Reviewer’s report

Title: Association between vitamin D deficiency and sepsis: a systematic review and meta-analysis

Version: 1 Date: 21 February 2015

Reviewer: James McNally

Reviewer’s report:

Overall I have no major concerns with the study or the findings. I do think that the authors should spend some time on presentation. Major compulsory revisions noted throughout.

When assessing the work, please consider the following points:

1. Is the question posed by the authors well defined?

A reasonable rationale is provided in the introduction. Sometimes the authors rely on the reader to draw conclusions based on statements made about results from papers. Overall points and ideas could just be stated more directly.

This applies to the research question as well. The objective of this systematic review was to comprehensively determine the strength of association between vitamin D status and ....”

Should also state secondary objectives and questions?

2. Are the methods appropriate and well described?

As written the methods are unclear and need expansion and clarification (**Major Compulsory Revisions):

• The methods indicate that they would have included studies with 1,25(OH)2D. Did they find any? What did they show?

• Please provide references for the 25(OH)D cut-offs? How did the authors operationalize this definition? Did they only includes studies that used this definition? How many different cut-offs were used in the identified papers? Could results have differed based on cut-off?

• The authors provide a definition for sepsis in the methods. How was the definition used or applied to the systematic review? Was it used to exclude articles?

• Did the authors receive assistance from a librarian or health information specialist with expertise in systematic reviews. Did a second librarian validate the search?

• Why did they choose longest follow-up period instead of most complete data. Why not use both papers in case they presented different types of data that were
relevant to the analysis.

• Please provide some basic information on the Newcastle Ottawa quality scale for the reader. Further explain how the authors (or the field) utilize the NCO score: range for poor, moderate, high quality. How was this information to be used? How did they operationalize the questions within the NCO. Controlling for first and second most “relevant” factors. From my experience, saying you are going to use this scale and figuring out how to use it is a very different thing.

3. Are the data sound?

• As prepared, table 2 is confusing and of limited value to the reader. Would recommend adding some detail to better describe the study to which they are referring and why the score is what it is. (**Major Compulsory Revisions)

• It would help in the text to indicate what the score is out of: selection scale of 2 (maximum 4), etc…

• The authors are relying too heavily on the table. Further, instead of stating “Reference 15” they should write out the authors name and date.

• (**Major Compulsory Revisions) The text in the results sections needs significant explanation and expansion describing how the results were presented and what the studies showed Some aspects that readers might find interesting would include: i) how did the studies define vitamin D status? ii) what assays were used? iii) When were the measurements taken? iv) What assays were used to measure?

• How many measured 1,25(OH)2D. What were the results

• The 25(OH)D results presented in table 1 are confusing.

  o As best I can tell only three of the studies presented vitamin D levels. The column header indicates that the values are in ng/mL. Reference 17 indicates 0.91 and 0.97. This does not make sense.

  o For the remaining studies a single number is presented. Is this for the entire cohort? Please make this more clear.

• For the paragraph describing the meta-analysis work

  o Second sentence is too long. Break into two different points.

  o For Figure 4… why does the 0 have a negative sign beside it?

• Is there value in doing fixed effects when the calculated heterogeneity was 0 and 5%.

• Meta-regression… Fully acknowledge the point that there was little heterogeneity in the odds ratio results between studies. Did they authors perform any preliminary analysis here. Odds ratio by illness sepsis illness severity or NCO score?

4. Do the figures appear to be genuine, i.e. without evidence of manipulation?

• Genuine
5. Does the manuscript adhere to the relevant standards for reporting and data deposition?

• Would request that the authors complete a PRISMA checklist. In doing so they will be encouraged to fill in the missing pieces. (**Major Compulsory Revisions)

6. Are the discussion and conclusions well balanced and adequately supported by the data?

Overall the discussion is too short and does fully discuss and make relevant the systematic review findings. (**Major Compulsory Revisions)

• What were the results and do they make sense biologically

• How are they relevant?
  o Prevention
  o Treatment – with reference to available RCTs including VITdAL-ICU

• What are the limitations?
  o With data - Measurements after illness… 25(OH)D deficiency might be secondary to illness or interventional… does this matter?
  o With using the results – prevention is difficult. Rapid normalization is not possible in certain ICU groups

• Recommendations?
  o More, better done, observational studies vs. clinical trials?

Smaller issues

• Authors too quickly jump to limitations at the beginning of the discussion. Would move to end of discussion. At some point in the discussion the authors could discuss that the lower levels may be related to

• Please remove the comment to low 1,25(OH)2D in the second paragraph

• Why are the authors referencing the pilot RCT on calcitriol - instead of the phase III trial by Amrein and Colleagues that suggested benefit.

7. Are limitations of the work clearly stated?

Reasonable. Really need to strengthen comments on how 25(OH)D levels may not represent pre-illness and how illness and interventional could impact 25(OH)D. (**Major Compulsory Revisions)

8. Do the authors clearly acknowledge any work upon which they are building, both published and unpublished?

Unclear how this fits into a larger program… or how they propose others use the results (**Major Compulsory Revisions)
9. Do the title and abstract accurately convey what has been found?

Acceptable. Might be worthwhile mentioning number of articles identified through the electronic search in abstract

10. Is the writing acceptable?

I appreciate the authors attempt to be concise. That said, I really do think the methods, results and discussion needs some additional planning and lengthening. (**Major Compulsory Revisions)

**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Needs some language corrections before being published

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

No to all questions.

It should be noted that I do research on the role of vitamin D in critical illness and am working under the current belief that whether primary or secondary to illness and ICU interventions that vitamin D deficiency is a modifiable risk factor for poor outcomes in the ICU setting