Peer Review File
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Reviewer A

Many thanks for pulling together this research on the very valuable co-trimoxazole drug studied in pediatrics. I think it adds to the available evidence base.

I have some minor comments for consideration:

Comment 1: Title - the terminology PIC is not known to many; perhaps an explanation or use of alternative terminology would be useful
Reply 1: Thank you for your advice. We have changed “the PIC database” in the title with “a public database”.
Changes in the text: We have modified our text as advised (see Page 1, line 2).

Comment 2: Can you clarify if all concurrent antibacterial were analyzed or just vancomycin? I agree the latter is a known nephrotoxin and thus of interest but I suspect any patients requiring systemic antibacterial for infection are at a greater risk of AKI (consequence of sepsis rather than a direct drug toxicity). If you just identify vancomycin, we could misrepresent the impact of sepsis induced AKI as vancomycin induced AKI, particularly if vancomycin is used for sepsis in your group. If we could extract all systemic antibacterial use to draw comparison against vancomycin, then I think this would correct for this bias.
Reply 1: Thank you for your advice. We have extracted most of the commonly used systemic antibacterial drugs, which has been added in Table 1. As shown in Table 1, there is no significant difference on the use of all the antibacterial drugs included between the two groups. Only variable with p value of less than 0.1 using univariate analysis, in this case, vancomycin, was included in the multi-variate analysis.
Changes in the text: We have modified our text as advised (see Table 1. Baseline characteristics).

Comment 3: Also, your methods state you will look for concurrent aminoglycosides but there is no inclusion in your table of concurrent medication of aminoglycosides. If this is available, it should be added
Reply 1: Thank you for your advice. In fact, among all the patients enrolled in our cohort, no patients undertook the treatment of aminoglycosides.
Changes in the text: We have modified our text as advised (see Page 5, Line 101).

Comment 4: Is there any ability to identify the indication of co-trim usage? I appreciate

you are unable to identify the dosing but if co-trim is used as low dose PCP/PJP prophylaxis this we would expect to be a lower risk of AKI and may affect your results. Is there any ability to ensure 'prophylaxis' is excluded?
Reply 1: Thank you for your advice. In fact, due to the nature of the PIC database, the indication of co-trim usage is unavailable, thus the exclusion of 'prophylaxis' is unlikely to be done.
Changes in the text: We have modified our text as advised (see Page 10, Line 209).

Comment 5: Were all variable from univariate analysis included in the later multi-variate analysis or was there some selective criteria (e.g. p value 0.1 or equivalent). PLease could the authors provide some more detail on this process if possible.
Reply 1: Thank you for your advice. In fact, the selective criterium is variables with p value of less than 0.1 using univariate analysis.
Changes in the text: We have modified our text as advised (see Page 6, Line 117).

Comment 6: Do the authors have the ability to identify what proportion of patients with co-trimoxazole associated AKI had treatment stopped due to this AKI?
Reply 1: Thank you for your advice. In fact, due to the nature of the PIC database, it's unlikely to identify what proportion of patients with co-trimoxazole associated AKI had treatment stopped due to this AKI.
Changes in the text: None.

Comment 7: The pROCK criteria will be very sensitive to AKI but I wonder whether it is identifying increases in serum creatinine independent to acute kidney injury. The clearance of serum creatinine can be affected competetive excretion of trimethoprim via proximal tubule (affect SCr but not renal function). Would it be possible to identify pROCK stage 2 and stage 3 cases of AKI within this study - these would be more clinically important cases and would better quantify this problem (pROCK stage 1 may not be clinical important).
Reply 1: Thank you for your advice. Among all the 24 patients of AKI, 3 cases were pROCK stage 3 while 8 cases were pROCK stage 2. We further explored the potential risk factors on pROCK stage 2 and stage 3 of AKI. However, logistics regression didn't show any significant results, except the baseline white blood cells count ($p=0.053$), also not statistically significant though.
Changes in the text: None.

Reviewer B

The authors retrospectively investigated the effect of TMP / SMZ on the development of AKI in children. This study is important and potentially interesting because TMP/SMZ is commonly used in the management of urinary tract infections in children. However, there are the following concerns:

Comment 1: Since serum creatinine levels are highly affected by child size, this retrospective study cannot rule out the effects of body size differences, especially at baseline measurements. To assess baseline renal function, it is advisable to compare estimated GFR, such as by using Schwartz's equation.
Reply 1: Thank you for your advice. In fact, only a very limited data on patients' weight and height was provided by PIC database which makes the calculation of estimated GFR unlikely.
Changes in the text: None.

Comment 2: Table 1: In the same context as above, it is necessary to make sure that there is no difference in body size between the two groups in order to compare serum creatinine levels for renal function assessment.
Reply 1: Thank you for your advice. As mentioned above, so limited data on patients' weight and height was provided by PIC database that the comparison can't be done.
Changes in the text: None.

Comment 3: Was there any relationship between the dose per body weight of TMP/SMZ used and the onset of AKI? Similarly, was there a difference in the dose of TMP/SMZ used between the AKI and non-AKI groups?
Reply 1: Thank you for your advice. As mentioned in our limitation part, the data on the TMP/SMZ dosage and indication (e.g. prophylaxis or treatment) are not available in PIC database, though other former study suggested that it may be related to the development of AKI
Changes in the text: None.

Comment 4: Did the authors list all the drugs used as concomitant drugs in Table 1? It is strange that there was no drug for the treatment of hematological malignancies, as hematological malignancies seemed to be the most common underlying condition in both groups. Many of the drugs used for malignancies are at risk of causing AKI, and some have a long duration of action. Therefore, the authors need to list and compare the frequency of use of anticancer drugs such as methotrexate, cisplatin, and bleomycin, which are at least prone to nephrotoxicity.
Reply 1: Thank you for your advice. We have checked the anticancer drugs used for the patients in the cohort. It turned out that no patient had a concurrent treatment of TMP/SMZ and cisplatin or bleomycin. The concurrent use of methotrexate was added into table 1. There is no significant difference on the use of methotrexate in two groups.

Changes in the text: We have modified our text as advised (see Table 1. Baseline characteristics)