Reviewer's report

Title: Dynamics of C-reactive protein and white blood cell count in critically ill patients with nosocomial gram-positive vs. gram-negative bacteremia: a historical cohort study

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Reviewer: Pedro Póvoa

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General

Dr. Dominique Vandijck performed a retrospective cohort study to assess if changes over time of C-reactive protein (CRP) and white cell count (WCC) in patients with bloodstream infections (BSI) could differentiate Gram positive from Gram negative pathogens. During the defined period of observation, specifically 4 days, from day (D) D-2 to D+1, the authors found that CRP change was twice as high in Gram negative BSI in comparison to Gram positive, 6.2 vs. 3.1 mg/dl, respectively (p=0.025). According to the authors opinion these different patterns could have potential benefits in terms of early initiation of antibiotic therapy.

Overall this paper deals with the issue of evaluation of serial measurements of infectious markers, in particular CRP and WCC, as predictors of infection, in this case both Gram positive and Gram negative BSI. However the manuscript has some methodological problems that turn the text somewhat confusing and difficult to read even though with a good sample size.

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Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)

1. There are several concepts that need to be clearly defined: a) when were the antibiotics prescribed, after the clinical diagnosis of BSI, after blood cultures became positive or in some patients was the first criteria and in other patients was the second; and in the case of coagulase-negative staphylococci BSI, in whom two successive positive blood cultures yielding coagulase-negative Staphylococcus on separate occasions within a 48-h period, as well as confirmation of clinical significance of bacteremia by the attending intensivist to have the final confirmation of BSI, when were the antibiotics prescribed in those patients; all these factors could have a significant influence in the changes of CRP and WCC after D0 once some patients were already on antibiotics while others were still with an untreated BSI; b) initial choice of antibiotics (page 7, 2nd paragraph): the authors should defined this concept; do the authors mean “the initial empiric antibiotic therapy” or is “the therapy started after the results of blood cultures became available”; c) definition of appropriate antibiotic therapy (page 6, 2nd line); one of the authors’ definitions of inappropriate antibiotics is no antibiotic being administered (!); I think that the correct definition of this situation is an untreated infection that is something different; the authors should give the numbers of BSI patients not treated empirically as well as the criteria to start antibiotics in some patients and on the opposite not to start in others; d) timing of appropriate antibiotics (page 7, 2nd paragraph), again the authors have to define in the Methods this concept; do they refer to the time delay between blood cultures and antibiotics prescription; what was the reason of such differences; why those differences were so marked between BSI caused by Gram negative and Gram positive pathogens that are both severe clinical conditions. The authors should clarify all these issues.

2. From the manuscript my guess is that this study is a retrospective analysis of data prospectively collected, as the authors selected a cohort of patients from the years 2003 and 2004. Additionally, the authors should explain how the data was collected from a central database or another methodology. This issue should be better clarified in the methodology.

3. The period of observation was very short, on the whole were just 4 days of follow-up, and before BSI diagnosis only 3 days. This is a major limitation of the present study because infection could have started some days before blood cultures sampling and as a result of the short period of observation the authors could have missed the very beginning of the infection. This could be the explanation of the finding that both patients with Gram positive and Gram negative BSI have already very elevated CRP (>12 mg/dl) at D-2. If the period of observation could be expanded to 5 or 7 days before D0 the results could have been different. Besides, the authors should elucidate the reason of lengthened the period of observation till D+1 when
patients should be already on empiric antibiotics that for sure could have some influence on CRP and WCC levels. Additionally the authors should give some information of the criteria to perform blood cultures that could have effect on infectious markers if they are performed later or earlier in infection course.

4. There is no information concerning previous antibiotic therapy as well as if the patients were on antibiotics in the days before D0. This issue could have a major effect on the studied infectious markers. As a result the authors should fully clarify this issue. In a study designed to assess the value of serial infectious markers in the diagnosis of BSI, my opinion is that patients already on antibiotics should be excluded from the final analysis as the definition of the first day of the new infection, D0, is very uncertain. If the authors want to analysed these patients they have to make one analysis for patients without previous antibiotics and another for patients already on antibiotics. This factor, previous antibiotic therapy, could also hypothetically have influence on the type of bacteria, Gram positive or negative, recovered from the blood cultures. 

5. The authors stated (page 7, 2nd paragraph) in Gram negative BSI CRP peaked at D1; however with such a short period of observation this could not be true as it could be later. Only with a longer period of observation the authors could identify the timing of peak concentration. 

6. The logistic regression analysis should be reanalysed since the authors entered the variables in the model in an incorrect way. In the present manuscript the authors want to study several variables as predictors of Gram negative or Gram positive BSI. As a result the dependent variable is BSI with a dichotomous result, Gram positive or Gram negative pathogen. CRP, WCC are the independent variables and moreover the model could be adjusted for age, sex, APACHE, etc. With the sample size of this study the authors could adjust the odds ratio without violation of the rules of multivariable logistic regression analysis. This issue needs to be completely clarified. 

7. Once the aim of the authors was to study the dynamics of CRP and WCC over time in BSI patients to differentiate between Gram positive and Gram negative pathogens the authors could have draw ROC curves for CRP and WCC in order to try to find the best cut-off of both markers. 

8. In Methods (page 6, 2nd paragraph) the authors described the criteria to assess the presence of organ dysfunction/ failure. The authors should explain the choice of these criteria since there are several other methods, well studied and validated with critical care patients, like the SOFA or MODS score e.g., designed to assess the clinical evolution of patients independently of the cause, infectious or non-infectious. 

9. In case of multiple determinations of CRP and WCC in the same day the authors recorded the highest value (page 6, 1st paragraph). However, these criteria could give misleading results. We could hypothesized that a patient could have a CRP and WCC determination at 23:00 of one day; taking into account the biology of CRP (Pepys, JCI 2003;111:1805) and WCC my guess is that the value at 6:00 of the following day would be almost the same. My suggestion is to collect the values of CRP and WCC daily and ideally all collected at the same hour. 

10. In this manuscript the authors assessed 198 episodes of BSI however they give no information if those episodes were on different patients or if on the opposite there are several BSI episodes in the same patient. From a statistical point of view only one BSI episode per patient could be included in the study. This issue needs to be fully elucidated. From figure 1 it seems that the 198 BSI episodes included in the study were diagnosed in 110 patients. Consequently, at least 88 episodes were recurrent BSI episodes. This problem has to be fully clarified.

11. Another issue that should be fully explained is the exclusion criteria. From the initial 198 BSI episodes the authors excluded almost half, more precisely 42%! The Candida BSI (N=20, with a good sample size) were excluded even though they carry a very bad prognosis in every study. Besides, the polymicrobial (N=40, an excellent sample size) could have also a different clinical course as well as a different course of the infectious markers that I think also deserves to be evaluated.

12. The authors should include a table with the baseline patients’ characteristics including length of ICU stay and mortality rate as well as a table with the microbiologic data and eventually the appropriateness of antimicrobial therapy.

Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

The manuscript also needs some english editing; examples: C-reactive protein and not c-reactive protein;
Gram and not gram.
The authors wrote in Background that patients present “subtle signs of the hosts’ response” in the beginning of BSI. This statement should be more objective and ideally with a reference. All abbreviations should be defined as NCCLS on page 5, ACCP/SCCM on page 9. This is a single centre study that also constitutes another limitation that should be stated. The authors stated on page 9 that the ACCP/SCCM sepsis criteria lack both sensitivity and specificity to define the presence or absence of sepsis. This affirmation is not entirely correct since these criteria are consensually considered very sensitive.

Discretionary Revisions (which the author can choose to ignore)

The authors could have differentiated between primary and secondary nosocomial BSI. The number of references is somewhat long; concerning reference #5 the authors should present a declaration from the editorial board of the journal declaring that the particular paper is in press.

**What next?:** Unable to decide on acceptance or rejection until the authors have responded to the major compulsory revisions

**Level of interest:** An article of importance in its field

**Quality of written English:** Acceptable

**Statistical review:** Yes

**Declaration of competing interests:**

I declare that I have no competing interests