Author's response to reviews

Title: Surgical site infection in critically ill patients with secondary and tertiary peritonitis: epidemiology, microbiology and influence in outcomes.

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Author's response to reviews: see over
To whom it may concern,

On behalf of my co-authors, I submit the enclosed manuscript for consideration by the *BMC Infectious Diseases* Journal. It has not been published in this or a substantially similar form (in print or electronically, including on a web site), nor accepted for publication elsewhere, nor is it under consideration by another publication.

There are not possible conflicts of interest (including financial and other relationships) for each author.
Appropriate Ethics Committee approval has been obtained for the research reported (if you need committee writing documents, please ask for it).

All authors send this letter as confirmation that they have read and approved the paper, have met the criteria for authorship as established by the International Committee of Medical Journals Editors, believe that the paper represents honest work, and are able to verify the validity of the results reported.

The present manuscript evaluates briefly the clinical importance of the surgical site infections over outcomes in the critical care scenario. This is important since there are not any studies addressing specifically the SSI issue in the severely ill.

Corrections have been done prior editorial assessment.

I hope I will be of your interest. Thank you for the opportunity of submitting this report.

If you need further information, please contact corresponding author,

Sincerely,

Juan Carlos Lopez-Delgado  
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Dear Sheryl Ramos, Dr. Vangelis G Alexiou and Editorial Team of *BMC Infectious Diseases* Journal,

First of all, thank you very much for considering our manuscript for review in your Journal. We are very honored for this opportunity and it is being a great experience due to the challenges that reviewers have requested for the present review.

We enclose this document responding to each point raised by the reviewers, together with a clean revised manuscript and a marked-up copy of the changes made from the previous version of this manuscript based on your advice. Specific changes have been marked due to the major and minor revision needed.

We would like to thank both reviewers for their comments, which have helped us to make significant improvements in this manuscript. We have clarified some points in compliance with reviewer’s advice that have improved the manuscript from the educational point of view. However, this research has the same limitations of any observational study. We would like to mention that we cannot provide completely all the data in some cases (such as the detailed pattern of antibiotic resistance of SSI) because we consider it does not add anything new to the current knowledge. However, the data required for reviewers has been reported. Finally, we would like to stand out that any of the comments provided by both reviewers have changed substantially the conclusions of our paper.

The manuscript has been reviewed again in full by a native English speaker (Prof. Michael Maudsley, from the Language Services of the Universitat de Barcelona - [maudsley@ub.edu](mailto:maudsley@ub.edu)) specialized in scientific English.

Our financial disclosure has not changed since the previous submission.

Thank you very much for considering us for publication,

Warm regards,

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Reviewers ‘report’ Title: *Surgical Site Infection in critically ill patients with secondary and tertiary peritonitis: epidemiology, microbiology and influence in outcomes.*

Version: 2. Date: 8 March 2015. Reviewer: **Emilio Maseda.**

Reviewer’s report: The study reports a 4-year prospective observational study in a single center. The primary outcome of interest was microbiology and mortality of SSI.

**Major points.**

1) The major problem I have with this paper is the microbiological method for obtaining the microbiological samples for diagnosis purposes. Tissue biopsy or aspiration sampling of infected tissue is the “gold standard” for culture of skin and soft tissue infection and is especially important with serious infection, systemic toxicity, or failure of initial therapy. Swab cultures are probably the most commonly used method to determine the resistance pattern of skin pathogens treated in nursing home residents. However, they are controversial through this method. We can obtain colonizer microorganisms that are not responsible for the infection. And furthermore, cultures of the superficial wound may be misleading because results may not reflect organisms in the deep tissue infection. Direct needle aspiration of an area of cutaneous inflammation may yield fluid for Gram stain and culture.

First of all, we would like to thank the judicious comments of the present reviewer. The microbiological methods for obtaining the microbiological samples are not explained appropriately enough throughout the Methods and Results section because we mixed obtaining sample methods with processing methods in the microbiology laboratory. It seems like we obtain a superficial skin/ wound swab sample instead of tissue samples. On the other hand, note that we explain in lines 126-28 “Tissue or exudate samples from the wound were also sent for microbiological analysis and culture. If necessary, drainage was performed, and any necrotic tissue was debrided and foreign material removed”. Indeed, our local protocol constrains us to perform this gold standard when it is indicated and/or possible. We obtained tissue samples and exudate samples, and direct needle aspiration was used when needed, in collaboration with the surgical team. Our objective was to obtain a sterile sample as much as possible in order to avoid colonizers of the superficial wound and a deep tissue sample when it was necessary. However, swabs are the most common methods for processing purposes in the microbiology laboratory (line 120 “For diagnosis purposes, microbiological samples were sent to the laboratory as swabs [...]”). Appropriate modifications have been done at the Methods section in order to avoid such controversy within our manuscript.

2) The authors state in Conclusion (p.2 and p.8) that “physicians should consider antibiotic resistant pathogens...”. However, the authors don’t show the resistance pattern of isolated microorganisms. It should be clarified whether isolates of *Enterobacteriaceae* are ESBL producers and whether isolates of *Pseudomonas aeruginosa* were carbapenem-resistant or not. In addition, the authors state in page 6, line 159 “antibiotic resistance to two or more antibiotics occurred in 64.9%”. The problem is that they didn’t provide data on which antibiotics were resistant to isolated microorganisms.
Reviewer is right in this comment since we cannot provide a recommendation and/or conclusion without showing our results. The rates of Extended spectrum beta-lactamase-producing Enterobacteriaceae (n = 30) and *Pseudomonas aeruginosa* carbapenem-resistant (n = 32) were 11.1% and 11.9% respectively. We have not provided data on detail, such as which specific antibiotics were resistant the isolated microorganisms, because the major part of the patients were correctly treated. This explains the lack of influence over mortality when a devastating complication such as SSI appears (The lack of influence is also explained by the severity of the critically ill, as we have added in our Discussion section). Thus, there is not any point in showing completely the pattern of resistance of our microbiology results, even when they are similar to those reported in the literature. In addition, it does not add anything new for educational purposes. We focused our research evaluate the microbiology population in our SSI without deepening in antibiotic resistance pattern since this changes depending on the local flora and the different characteristics of the hospital. However, we have provided the required information within our manuscript. We suggest that physicians should consider antibiotic resistant pathogens because there is a higher probability when SSI appears.

3) The authors should give information on the microorganisms that were isolated from intra-abdominal fluid and if there is any relation to the microorganisms that were isolated in the surgical site infection.

The microorganisms isolated from intra-abdominal abscesses were the same of those isolated in SSI samples in the 20.9% of the patients (n=34). The incidence of multi-resistant isolated microorganisms was similar to other patients with SSI (11.7% beta-lactamase-producing Enterobacteriaceae (n=4), 15.62% *Pseudomonas aeruginosa* carbapenem-resistant (n=5), 2.9% *Acinetobacter baumanii* (n=1)). The relationship between intra-abdominal abscesses due to SSI was not established at the time of diagnosis since microbiological results from intra-abdominal abscesses have appeared before the occurrence of SSI. In addition, there was not any anatomical relationship between deep SSI and intra-abdominal abscesses based on surgeon team evaluation. This information is briefly described in the Results section.

**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 declare that I have no competing interest' below.**
Reviewer's report: Thank you for giving me the opportunity to review this manuscript. The paper is extremely well written, and concerns an interesting and important complication of surgery. I would be happy to recommend the article for publication after the following consideration of the following points:

Thank you very much for your comments, which are really appreciated. We are much honored to be reviewed by yours.

Minor Essential Revisions:

1. Please could the authors advise how they arrived at the figure of 64.4% for the 200 SSI episodes occurring in men?

   This percentage was wrong calculated. See appropriate correction in Tables 1.

2. I would suggest that the more common species of microorganism are listed first (e.g. Pseudomonas spp. (n = 44 52, 19.3%) and Escherichia coli (n = 55, 20.4%) should be swapped round).

   The more common species of microorganisms are listed first at the Results section due to reviewer’s advice.

3. Line 77: please note: Centers for Disease Control and Prevention (Centers rather than Center).

   This is changed due to reviewer’s advice.

4. Line 106: please amend to "data were" rather than "data was."

   Amendment performed due to reviewer’s advice.

5. Line 125: please amend to "the ICU physician" or "ICU physicians."

   Amendment performed due to reviewer’s advice.

6. The authors comment that the SSI rate of 53.1% in the study group was higher than the rest of the hospital (20.6%). Are you able to provide any raw data to support this, even if it is simply the total number of SSIs and the total number of patients?

   This data has been provided at the beginning of the Results section. More specific data cannot be provided due to hospital restrictions.

7. Please double check all percentages presented and report to 1 decimal place throughout.

   We have checked all percentages presented and we have reported 1 decimal throughout the whole manuscript due to reviewer’s advice.

8. Line 164-165, please amend from "with the use of multiple, simultaneous or sequential antibiotics being common..." to "with the use of multiple, simultaneous or sequential antibiotics being used in 72.5% of cases (n=195)." The Results section should simply present the results objectively and the fact that this is "common" should be commented on in the Discussion section, if appropriate.

   Amendment performed due to reviewer’s advice. The word “common” was use inappropriately.

9. The Discussion section states that SSI had little impact on in-hospital mortality, when in fact, the data suggest that mortality was lower in those with SSI. This is counter-intuitive and some explanation of this point should be given.

   Despite mortality was lower in the group with SSI, note that the group without SSI experienced higher severity of illness reflected by higher APACHE and SAPS scores.
Thus, most of them died the next days after ICU admission and they did not develop SSI. Indeed, SSI was not associated with higher mortality in our population in multivariate analysis was performed including confounders that reflected disease severity. However, when we performed the same type of analysis, the presence of SSI was independently associated with longer ICU stay. We have to tend into account the characteristics of our cohort. Thus, the influence of SSI over mortality in such severe group of patients is poor. We have briefly explained the counter-intuitive contradiction regarding mortality in those patients at the end of the results section and underlined the difficulty for extrapolating our results in other less severely ill populations.

10. Line 189: please amend "higher" to "a greater number of..."
Amendment performed due to reviewer’s advice.

11. Line 201: please insert full stop after "concentrations."
Amendment performed due to reviewer’s advice.

12. Line 238: please note spelling, "can" rather than "cab."
Amendment performed due to reviewer’s advice.

13. Figure 1 appears unclear in its present form. Please could the authors ensure a clearer figure is submitted prior to publication.
A clearer figure has been submitted due to publication purposes based on reviewer’s advice.

14. Table 1: I would suggest that raw data are presented initially in the table, with percentages in brackets, i.e. n (X %), rather than percentages first as are currently presented.
This is changed due to reviewer’s advice.

15: Table 1: The P value for "Number of drainage" is not in bold. It is below the cut-off of 0.05 for significance, and so should be highlighted. Also, the term "number of drainage" could be amended to be more explanatory.
“Number of drainage” refers to the number of drainages on ICU admission after abdominal surgery. This is explained in Table 1. We have also written in bold the P value of this variable.

16. Table 2: Following on from point 2 above, I would suggest that the table is organized so that more common pathogens are at the top of the table, perhaps leaving the category of "other" at the bottom, but maybe having some explanation of what would be in the "other" category.
The more common species of microorganisms are listed first as per reviewer’s advice. We have reviewed our microbiology results and we have included them in Table 2. We have realized there are some transcription errors in the transcription of our microbiology results and those have been corrected appropriately. Fortunately, this has not been influence the conclusions of our manuscript.

Good luck with your resubmission!

Level of interest: An article of importance in its field.
Quality of written English: Acceptable.
Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.
Declaration of competing interests: I declare that I have no competing interests.