Reviewer’s report

Title: The influence of statin exposure on inflammatory markers in patients with early bacterial infection: pilot prospective cohort study.

Version: 2 Date: 29 May 2014

Reviewer: Peter Kruger

Reviewer’s report:

The influence of statin exposure on inflammatory markers in patients with early bacterial infection: pilot prospective cohort study

The authors describe an interesting and well performed prospective observational study to evaluate the progression (or regression) of clinical and laboratory markers of systemic inflammation in a cohort of non surgical patients admitted to hospital with presumed infection. In addition to the description of laboratory and clinical outcomes the investigators assessed the influence of prior statin use, age, gender and coexisting disease.

Markers of systemic inflammation tended to fall away over time in most patients with progression or deterioration (defined as more SIRS criteria that present on day 1) seen in about 30% of the cohort. The authors comment that larger studies would be required to identify patients at a high risk of deterioration.

I think the methodology is appropriate and the study has been conducted to a high standard and the report well written.

Major comments to be addressed:

Several issues warrant some clarification

1. The manuscript should reflect these are non surgical patients and this could also be mentioned in the discussion.

2. Given the slight increase in SIRS over time in prior statin users do the authors have any information on what happened with continued vs. discontinued statin use in these patients during their hospital stay - perhaps this could be included in the text.

3. I think the authors should reconsider the use of the word “low” when describing the mortality outcomes – This may be better framed with some sort of comparison – I agree it is low compared to that seen in critically ill patients but I suspect a 1:20 chance may not be universally regarded as low (it is, for example higher than often seen with hospital admission for myocardial infarction).

4. How was vital status at 30 days verified? Could the authors provide further detail. Discharge from hospital alive prior to 30 days is not always equivalent to still alive at 30 days unless some specific additional enquiries are made.
5. It would be worth mentioning in the methods that the blood tests described were not part of a study protocol and results were only available if these were collected as part of usual patient care. This introduces the fact that the data presented for these is incomplete. I think the results would be enhanced if the authors present the number of patients that remained in the study on each subsequent day so we have a denominator for the number of CRP / WCC results – so figure 3 might have 48/58 and 138/151 at study entry and then go on to detail the number of patients still in hospital at each of the subsequent time point.

6. Please clarify in Figure 1 if the “numbers of patients with data” is the total cohort – did any patients have missing data for this, the primary outcome measure?

7. I think the paper would be enhanced with a little more detail around the “progression” definitions. Did the additional SIRS criteria occur in the subsequent days (so really progression of this illness) or “pop up” a few days later (raising the possibility of some new process).

8. Similarly – perhaps some more details around ICU/HDU and death. How many patients that died went via the ICU? or were these mutually exclusive groups? As a composite end point (Died or care escalated to ICU/HDU might increase the frequency of events?). Similarly are any details available on cause of death – was it thought to be related to the infection progression or a new problem?

9. Some of the literature in the progression of disease reflects that in some patients it is “failure to improve” rather a deterioration that results in their poor outcome. Do the authors have information if a subset “failed to improve” so SIRS persisted rather than declined and if so did that group have any different outcomes from those patients where SIRS resolved?

10. Along these same lines did the people who died or went to ICU/HDU actually deteriorate to achieve the SIRS definition they applied. This might be a very useful additional analysis to better inform the larger question behind this study “why patients die, deteriorate or fail to get better from infections”.

11. I found the 3rd paragraph of the discussion confusing. Several papers have looked at progression / regression of SIRS over time, mainly in ICU patients as the authors point out. Please clarify that the “prognostic value” they refer to is for detecting culture +ve sepsis rather than other clinical outcomes. The authors may wish to review the paper by Lai N.A et al (The predictive ability of a weighted systemic inflammatory response syndrome score for microbiologically confirmed infection in hospitalised patients with suspected sepsis. Critical Care and Resuscitation, 2011: 13 (3) – 146-150) as this follows a similar cohort and shows a clear increase in mortality for increased numbers of SIRS criteria at baseline – so perhaps some prognostic value exists for outcome / illness severity if not for predicting positive microbiology.
Minor comments to be addressed:

1. opening paragraph background – 3rd sentence , after ref 4-6 ? should this be a full stop

2. The following sentence could be reworded to improve clarity – “ minimal treatment effects of harm…” ?

3. The authors describe the primary outcome as “evolution of systemic inflammatory response syndrome” – perhaps this should be clarified a little as evolution is often associated with progression / increases ?

4. Could the investigators comment on the choice of 38.3 as the upper temperature criteria – while this is listed in the cited 2003 levy paper the original SIRS criteria used 38 ( as is also mentioned in this paper)

5. In the discussion 2nd paragraph – “hospitalised patients with infection” maybe preferable to use “infected hospitalised patients”. ( ? and perhaps even non-surgical hospitalised patients.)

6. Caption for figure 2 and 3 and the mention in the text of changes in WCC or CRP. I think would be clearer and more correct if “over time” were added to the complete the eg. …. change in WCC or CRP “over time”.

7. Table 1 might be clearer with a slight format change – the AVPU section could put the n= in each column along that row to better reflect the totals below are a cumulative subsection

8. Please clarify that in Table 2 – the supplemental oxygen , days 2-10 row is “ at anytime in this time period” ie. yes / no

**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