Author's response to reviews

Title: Adherence to recommendations by infectious disease consultants and its influence on outcomes of intravenous antibiotic-treated hospitalized patients

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Author's response to reviews: see over
Dear Dr. Shabir Madhi,

Thank you for the comments received for manuscript MS 1382221580682231 that have helped us to improve the manuscript. Attached we are sending the revised version that has been agreed by all authors and the response to reviewers.

Hoping this new version merits publication in your journal,
Sincerely yours,

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Response to reviewers

Referee # 1

- The study question is well posed and methods are appropriate and well described. (?chose to use p < 0.001 to account for multiple comparisons – not sure if this is acceptable.) The discussion and conclusions are appropriate, but could try to avoid repetition of some of the findings. Otherwise well written, the abstract and title are accurate.

Due to the multiple comparisons in the present study, the Bonferroni correction was applied and the p<0.001 was used to minimize type I error.

The discussion has been reviewed in order to maintain only pertinent findings for comment. This has been highlighted in yellow.

- The finding that microbiological tests were more frequently requested in patients randomized to the intervention, and that there was a higher percentage of positive cultures, suggests that ID consultation in addition to antibiotic advice also consciously or unconsciously influenced test request practices, and possibly led to more appropriate selection of sites for microbiological tests.

We completely agree with the reviewer, and a comment has been included in the discussion section. Page 15, second paragraph.

- Table 2 and possibly Table 3 do not add very much value to the study.

We think that a description of comorbidities, type of infection and site of infection could be important in order to show that study groups were homogeneous. If this information lacks, the reader could have doubts about comparability between groups.

We express the information in tables in order to avoid long descriptions in the text.

- Characteristics of antibiotic treatments prior to ID recommendations: this section could be condensed/ clarified.

Page 11, last paragraph: The followed paragraph has been deleted: “Antibiotics were administered as monotherapy in 833 out of 1173 patients (71.0%) and treatment was initiated in the Emergency room in 258 patients (out of 1173, 22.0%), significantly more frequently in the intervention group (p<0.001).” This data is shown in table 5. Information on adequacy between groups, main reasons for inadequacy and changes in initial treatments were described since these items are directly related with the study objectives.

Referee # 2

Major compulsory revisions

- There are a lot of statistical tests and multiple comparisons. There are also many tables. It is due to the fact that authors always perform a lot of comparisons (group with intervention vs group without intervention and according to the three groups of adherence). So the readers might be lost in such amounts of results. Maybe it would be clearer if the authors could group together partial and non-adherence and compare with complete adherence or group partial and complete and compare with non-adherence.
We made statistical many comparisons in order to answer the questions of the study purposes. Baseline demographic and clinical characteristics, comorbidities, type and site of infections, microbiological data, treatments and outcomes were necessarily compared between groups to explore if there were differences. We think that since differences were found between partial vs. complete adherence and vs. non-adherence, all study groups in relation to adherence should be described and analysed in separate, for more clarification.

- The authors chose a threshold for statistical significance <0.001. However, they report several differences with p>0.001 as if there were statistically significant (Results, paragraphs 2, 3, 5, 7, 8) in the bivariate but also in the multivariable analysis.
The text has been revised and accordingly modified to clarify differences showing statistical significance from those not reaching significance. This has been highlighted in yellow.

- The way the authors chose to select the variables in the logistic regression models is not clear enough. A step-wise procedure (I suppose backward) was performed to select the variables independently associated with adherence or clinical success but they also report that the models showing the highest R² were considered.
The model chosen was the model showing the highest R² with the minimum number of explicative independent variables for the dependent variable considered.

- In the first paragraph of Results, 1185 patients were randomized but 1173 patients were finally considered. In the figure 1, we understand that 12 patients were excluded because they had an ID consultation. I think that it would have been better not to exclude them and to perform an intention-to-treat analysis as it is recommended in randomized trial. The authors should add this fact as a limit.
Patients were eligible for the study if they were treated at least 3 days with i.v. antimicrobials as identified by the Pharmacy department, and 81 patients were excluded because ID consultation prior to randomization. In these cases, we considered that the inclusion of written recommendations by IDs in clinical records would not have meaning.
In addition in the non-intervention group, physicians seek for oral ID consultation in 12 cases. In these cases, adherence to written ID recommendations (primary study objective) could not be assessed, and patients could not be part of the non-intervention group (they had oral recommendations). For this reason data from these patients were not recorded in case record forms. Therefore an intention-to-treat analysis is not feasible.

- Table 7: in the footnote it is written that success was used as depend variable but results are not reported that way. Eg: nosocomial infection has an OR of 4.12 and authors write that it is associated with clinical failure.
Thank you for your comment, we have realized that there was an error and it has been corrected in the table and throughout the manuscript. This has been highlighted in yellow.

- In the abstract, the results reporting independent characteristics associated with
adherence or clinical success are not clear enough.
The text of the abstract has been reviewed and, following your suggestion, independent variables associated with clinical failure have been clearly stated. This has been highlighted in yellow.

Minor essential revisions

- **The authors should explain how was assess the clinical success**: based on which criteria?
  Definitions of cure and improvement have been included. Page 8, last paragraph.

- **The authors should define nosocomial infection and healthcare infection**
  Definitions have been included. Page 7, last paragraph.