Reviewer's report

Title: Cytokine responses to Staphylococcus aureus bloodstream infection differ between patient cohorts that have different clinical courses and outcomes of infection.

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Reviewer: Andrew Edwards

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The manuscript by McNicholas et al describes the measurement of cytokines in the blood of patients with S. aureus bacteraemia. The question is well defined and the methods appropriate. The key finding is the identification of cytokines that are differentially expressed in patients with complicated vs uncomplicated infection, and those with renal disease. Whilst the study provides some interesting data, there are several issues that detract from the impact of the findings:

Major compulsory revisions:

1. The authors state in both the introduction and discussion that renal patients rapidly recover from S. aureus bacteraemia and rarely develop complications. Whilst this may be true, it must be supported by data, especially since studies by others have found S. aureus bloodstream infection in renal patients to be as severe as in non-renal patients [e.g. Lee et al., 2013 Diag Micro Infect Dis; Bassetti et al., 2012 Clin Micro Infect; Kang et al., 2010 J Infect]. Indeed, the data presented in line 244 of this manuscript indicates that complication in renal patients is as likely to occur as in other patients.

2. Patients with renal disease were included in the study because they may suffer from repeated S. aureus bacteraemia. It is true that this cohort is particularly at risk but there is no evidence provided that the patients included in this study have suffered from previous episodes of bacteraemia.

3. It is not clear which cytokines were screened for using the cytokine array and why these were chosen, or why a 1.4-fold change was chosen as the cut-off value. This needs to be explained.

4. It is unclear why cytokine concentrations were determined per mg protein, rather than per ml volume.

5. It is unclear why IL-6, GRO-gamma and RANTES were selected for further study. Were these the only ones to show differences between study groups? If so fine, but this needs to be stated. It is also unclear why pooled plasma was used to examine leptin levels – a single sample could hugely influence the overall level using such an approach.

6. The authors focus on the statistical significance of differences in cytokine levels between patient groups, but do not describe the magnitude of the differences (biological significance).
7, The presentation of data as bar graphs with SEM is not particularly useful in assessing the inter-patient variability of data. It would be useful to see the full range of values, especially if such data are to be considered as prognostic markers (lines 271-272).

8, Table 2 - it’s not clear what is being shown. The changes in the apparent size/intensity of the dots looks greater than the fold-differences described. How is the assay calibrated?

9, The authors state that they could not obtain baseline cytokine values from the study patients, which would certainly be a big undertaking. However, data from matched controls would be extremely useful in the interpretation of the data, especially since the authors cite evidence (lines 249-259) that cytokine levels in renal patients can vary in the absence of infection.

Level of interest: An article of importance in its field

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 interests