Author's response to reviews

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

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Author's response to reviews: see over
Author's response to reviews

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

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Author's response to reviews: see over
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: 11 August 2014

Reviewer: David Selewski

Reviewer's report:

Greenberg et al have adequately addressed my concerns in this very well written revision. I have only a few minor suggestions to improve the manuscript.

1. It may be worth making mention of the KDIGO recommendations on follow-up of patients with CKD from the KI article.
   We have added the following sentence to page 6: If CKD or proteinuria is identified, patients would then be followed every 1 to 12 months as dictated by the KDIGO CKD guidelines. This frequency of follow-up in CKD patients is dictated by GFR, albuminuria, underlying comorbid conditions, disease state, and those at higher risk of progression.

2. Also may be worth citing the article by Askenazi et al that outlines follow-up recommendations:
   -- Do Children With Acute Kidney Injury Require Long-term Evaluation for CKD? Askenazi AJKD
   We have added the following sentence to page 6: A recent editorial by Askenazi proposed that after an AKI children should have follow-up within 1 month of hospital discharge, quarterly for two visits, and then annually for two years.

3. The first paragraph of the discussion could be more strongly worded/strengthened. Highlighting the fact this is the first large systematic review in children to evaluate this question
   We added the following sentence to the beginning of the discussion: This is the first systematic review and meta-analysis evaluating the long-term outcomes after pediatric AKI.

Level of interest: An article of outstanding merit and interest 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
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:
4. 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.
   Thank you for this feedback. We have removed this sentence from the manuscript.

5. 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 in table 1
   Thank you for pointing this out. 5 years was actually the median age at AKI onset. We modified the table to reflect this. As suggested, we changed Table 1 and now indicate median by using an asterisk.

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.
   As suggested we have changed the sentence to:
These findings may have implications for care after an episode of AKI in children.
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”

We have changed the sentences as follows:
The increased incidence of AKI disproportionately affects children with chronic medical diseases who are hospitalized frequently and now living longer lives. This represents a shift in the epidemiology of AKI, in which AKI is now more often associated with complications of a child’s medical or surgical hospitalization 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”.

When we mention pre-clinical studies we are referring to animal research. We changed the wording to reflect this:
This paradigm has been refuted by a multitude of animal research and clinical studies. In addition we replaced the word “scarring” with “fibrosis”:
This inflammation contributes to fibrosis of the kidney and long-term renal dysfunction.

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).

The sentence has been changed to specify the long term renal outcomes:
Multiple observational studies in adult populations have shown that AKI is an independent risk factor for CKD, ESRD, and mortality.

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.”

These three changes were made to the manuscript.

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.

We have added the following to the outcome measures and statistical analysis section:
We also reported the pooled incidence of each outcome which designates the frequency of each specific long-term outcome. Both cumulative incidence rate and pooled incidence are weighted values.
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.

   The sentence in the first paragraph of the results section was changed to read: All of the primary studies reported on renal outcomes in children after discharge from a hospitalization during which they had an episode of AKI. All 10 studies were cohort studies and only one was conducted prospectively.

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.

   Thank you for pointing this out. This was changed to six definitions: Six different definitions of AKI were used (Table 2).

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

   This number is a mean. The sentence was changed to reflect this: A mean of 44% (range 17-100%) of the patients in the detailed follow-up cohort were acutely dialyzed for their AKI episode.

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.

   We added 5 references for the GFR estimating equations. The sentence from page 10 was changed to: Six different methods of estimating GFR were used.

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

   The second period on these pages were removed.

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……..”

   The sentence was changed to: As there was no comparator group within the studies, we compared long-term mortality rates after AKI with mortality rates of other pediatric cohorts detailed in Figure 2.
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”

We changed the sentence and removed the words “considerable incidence”. The sentence is now written:
We calculated the cumulative incidence rates and pooled incidence of long-term kidney complications such as proteinuria, hypertension, abnormal GFR, CKD, and ESRD after an episode of AKI.

We also changed the following sentence to read:
None of the studies included a control group that would allow us to understand the attributable risk of these complications that would be related to AKI.

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…..”

Thank you for this advice. The sentence was changed to:
Despite the tremendous growth of AKI clinical research over the past decade, clinical studies in children and adults have yet to establish that preventing an episode of AKI decreases the risk of development of CKD and premature mortality.

15) For 2nd paragraph of discussion (page 13), suggest changing “whether this is a fixed abnormality of no clinical consequence or an 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.”

The sentence was changed as follows:
….whether this is a fixed abnormality of no clinical consequence or an abnormality that will progress to CKD and ESRD.

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

The change was made to:
…..recurrent episodes of AKI.

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

Dehydration was changed 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.

We have changed “lost to follow-up” to “loss to follow-up”.

We also added a sentence to explain the higher proportion of proteinuria in the Viaud study:
This higher proportion of proteinuria may be attributed to the small sample size and a longer median follow-up time of 16 years.

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).

We made the suggested changes and the sentences now read:
Other limitations of this study include small sample sizes and high rates of loss to follow-up.
These sicker patients may have inflated our calculated outcomes and led us to overestimate the amount of renal dysfunction after AKI.
It remains to be determined whether all patients with AKI need to monitored or just those with more severe or prolonged AKI.
CKD-related complications such as proteinuria or hypertension could then be treated with a renin-angiotensin-aldosterone antagonist such as an ACE-inhibitor or an angiotensin receptor blocker.

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.

The final sentence was rewritten. To be more inclusive I changed general pediatricians to primary care providers. I didn’t include ‘other pediatric subspecialists’ as I thought CKD screening would more appropriate in the primary care setting by a patient’s PMD (like in adult medicine) rather than by a patient’s cardiologist. The final sentence now states:
Primary care providers will likely become more involved with CKD screening as more children with chronic medical diseases 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