Author's response to reviews

Title: Reappraisal of the outcome of healthcare-associated and community-acquired bacteramia: a prospective cohort study.

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Author's response to reviews: see over
The editor BMC Infectious Disease
Dear Sir,

Please find attached a reviewed version of the manuscript “Reappraisal of the outcome of healthcare-associated and community-acquired bacteremia: a prospective cohort study” to be considered for publication in BMC Infectious Disease.

We really thanks reviewers’ suggestions as they have proposed interesting and important changes and valuable information has been included.

As suggested we have removed table 1 which had been partially published previously and have included a table with individualised information of inadequate treatments.

A point per point answer of reviewers’ comments has been included above. Please do not hesitate to contact me if you have any concern regarding the manuscript.

Sincerely,
Pilar Retamar Gentil, MD, PhD
First and corresponding author.

Reviewer 1:

Major Issues
1. The authors present data (which is quite delayed) – specifically when looking at outcomes following a BSI event and are (somehow?) related to a prior work involving BSI published in 2010. This prior manuscript focused more on an epi background, and only briefly addressed factors associated with mortality. It needs to be clarified how the two data sets are separate and where overlaps exist – as the numbers look to be different.

Answer: the present report refers to the same cohort. Differences in number are because blood samples taken in the emergency department without an inhospital stay were not included (those were 1 CO and 3 HCA episodes). We have included this information in the method section (lines 92-93).
2. The relevance of the data presented now that was collected in 2006 in relation to community epidemics of MRSA and ESBL Enterobactericeae is questionable. The authors describe their data in a “current state” which is not strictly appropriate.
Answer: we agree with this comment. The discussion section has been modified to refer to the time the data was collected (lines 244-254).

3. The authors conclude that outcomes are no different for CA and HCA infections and that criteria need to be revised. This certainly is at odds with other published data and their own findings. With the evident different etiologies, and different treatments provided – it would seem that the HCA-CA condition was recognized in their cohort and compensated for appropriately with individualized management strategies.
Answer: we also believe that the HCA-CO condition was recognized and compensated as it is remarked in the discussion section (lines 268-278).

4. The inclusion of pneumococcus as a cause of BSI and the definition of inappropriate treatment is somewhat misleading as penicillin remains the drug of choice even in resistant isolates outside of CNS infections. Given the high number of pneumococcal isolates in their data set (particularly in the CA-HCA population) – what is the impact if these are removed?
Answer: considering the pneumococcal isolates the number of inadequate treatments were 23/149 (15%) in the CA subgroup and 32/192 (18%) in the HCA-CO subgroup that is not statistically different (p=0.63). If we remove the pneumococcal isolates the inadequate treatments are 22/122 (18%) and 31/181 (17%) in CA and HCA-CO respectively with no difference found (p=0.84).

Minor Issues
1. The authors refer to ESBLs in the manuscript as being a potential factor in observing more resistance in the community and increased risk of inadequate initial treatment. The data in Table 4 merely reports cefotaxime resistance for the Enterobactericeae – are we to presume this to equate to ESBLs?
Answer: all of them were ESBL producer, to clarify this concept a note has been attached to table 3 (table 4 in previous version).

Reviewer 2
Major comments:
1- The biggest issue here is that the mortality results were, in part, previously published (reference #10). In fact, the entire Table 1 is copied from the same reference, which the authors acknowledge. Is it really worth running a multivariable model to analyze mortality if there was no difference in the univariate model between HCA and community-acquired (CA) BSI as already shown in reference #10, Table 1 and mentioned in the Introduction section of the manuscript? The only interesting finding in the mortality analysis is that inappropriate therapy was associated with mortality, but this is not news.

Answer: regarding this comment we have decide to remove Table 1 and to remark the more interesting findings in the methods section (lines 95-104). We believed that to run a multivariate model would add consistency to our previous findings and could help to control by potential confounders.

2- It is obvious why there was no mortality difference between CA and HCA BSI in this report. First, more patients with HAC BSI had coagulase-negative Staph than CA BSI (10% vs. 5%). BSI due to coagulase-negative Staph is known to have very low mortality, if any. Second, it is almost certain that patients with HCA BSI received broader spectrum antibiotics than those with CA BSI. It would be interesting to show that difference in the manuscript.

Answer: the differences among treatments used in HCA and CA are shown in the results section (lines 195-209). In relation to this comment and the comment number 5 we have decided to include a table with the individualised inadequate treatments according to acquisition, aetiology and main resistances (table 5 in the reviewed version).

3- It would be interesting to examine mortality for Gram-positive and Gram-negative BSI separately. I assume mortality is higher for HCA BSI due to Gram-negative bacilli than CA BSI due to Gram-negative bacilli, given higher proportions of BSI due to P. aeruginosa and Enterobacter spp in the HCA group. The limitation of this analysis is that the study may not have adequate power to detect the difference in mortality if stratified by Gram-positives and Gram-negatives.

Answer: regarding your comment we have performed a stratified analysis of mortality for Gram-positive and Gram-negative BSI comparing HCA and CA BSI. We have found that difference in 14th-day mortality among Gram-negative is statically significant (7% in CA vs 17% in HCA, p=0,05). We have included this result in the reviewed version (line 152-155).
4- My suggestion is to focus on the risk factors for inappropriate antimicrobial therapy in community-acquired (not community-onset) and HCA BSI in 2 separate models. This will help identify the group of patients with community-acquired BSI who should receive broader spectrum antimicrobial coverage. I agree with the authors that the time has come to expand the definition of HCA BSI to include patients with outpatient invasive (urinary) procedures, etc., to capture more cases of BSI due to resistant organisms that usually end up receiving inappropriate therapy (which is associated with mortality as in the current and past literature).

Answer: we appreciate and thanks this suggestion but the small size do not allow the development of two different models with significant statistical power (regarding the mortality rate in each subgroup, only one or two predictors could be included in each multivariate model).

5- On the same note. It would be very interesting to explore the 23 patients with CA BSI who received inappropriate therapy in more detail. Did they receive a third-generation cephalosporin for P. aeruginosa or ESBL producing (or cefotaxime-R) E. coli or Klebsiella spp? Did they receive a fluoroquinolone for a FQ-R Gram-negative bacillus? Or did the majority of them receive no antimicrobial agents in the first 24h. It would be as interesting also to discuss antimicrobial therapy in detail for the 34 patients with HCA BSI who received inadequate therapy (how many did not receive antipseudomonal agents? How many did not receive vancomycin for empiric therapy of Gram-positive BSI? How many received FQ for FQ-R Gram-negative bacillus? etc.) This will generate very interesting data on why did some patients receive inappropriate therapy and provide opportunities for improvement. Summarizing this data in a table would be very useful.

Answer: table 5 has been included with the inadequate treatments regarding the microorganism, the acquisition (CA and HCA) and the resistances. Essential information from this table has been included in the results section (lines 210-19).

6- Resistance: The study is not powered to examine antimicrobial resistance for any individual organism. For example, there were only 57 and 71 HCA and CA E. coli BSI (the most common organism) in the study, respectively. Fluoroquinolone resistance was clearly more common in HCA than in CA E. coli BSI (37% vs 25%) and methicillin resistance was more common in HCA than CA S. aureus BSI (27% vs 0%). Both were not statistically significant due to under power. That needs to be clearly stated in the Discussion section.
Answer: we thank this comment. An explanation has been included in the text (lines 270-278).

Minor comments:
1- Please use the term BSI throughout the title and text for consistency. You may use “bacteremia” as a key word.
Answer: the term BSI has been corrected along text. “Bacteremia” has been included as a key word (line 55).
2- I would use the term HCA, not HCA-CO, throughout the text to make things less confusing for readers.
Answer: we agree with this comment. The term HCA-CO has been changed to HCA along the text.
3- Please define STROBE, SAEI and SAMPAC prior to first use.
Answer: the terms have been defined in lines 82 and 6-8 respectively.
4- The word “Enterobacteriaceae” is misspelled in Page 4, line 71.
Answer: corrected in the text (line 74).
5- Did the study run from October 1 to December 31? Please specify.
Answer: specified in the text (line 89)
6- Please use “0” in Table 1 instead of “-“
Answer: Table 1 has been removed.
7- The authors cite the wrong reference for the Pitt bacteremia score (reference #19). They should cite one of the original papers that described or updated the score such as the one by Paterson DL, et al in Annuals of Internal Medicine in 2004.
Answer: the cite has been corrected following your suggestion.
8- Table 3: Regarding the odds ratio for Pitt score, is this per point or per the entire range?
Answer: the Pitt score was recodified and dicotomised to be included in the multivariate model. The cutt –of were a score of ≥2. This has been corrected in Table 3 in the reviewed version.
9- Was BSI due to Candida spp included in the study?. If not, then please mention this in the Methods section.
Answer: Yes, they were included. Only one episode was caused by Candida spp. included in the HCA subgroup.
Reviewer 3:

The first part of the conclusions is clearly supported by the data but in the second part it is not clear how the findings suggest that the criteria for HCA BSI should be reviewed. Although the title truly represents what was done in the study it may be modified to convey what has been found.
Answer: the conclusion has been modified according to your comment.

Minor Essential Revisions
Page 4 line 62: Suggesting "comprise" instead of "increase". Answer: corrected (line 64)
Page 5 line 97: ref # should be 16 not 15. Answer: corrected in the text (line106).
Page 8 line 162: Suggesting "pathogens" instead of "aetiologies". Answer: corrected (line 168).
Page 8 line 171: "in community" is redundant. Answer: the term has been removed (line 181).
Page 9 line 190: 28% vs. 28% cannot produce a p value of 0.1. Answer: thanks for the correction. It was mistaken as it should 28% vs 41%.
Answer: corrected in the text (line 199).
Page 11 line 222: Only ref 7 included patients who were not hospitalized. Refs 5 & 9 included hospitalized patients only.
Answer: corrected in the text (line 241).
Page 11 lines 223-4: The meaning of this sentence is not clear.
Answer: we have modified the sentence to make it more understable (242-244).
Page 12 line 249: Was MDR explained anywhere earlier in the text?
Answer: it was explained in the background section (line 70).
Page 12 line 257-9: Suggesting remodeling this sentence as follows: All three variables are known risk factors for certain types of pathogens or resistances that are not typical for strict community pathogens, and they should be taken into account when considering empirical therapy.
Answer: the sentence has been remodelled (288-290).
Page 12 line 261: Suggesting: similar to previous studies dealing with an outcome impact of HCA BSI. The findings would not be
Answer: changed (lines 292-294).
Table 1 It is not clear what does "Data from reference 10" mean. If this study population is based on a cohort that was included in a previous study it should be clearly stated in the "patient selection" section, and preferably also in the ABSTRACT. It is suggested that the total number of patients in each column be added to the table and it should be stated that the numbers in parenthesis are percents. "R" and "MDR" explanations in the footnote are redundant since they are not mentioned in the table.

Answer: the table 1 has been removed. The present study is a subanalysis of a bigger bacteremia cohort. The epidemiological features of the global cohort have been reported before as explained in the methods section (lines ).

Table 2. The numbers in 2 cells are distorted, line: "Severity of SIRS", column: "dead at day 30". The term "CNS" is misleading since it may be considered "central nervous system" (especially when appearing immediately after "Source of bacteremia" category. It should be changed to "CONS", which is a more accepted term.

Table 4. Line "Klebsiella spp." Third column "K" should be replaced by "N". Wherever "#-lactam/#-lactam inhibitor" is mentioned it should say "#-lactam/#-lactamase inhibitors".

Reviewer 4:
Major issues
Methods:

1. The methods need to state clearly that the patients with community onset bacteremia not admitted to hospital were not included in this study is this is a significant source of bias in determining outcome.

Answer: we appreciate the comment. We have included a sentence remarking this issue (see text line 88).

1. This report analyzes 341 episodes of a specific cohort previously published (reference #10). The previous reference includes 821 episodes of bloodstream infection of which 476 were hospital-acquired. As such 345 are community onset. I presume only four cases were not admitted to hospital but this should be stated in the methods. Many readers may not be familiar with this prior publication.

Answer: we have included a sentence with this information in the methods section (line 89-90).
Results:

1. Line 140-146 is somewhat confusing as they include data from a previous study. It may be easier for the readers if this was a separate paragraph (The second starting on line 141-145).

   Answer: this has been corrected in the text. Also the reference to table 1 has been removed as this table is not included in the reviewed version.

2. A table of the multivariate analysis for risk factors of inappropriate empirical therapy may be easier for the reader to incorporate as knowledge.

   Answer: data of multivariate analysis has been included in an added column added to table 4 (tabla 5 in previous version).