Author's response to reviews

Title: Additional risk factors for infection by multidrug-resistant pathogens in healthcare-associated infection: a large cohort study

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Version: 3 Date: 31 October 2012

Author's response to reviews: see over
In reply to the reviewers of the manuscript numbered MS: 9249473577886342 – “Risk factors for multidrug resistance not included in the definition of healthcare-associated infection and their impact on antibiotic therapy and hospital outcome”, we provide a point-by-point reply to each concern raised.

First of all we thank the Reviewers for their helpful comments. We have made the necessary changes in the manuscript as suggested by the Reviewers and feel that we have improved the manuscript.

Reviewer: Dr. Anna Levin

The English needs an extensive review

Answer: We agree with the reviewer and the re-submitted manuscript has been edited/reviewed by a native speaker of English through edanz.

The tittle is difficult to understand

Answer: Thank you, we agree and have changed the title of the manuscript to: “Additional risk factors for infection by multidrug-resistant pathogens in healthcare-associated infection: a large cohort study“

1. The introduction should be reviewed as I considered it a bit confusing
Answer: Thank you, we agree and have reviewed the introduction making it more focused and clear. All the changes made are clearly signalled in the re-submitted manuscript.

2. Probably the objective – to evaluate the implications of the community-acquired resistant infections – should not be stated as an objective in itself. To evaluate whether resistance is a prognostic factor would require an extensive analysis taking into account factors as age, delay in starting adequate therapy, severity of clinical condition, etc, and would thus require a multivariate analysis. As this is not the main objective of this study, I suggest it be left out of the stated Objective. The last paragraph of the Results is interesting and should be maintained.

Answer: Thank you for the suggestion. We have changed it accordingly and the Objectives were clarified: “The purpose of this study was to identify additional risk factors for HCAI, which are not included in the current definition of HCAI, associated with infection by multidrug-resistant (MDR) pathogens, in all hospitalized infected patients from the community. ”

The last paragraph of Results was maintained.

3. The definition of MDR is a bit confusing. If bacterium is resistant to one of the classes of drugs, can it be considered multi-resistant? For example, if Acinectobacter was resistant only to ciprofloxacin was it considered MDR or if a gram-negative rod was resistant only to amoxicillin-clavulanate was it considered to be MDR? Please clarify the definition.

Answer: We have adopted the definition of MDR organisms used by 2006 CDC guidelines for “Management of Multidrug-Resistant Organisms in Healthcare Setting” by Siegel JD, Rhinehart E, Jackson M, L C, Committee at
HICPA; accessed in

We used the exact definition: “that defines multidrug-resistant organisms as bacteria that are resistant to one or more classes of antimicrobial agents” to clarify the definition we added “that are recommended as first line therapy”. To draw back from the literature controversy on this definition we have choosen one adopted by the Atlanta Centers for Disease Control.

4. On page 8 the authors defined “immunossupression” on line 2, and then changed the definition on line 15. I did not understand. The same occurred for cancer. Maybe this could be simplified.

Answer: Definitely, we have made the necessary clarifications. Thank you.

5. In the section “Statistical analysis”, the authors listed statistical tests used but in no part of the manuscript did they described how the study was performed. There should be a section in which the outcome studied should be stated and in which there is a description of what groups were compared.

Answer: We agree. We have added a second paragraph in the first section of Methods clarifying the main outcomes: “The primary outcome of interest was infection by a MDR pathogen.”

We also review the statistical analysis section clarifying the tests used according to studied variables characteristics and a description of the comparisons made in table 1 and 4.
6. In table 2, it is not clear what groups were compared. It seems that only community-acquired infections were included but this was not stated in Methods. In Methods the analysis should be described.

**Answer:** We have included in the methods section the following statement: “All variables potentially associated with MDR pathogen infection (including MDR-GN and ESKAPE pathogens) were studied among all infected patients admitted from the community, those with CAI and HCAI, and included: age, sex, previous antibiotic therapy, hospitalization in the previous year, immunosuppression, chronic hepatic disease, chronic heart failure, chronic respiratory disease, chronic hematologic disease, cancer, diabetes, atherosclerosis and decreased functional capacity (Karnofsky index <70). Those with a clear association in the univariate analysis ($p < 0.1$) were included in the multivariable analysis. The results of the multivariable models are expressed as odds ratio (OR) with 95% confidence interval and $p$-values. The calibration was tested using the Hosmer-Lemeshow goodness-of-fit test. The significance level was defined as $p < 0.05$.”

We think it is clearer now, thank you.

7. In table 1, the 5th variable in column 1 is “Infection”. To present an infection seemed to be an inclusion criterium, thus should have been present in all patients. Please clarify.

**Answer:** The variable is in fact severity of infection divided in four categories of increased continuum of severity of disease: localized infection without systemic inflammatory response syndrome (SIRS), sepsis (infection plus SIRS), severe sepsis (sepsis plus organ dysfunction) and septic shock (sepsis-induced hypotension persisting despite adequate fluid resuscitation along with the presence of perfusion abnormalities). We have arranged it graphically to make it clearer.

Thank you very much.
Reviewer: Dr. Peter Wilson

This study is descriptive and it should be clear where data could not be found. This was prospective recruitment. Do the authors mean there was no missing data at all as stated in the discussion?

Answer: Yes, there was no data missing per item as declared, data not readily available in the patients’ files where collected afterwards (like final microbiology data).

On p7 the definition of multiresistance in acinectobacter is not clear – do the authors mean one of the listed antibiotics?

Answer: Thank you for your question. We have adopted the definition of MDR organisms used by 2006 CDC guidelines for “Management of Multidrug-Resistant Organisms in Healthcare Setting” by Siegel JD, Rhinehart E, Jackson M, L C, Committee at HICPA; accessed in http://www.cdc.gov/ncidod/dhqp/pdf/ar/MDROGuideline2006.pdf.

We used the exact definition: “that defines multidrug-resistant organisms as bacteria that are resistant to one or more classes of antimicrobial agents” to clarify the definition we added “that are recommended as first line therapy”. To draw back from the literature controversy on this defenition we have choosen one adopted by a well recognized organization, the Center for Disease Control.

P10 How many were assessed and did not fit the inclusion criteria?

Answer: Thank you for your suggestion we have added in results the following statement: “During the study period a total of 3733 patients were assessed and 1035 (28%) met the inclusion criteria of having infection according to the CDC definitions of infection.”
There was no difference in mortality – yet the rate of inadequate antibiotic therapy was affected. Please explain why....

Answer: That is a very good question but with the available data we do not have a scientific explanation for that fact. May be that the fast knowledge of microbiology results have led to an early adjustment of antibiotic therapy, before the patient became severely ill and mortality increased, but we do not have data to make such analysis.

With the available data we looked if infection by MDR pathogens and/or inadequate antibiotic therapy were independent variables for hospital mortality through a multiple logistic regression model that also included all variables described in table 2. The results confirm that infection by a MDR pathogen was not independently associated with higher mortality. Variables independently associated with higher hospital mortality were: karnofsky <70 (adjusted OR = 2.464), adequate antibiotic therapy (adjusted OR = 0.537) and SAPS II (adjusted OR = 1.102 per point).

This analysis was not included in the manuscript considering that the main outcome studied was infection by a multidrug-resistant pathogen. The impact of healthcare-associated infection in adequacy of initial antibiotic therapy and hospital outcome is addressed in a different manuscript.

Having derived a risk model this needs to be tested on a new cohort of patients – is it predictive?

Answer: Yes, we agree with the reviewer. The study was not planned to have a second cohort and data collection has already finished. On the other hand we think that the scientific findings will be more robust if confirmed at different centers, that is why we have concluded with the statement “Further research involving a large number of patients from different institutions and geographic areas is warranted to confirm these findings.”
There are several spelling and grammatical errors

**Answer:** Thank you, we have corrected them accordingly.

The authors should explain why they have made a new group ESKAPE – what is the rational? Why have these been selected out?

**Answer:** Thank you. The ESKAPE group has been proposed by Rice in 2008 (Rice LB. Federal funding for the study of antimicrobial resistance in nosocomial pathogens: no ESKAPE. J Infect Dis 2008; 197:1079-81) and adopted by Infectious Diseases Society of America (IDSA) to emphasize that they are a cause of a majority of hospital infections and effectively “escape” the effects of antibacterial drugs. They represent a major problem in the occidental world and in that sense the authors though pertinent to discuss MDR pathogens altogether as well as stratified by 2 major groups: MDR-gram negatives and ESKAPE group.

Needs some language corrections before being published

**Answer:** We agree with the reviewer and the manuscript has been edited by a native speaker of English through edanz.

Thank you very much.