Author’s response to reviews

Title: Treatment of disseminated coccidioidomycosis with diffuse pneumonia by caspofungin and fluconazole

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Author’s response to reviews: see over
Dear Editorial Team:

I thank the editors and referees of the ‘BMC Infectious Diseases’ to review our manuscript carefully. The manuscript has been revised according to the referees’ comments.

The following revisions are made:

First of all, the title of the manuscript has been changed to “Treatment of disseminated coccidioidomycosis with diffuse pneumonia by caspofungin and fluconazole” which we think more appropriate for the present case.

**Points suggested by referee #1** (Reviewer, Dr. Carloe A. Sable)

Minor Essential Revisions

1. **Referee’s comment**: Please describe why caspofungin plus fluconazole was selected as therapy after the patient did not respond to AMB. There are limited data to support
this treatment approach and readers would benefit from learning why this treatment was selected.

**Answer:** When our patient did not respond to amphotericin B therapy, which was the recommended agent according to IDSA guidelines (2000), we reviewed the literatures for a new antifungal agent. Only a new available antifungal agent was caspofungin. Since limited clinical and *in vitro* data of caspofungin, we could not choose caspofungin as a monotherapy agent. The action mechanism of caspofungin is different from azoles and to the scarcity for evidence *in vitro* antagonism when combined with other antifungal agents led us to consider combination therapy. Itraconazole has absorption problem and serum concentrations could not be measured in our institution. Thus, we chose fluconazole as a combined agent with caspofungin. While we are preparing the manuscript, updated IDSA guidelines (2005, Sept.) recommended the use of high-dose fluconazole for the treatment of diffuse coccidioidal pneumonia. While the high-dose fluconazole was not suitable to some Korean patients for fungal infections because of frequent elevation of hepatic transaminase level, we thought the combination therapy was more appropriate for the present case.
We have described the details regarding the choice of therapy in the Discussion from line 4 on page 9 to line 8 on page 10 in the revised manuscript.

2. Referee’s comment: Reference 12 does not describe efficacy of caspofungin in a murine model of cocci. Please correct.

   Answer: Reference 12 has been changed to reference 10 [Gonzalez GM et al, Antimicrob Agents Chemother 2001, 45(6):1854-1859] on line 10 of page 8 in the revised manuscript.

Discretionary Revisions (which the author can choose to ignore)

1. Referee’s comment: It would be helpful to provide some additional detail on the clinical status of the patient (beyond defervescence) during combination therapy.

   Answer: We have described additional details on the clinical status of the patient
Forty-nine days after the combination therapy, his peak body temperature had decreased to below 38°C and dyspnea had subsided and his serum CF titer had decreased to 1:8. However, his cough still remained. By day 125 of the combination treatment, the patient had defervesced and all his respiratory symptoms had subsided. Moreover, his skin lesions had nearly resolved, although some still remained on his face and a serum CF titer was undetectable, and on day 131, caspofungin therapy was stopped.

2. **Referee’s comment:** Follow up CF titers after stopping caspofungin and recent data (sept 2005) would be helpful.

**Answer:** We have described follow up CF titers on line 12 and 16 of page 6 in the revised manuscript as follows:

On day 194, his follow-up CF titers increased to 1:256 without any worsening of respiratory symptoms, skin rash and chest X-ray. A follow-up examination, performed 5 months following completion of the combination treatment, revealed minimal residual nodules visible on a chest X-ray and
computed tomography scan (Fig. 1, bottom) and CF titers decreased to 1:128.

3. **Referee’s comment**: Did the patient experience any residual clinical pulmonary abnormalities?

**Answer**: No. The patient remains clinically healthy and did not experience any residual respiratory symptoms including cough, dyspnea, chest pain, etc. However, CT scans revealed minimal residual nodules as of September 2005. Because we did not carry out a pulmonary function test, we could not explain the abnormality of pulmonary function. We think that the patient may have normal pulmonary function based on his condition.

**Points suggested by referee #2** (Reviewer, Dr. Duane Hospenthal)

Major Compulsory Revisions

1. **Referee’s comment**: Abstract/Background/Discussion - Amphotericin B is not the current recommended therapy. This statement is incorrect in each of these sections and
Answer: Although our patient was a case of disseminated coccidioidomycosis, chest X-ray and computed tomography findings clearly indicated diffuse coccidioidal pneumonia. Therefore, to clarify this point, the title has been changed to “Treatment of disseminated coccidioidomycosis with diffuse pneumonia by caspofungin and fluconazole.”

For the treatment of diffuse coccidioidal pneumonia, the IDSA guidelines (2000, April) recommend initial amphotericin B. In September 2005, updated IDSA guidelines were published that recommend amphotericin B or high-dose fluconazole. However this was not available at the time of treatment.

This statement has been described in the Abstract (page 2), Background (first paragraph on page 3), and Discussion (first paragraph on page 10) of the revised manuscript.

2. Referee’s comment: Abstract, sentence 2 - This sentence is incorrect.

Azole monotherapy is the recommended treatment.
**Answer:** Our patient was a case of disseminated coccidioidomycosis. However, the patient presented with a miliary pattern on a chest X-ray and we treated as for diffuse pneumonia. We changed sentence 2 in the Abstract to: Ampotericin B is more frequently used as initial therapy if deterioration is rapid.

Minor Essential Revisions

3. **Referee’s comment:** Case presentation - It would be nice to know where this patient was likely exposed to coccidioidomycosis as it is not endemic to Korea.

**Answer:** In the revised manuscript, we have described how this patient was exposed to coccidioidomycosis on lines 6–9 of page 4 as follows: “During August to September 2004, he traveled to Corona, California where he developed his current symptoms and was treated for bacterial pneumonia. However, his symptoms worsened rapidly and he returned to Korea.”

4. **Referee’s comment:** Case presentation - It would be helpful to the reader to know why the combination of fluconazole and caspofungin was selected in this patient.
Versus fluconazole, high dose fluconazole, or itraconazole.

**Answer**: This comment was made by both referees. Corrections are as described for referee #1.

I hope that the revised manuscript will better meet the requirements of the ‘**BMC Infectious Diseases**’ editorial team for publication. I thank you again for considering our paper. The manuscript has been reviewed by a native English speaker and the grammar and syntax have been improved.