Dear BPG Editorial Office,

We thank you for your input on our manuscript entitled 'Post-Transplant Erythrocytosis: A Review.' We have addressed individual comments below.

Reviewer 1:

The paper is review. They have made a summary of available literature on the field of PTE in post kidney transplant patients, using the most commonly used guidelines.

Thank you for your comments.

Reviewer 2:

Comments to the author:

Overall it is an informative and nice review article, and importantly I found no other comprehensive review article on the subject in the literature. Yet there are some limitations in the protocol used for the review.

Authors nicely give the topics important on the subject in their subsections, however, their attendance to the subjects is more general & not evidence-targeted. You give nice data in the tables, but not using them well in the text. If it was my article, I would have instead given for example data of studies in favor of enalapril, then those against it, or those in favor of other therapeutic protocols, referring their data to the tables; to investigate the subgroups of patients with special characteristics most benefit of any therapy strategy and those who might benefit the other one; discussing the dosing of the therapies and associating them with either the therapeutic or adverse effects, and analyses to define what treatments were most effective, with the least adverse effects. For example in table 3, two studies reported in favor of theophylline, one found no significant reduction, and two reported an increase in the Hct. A more precise in the patients' demographics (i.e. age, immunosuppression, deceased vs. living donor; dialysis before transplant, duration of taking the drug and so on) might reveal factors that might have contributed in the differential observation.

Also an analysis to find any differentials in the demographic factors of patients who have developed PTE or not would be informative on the potential risk factors. For example, the percentage of the people with living vs. deceased donor TRx developed PTE; differentials in age, gender, surgical protocols, immunosuppression regimen/blood levels, comorbidities (i.e. cardiovascular; liver disease; DM; HTN etc), time on dialysis, graft functioning indices, seropositivity for infections and so on. I know you will say we have already mentioned them in

the review, yes, but I mean to precisely and evidence-based step, to say in what studies there were evidence in favor of them and in which ones not or even against them; and try to make conclusions based on the overall reviewed data & independent of single study conclusions, and wherever possible to conduct meta-analyses.

Thank you for this feedback.

Response 2.1.

We have added additional comments in the text about the risk factors under "Risk Factors" described in the following text:

"Well-established risk factors for PTE have been described over the past few decades. These known risk factors include the male gender [3, 37-40], retention of a native kidney with adequate erythropoiesis before transplant [3, 5, 36, 37, 39, 41-44], renal artery stenosis [37, 38, 45]and patients with a well-functioning graft. [3, 36, 39, 43, 46] These risk factors are consistently present in the majority of recipients who develop PTE.
Age and pre-transplant dialysis need may also contribute to PTE as demonstrated in the following studies. In their study published in 2020, Alasfar et al noted younger recipient, young donor age and PKD were risk factors associated with the development of PTE. [6]
In our own examination of PTE in KTRs at our institution, we found that non-preemptive transplant was significantly associated with the development of PTE [HR =2.32 (95% CI: 1.55-3.47) P <0.001, on univariate analysis); HR = 3.86 (95% CI: 1.56-9.56) P = 0.003 on multivariate analysis)] [40] These recently-published risk factors are highly plausible, but more studies will need to corroborate them before we consider them well-established risk factors."

Response 2.2.

We included more detailed info about the studies in Table 3 under our "Treatment" Section as follows:

"Theophylline has had varied results in several studies. As described in 3 studies, theophylline has been shown to decrease Hct by 4-15% in patients with PTE. [61, 62, 64] Notably, in the 2 studies cited whereby Hct after theophylline administration, one was case report (n = 1) who discontinued theophylline after four weeks due to side effects, while the other study (Trivedi et al) showed an increase in Hct that was not statistically significant. [32, 63] More importantly, the Trivedi study directly compared fosinopril and theophylline and showed a statistically significant difference in terms of change in

hemoglobin (baseline to three months 2.8 ± 1.7 vs. −0.7 ± 0.69 gm/dL; $P = 0.017$) and hematocrit (baseline to three months 9.0 ± 6.0 vs. −2.3 ± 2.7% $P = 0.027$) [32]. Notably, almost half (44.4%) of the theophylline arm dropped out of the study due to medication intolerance, consistent with other literature describing theophylline's narrow therapeutic index[3 24]. Further supporting this observation of ACE-I/ARB compared to theophylline is the study from Ok et al. After a month washout period, they treated the KTRs randomized to theophylline with 10mg of enalapril and saw improvement in mean Hct at 2 months (pre-treatment Hct 55% ; range = 52-64) vs post-treatment Hct (46% ; range = 40-53) and 3 months (post-treatment Hct 41% ; range = 33-47)[24]. These studies are summarized in Table 3."

We also attempted to draw more concrete conclusions based on our analysis of the evidence in the studies we referenced as indicated in the following text:

See text in Response 2.2.

"In summary, several studies have shown that ACE-I/ARBs are first-line therapy, phlebotomy is second-line, and that theophylline is a limited alternative both in terms of efficacy and tolerance."

Reviewer #3:

Comments to the author:
The paper entitled "Post-Transplant Erythrocytosis: A Review" is well-written short review, which needs following revision to make it up-to-date. 1. Title: Post-transplant does not indicate the type of organ transplanted. So I would suggest to change it to post-renal transplantation. 2. The method of literature review (data collection) needs to be clearly written. 3. The references are too old (from 90s mostly). There are many recent publications over last 10 years and the authors have published their own data on February this year, which need to be included. 4. Every section should have an up to date information with recent references.

Thank you for this feedback.

Response 3.1

Post-transplant erythrocytosis appears to be common terminology used throughout the literature with the assumption that this develops after kidney transplantation (either alone vs in combination with other organ transplant). Nonetheless, for clarity, we have updated our title as such:
"Post-Transplant Erythrocytosis after Kidney Transplantation: A Review"

Response 3.2
We have updated our manuscript to include the following description of our search methods in the following text:

"We conducted literature searches in PubMed, EMBASE, Cochrane, CINAHL (Cumulative Index to Nursing and Allied Health Literature) from database inception to 2/2021, as well as Google Scholar and reference lists of relevant studies and review. We limited our search to studies to include only those with available full text and English language."

Response 3.3.
Using our methods as described in Response 2.2, we did not find more recent studies beyond the early 2000s. Most trials done to test medications for PTE were done in the 1990s and early 2000s. We have included all of the most recent studies including our recently published study (Alzoubi et al, Clinical Transplantation, 2021) in addition to the Alasfar study from 2021.

Response 3.4
Sections were updated for organization to include up to date information with recent references.

We hope our revisions adequately address the concerns and questions raised by your team. Please let us know if there are any further questions.

Thank you,

Kurt Swanson MD