Author's response to reviews

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

Authors:

Pilar Retamar (pilaretamar@hotmail.com)
Mª Dolores López-Prieto (lolalopezmicro@hotmail.com)
Marina de Cueto (m@marinadecueto.e.telefonica.net)
Clara Natera (cnatera@telefonica.net)
Enriqué Nuño (enunooal@hotmail.com)
Marta Herrero (marta_hr@yahoo.es)
Fernando Fernández-Sánchez (ffsgranada@hotmail.com)
Ángel Muñoz (somafe2000@yahoo.es)
Francisco Téllez (PTELLEZP@terra.es)
Berta Becerill (med007378@saludalia.com)
Ana García-Tapia (parvovirusagatapia@yahoo.es)
Inmaculada Carazo (concepcion.carazo.sspa@juntadeandalucia.es)
Raquel Moya (draraquel@terra.es)
Juan E Corzo (juanecorzo@telefonica.net)
Laura León (NORLAURA@terra.es)
Leopoldo Muñoz (lmunnoz@yahoo.com)
Jesús Rodríguez-Baño (jesusrb@us.es)

Version: 3 Date: 11 July 2013

Author's response to reviews: see over
Seville, 10th July 2013

The editor BMC Infectious Diseases

Dear Sir,

Please find attached a revised 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 Diseases. We also provide a point-by-point response to the reviewer´s suggestions.

Sincerely,

Pilar Retamar, PhD MD
First and corresponding author

Reviewer 1:

Major Issues
1. Is this a 2 or a three month study – in abstract 2 months, in data set states Oct 1 – Dec 31 which would be three months.
Answer: thanks for the correction. They were three months. The abstract has been corrected (line 40).

Minor Issues
1. Outcome of “inappropriate therapy” needs to qualified by the fact that very broad spectrum therapy was generally used for HCA (carbs and b-lactam+inhibitor combinations were most commonly used). Which patients received >1 drug class needs to be commented on.
Answer: there were the same number of combined treatment with >1 drug class among CA and HCA BSI (34,1% vs 34%, p=0,99), although the combination cephalosporin plus levofloxacin was more common among CA episodes (29% vs 21% in HCA BSI, p=0.32) and the combination cephalosporin plus vancomycin was more common among HCA BSI (14% among CA vs 23% in HCA, p=0.49). These differences were not significant. This comment has been included in the results (lines 214-219).

2. Definitions of ESBLs – how was this ascertained – all that is eluded to was 3rd gen cephalosporin resistance. Still not explained.
ESBLs were defined as enzymes conferring resistance to some or all penicillins and oxy-imino-beta-lactams (e.g., ceftazidime, cefotaxime and cefepime) but nor cefapmycins or carbapenems, which are inhibited by beta-lactam inhibitors. Isolates with a MIC to cefotaxime or ceftazidime were screened for ESBL production by the disk diffusion method with Mueller-Hinton agar plates with disks containing 30g of cefotaxime and ceftazidime with or without 10g of clavulanic acid, as recommended at that time by CLSI. ESBL production was confirmed by the microdilution method if a 3 twofold dilution decrease in the MIC of either ceftazidime or cefotaxime tested in combination with clavulanic acid versus the MIC of each agent when tested alone was observed. A brief explanation of this has been included in the text (lines 107-110).

3. In the conclusion - Inadequation?
Answer: we found this term in the results and discussion section. This term has been changed by “inadequate treatments” (line 223, 296).

4. *S. pneumoniae* penicillin resistance and inappropriate therapy needs to be better explained given the ability to overcome MIC, and preference to use penicillin still in non-CNS infections. Are there meaningful changes to the conclusions with these datapoints suppressed. Still not commented on.
Answer: empirical therapy was considered appropriate when an active antimicrobial agent (according to susceptibility data) was administered at recommended doses within the first 24 h after the blood cultures had been performed, and inappropriate otherwise (lines 129-132). *S. pneumoniae* isolations were considered resistant to penicillin when MIC was ≥4 regarding CLSI recommendations. There were 2 isolations of penicillin resistant *S. pneumoniae* among CA BSI and 5 among HCA. From them only 1 case in the CA group and 2 cases in the HCA were considered non-adequatly treated because the treatment was delayed (included in table 5). If we suppress penicillin resistant *S. pneumoniae* BSIs from the database the proportion of adequate treatment among CA and HCA BSIs were respectively 84,7% vs 81,9% . This difference was still not significant (p=0,49).

5. The second last paragraph seems to fall apart
Answer: we regret we do not understand which paragraph the reviewer refers to (in the conclusion? In discussion?).

Reviewer 2:
1- Higher mortality among HCA as compared to CA Gram-negative BSI needs to be highlighted in the abstract and Discussion section, with comparison to other studies of Gram-negative BSI. This may be followed by an explanation of why there was no difference in overall mortality of BSI, which is higher proportion of coagulase-negative Staph among HCA BSI.
Answer: we agree with this comment. We have include it in the abstract (lines 47-49) and discussion (lines 235-237)
2- The term HCA-CO is still used in Table 3.
Answer: the term has been corrected in the table.
3- Page 13, line 285: I disagree with the authors that amoxicillin-clavulanate is a first line agent for CA BSI. Resistance rates to amoxicillin-clavulanate and ampicillin-sulbactam among CA E. coli bloodstream isolates have approached 40% in many high-quality studies in the USA. The authors of such papers (and the IDSA guidelines for treatment of intra-abdominal infections) have recommended against the use of these 2 agents for serious CA E. coli (and other Gram-negative) infections. It is important to mention this in the Discussion section and cite the appropriate references to support this statement.
Answer: resistances rates in Europe, particularly in Spain, may differ from USA rates. In 2007 E.coli resistance rate to amoxicillin-clavulanic was about 10-15% as seem in some Spanish publications at that time (25, 26); so the Andalusian Society of Infectious Diseases recommended amoxicillin-clavulanic as first to treat intraabdominal and urinary tract infections (23, 24). Nowadays this rate has increased up to 30% so urinary and intraabdominal guidelines have been modified. This comment and references have been included in the discussion section (lines 298-302).

Reviewer 4:
The authors have revised the manuscript and addressed all my questions in their response.
Answer: thanks. No answer required.