Reviewer's report

Title: Long-term risk of chronic kidney disease and mortality in children after acute kidney injury: a systematic review

Version: 1 Date: 25 August 2014

Reviewer: Cherry Mammen

Reviewer's report:

Overall, the manuscript is greatly improved and has addressed the reviewers' concerns. However, further revisions are needed before the manuscript is suitable for publication.

Major Compulsory Revisions:

1) I understand why the authors have not chosen to include "hyperfiltration" for one of their outcomes and I agree with the 1st reason (that with the current guidelines/definitions, hyperfiltration is not used to define those with CKD or at risk of CKD), but I do not agree with the 2nd reason (that a mGFR>150 is within 1SD of the mean GFR between 2 and 21 years). This has not been studied well or confirmed in the pediatric population. This statement should be removed from the manuscript as the true threshold for defining hyperfiltration in pediatric aged patients has not yet been determined.

2) Thank you for adding the Viaud article (published as a letter to the editor) to your systematic review. However, there seems to be a major discrepancy in Table 1. You state that the mean age of F/U was 16 years and that the mean age at follow-up was 5 years. Please look into this discrepancy. This leads to another point about using "mean" F/U and "mean" age at F/U compared to "median". With such small sample sizes and likely skewed data in many studies, median seems more appropriate. One issue is that in some studies mean may be reported instead of median and vice-versa, whether it was appropriate or not. Perhaps you can put "mean/median follow-up" in the heading and for ones with a median vs mean, you could put an asterix to differentiate the 2.

Minor Revisions:

1) In the conclusion paragraph of the "abstract", suggest changing “the episode of AKI” to “an episode of AKI” as “the” almost implies that these children only have one episode of AKI, which is often not true.

2) In the 1st paragraph of background (page 5), suggest changing “chronic medical problems” to “chronic medical diseases” or “chronic medical conditions”. Also suggest changing “in which AKI is associated with complications....” to “in which AKI is now more often associated with complications...... compared to primary renal disease”

3) In the 2nd paragraph of background (page 5), what do you mean by
“pre-clinical” studies? Did you mean animal studies? This seems more appropriate in this paragraph. Also, suggest replacing “scarring” with “fibrosis”.

4) In the 3rd paragraph of background (page 5), the authors mention that observational studies in adults have shown that AKI is an independent risk factor for CKD and other long term renal outcomes. Please be more specific for “other long term renal outcomes” (ie mortality, need for dialysis/ESRD).

5) In last paragraph of background (page 6), suggest changing “after resolution of an AKI” to “after resolution of an episode of AKI” or “after resolution of an AKI episode.” Also suggest changing “chronic disease” to “chronic diseases” and changing “developing multiple AKIs over time” to “developing multiple AKI episodes over time.”

6) In 2nd paragraph of Outcome Measures and Statistical Analysis section (page 8), please add that you have also reported on pooled incidence for each outcome (in addition to cumulative incidence rates per 100 patient years) and what “pooled incidence” means in this systematic review. Please mention if these were weighted or non-weighted values for both cumulative incidence rates & pooled incidence.

7) In 1st paragraph of results section (page 9), the authors mention that all primary studies reported on renal outcomes in children after discharge from hospitalization “for” AKI. This is not true. These children were mostly admitted with something else (eg: cardiac surgery, not AKI) and AKI was a complication of their hospitalization. Please change the sentence accordingly. Also, please mention that all of these studies were cohort studies and that all but one was retrospective.

8) In 2nd paragraph of Results (page 9), the authors mention seven different definitions of AKI were used. From table 2, I have counted six different definitions. Please clarify. Also in this paragraph where you are explaining the variable follow-up times, please clarify if studies followed patients once after AKI or if patients were followed multiple times (ie a true longitudinal cohort study). I believe that all the studies followed patient one time, but cannot be sure.

9) In last paragraph of Results (page 9), is 44% of patients requiring acute RRT a mean or median? Please specify.

10) In “Decline in GFR after AKI” paragraph (page 10), change “Six different methods of estimating GFR was used” should be changed to “Six different methods of estimating GFR were used.” Also, please reference the Schwartz formula in this paragraph and if any other estimating equation was used (eg: Mammen study used a locally validated Schwartz formula (Mattman A et al) and perhaps the revised bedside Schwartz if it was used in any study.

11) The authors have mistakenly placed 2 periods after a few sentences in the manuscript (eg: page 10, 11, 14). Please correct.

12) In the paragraph on page 11, change “we compared long mortality rate after
AKI with mortality rate” to “we compared long term mortality rates after AKI with mortality rates of………”

13) In the 1st paragraph of discussion (page 12), the authors mention that “After an episode of AKI, there is considerable incidence of long term complications such as ……….” What does “considerable incidence” mean? This is not clear. For example, I do not consider the ESRD incidence rate or pooled incidence very high at all for pediatric patients. Please consider changing the wording of this sentence. Please also consider changing “None of the studies had a control group” to “None of the studies included a control group”

14) In the bottom of the 2nd paragraph of discussion (page 12), consider changing “Despite AKI epidemiologic and clinical research, clinical studies in children and adults” to something like “despite the tremendous growth of AKI clinical research over (or in) the past decade, studies in children and adults have yet…..”

15) For 2nd paragraph of discussion (page 13), suggest changing “whether this is a fixed abnormality of no clinical consequence or a initiating defect that will…..” to “whether this is a fixed abnormality of no clinical consequence or an abnormality that may progress to CKD and ESRD.”

16) In first paragraph of page 14, suggest changing “recurrent AKI” to “recurrent episodes of AKI.”

17) In 2nd paragraph of page 14, suggest changing “dehydration” to “volume depletion”

18) In 1st paragraph of page 15, change “lost to follow-up” to “loss to follow-up”. The authors mention in this paragraph the range of proteinuria that is partly due to the method of measurement. They also mention that the Viaud study used a more strict threshold, but a high proportion of those with proteinuria. This is likely due to the lengthy F/U (?mean 16 years) and perhaps the element of long follow-up time being related to the development of proteinuria compared to other studies. This should be briefly mentioned.

19) In 2nd paragraph on page 15, suggest changing “high rate of loss to follow-up” to “high rates of loss to follow-up”. Also suggest changing “the sicker population would…” to the “sicker population may…”

In 3rd paragraph on page 15, suggest changing “those with severe or prolonged AKI” to “those with more severe or prolonged AKI”. Please spell out “RAAS antagonists” and suggest adding “including ACE inhibitors or angiotensin receptor blockers” For this sentence, please mention when you would considering starting an RAAS antagonist considering we have no evidence in the AKI population (ie what would be the indication, ?HTN, ?proteinuria).

20) The final sentence needs to be reworded (perhaps a bit softer and more inclusive). Perhaps add “Physicians (or physician groups) other than nephrologists including general pediatricians, family physicians, and other
pediatric sub-specialists may be extremely important (or valuable) for CKD screening as more of these children (don’t add the premature piece as you have not touched on this age group and their specific issues) are surviving their AKI and living longer.

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

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

**Statistical review:** Yes, and I have assessed the statistics in my report.

**Declaration of competing interests:**

I declare that I have no competing interests