsy, and 14 patients showed positive culture. (Page 12, Line 1-3, underlined).

- Could the authors indicate the species among the 4 Mucor?
Response: Thank you for your suggestion; however, we cannot identify the Mucor species in our institution currently.

- Some additional date concerning Aspergillus galactomannan antigen should be interesting, for example the mean value (+/- SD) in the seven patients with positive results.
Response: The mean value (standard deviation) of Aspergillus galactomannan antigen in the seven patients with positive results was 2.32 (1.86), compared with those with negative results 0.13(0.07). The p level (0.048) is below 0.05. (Page 12, Line 9-12, underlined).

- What were the dose and duration of antifungal therapy?
Response: The maintenance dose of each antifungal agent is as followings: Amphotericin B 1-1.5mg/kg/day, Amphotericin B liposomal 3-5mg/kg/day, Capsofungin acetate 50mg/day, and Voriconazole 400mg/day. We add the information on Page 9, Line 6-8, (underlined).

- Could the authors provide some information on the interval between diagnosis and surgical debridement?
Response: The median interval between diagnosis and surgical debridement is 11.5 days (range 1-38 days). (Page 14, Line 3-4, underlined).
C. Discussion

The authors should start the discussion by better summarizing the main results including the protective effect of surgical debridement which is really a key message of their study.

Response: Thanks the reviewer’s opinion. We revised it according to your suggestion.

(Page 15, Line 3-5, underlined).

D. Table 1

- How many patients received Amphotericin B vs Ambisome?

Response: 33 patients received amphotericin B, and 7 patients received both agents during the treatment of IFS.

- At the bottom of the table, something is probably missing: “Amphotericin B and ?????”

Response: Thanks! This type-error occurred during we transformed the Word files. We edit the table 1 correctly.

We appreciate those comments and suggestions of the editor and reviewer to improve the quality of our manuscripts. We also thank you very much for your agreement for delay about our manuscript and kind consideration for possible publication of our paper in “BMC Infectious Diseases”. We hope our data could provide some information about the invasive fungal sinusitis in patients with hematological malignancy.

Thank you very much for your kind attention to our paper.
Sincerely yours,

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