Peer Review File
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Reviewer Comments

Reviewer A
Comment 1: This is an excellent review. It is comprehensive and easy to read. The diagrams are appropriate and very helpful.

With the revisions, mostly clarifications and issues of accuracy of terms and mechanism, would recommend publication.
Reply1: Thank you very much; your kind words mean a lot to us. We are particularly happy that you find the diagrams appropriate and useful, as this is exactly what we intended so that these articles to be used as a reference diagnostic aid.

Comment 2: This is a very comprehensive and well written clinical review and approach paper. The figures and algorithms shown are easy to follow, logical, and presented clearly.

Some comments for clarification. Some may seem nitpicky but would be helpful to clarify and be as accurate as possible re: mechanisms without being burdensome in that regard.
Reply 2: Your comments are not nitpicky at all as the details that you have picked up on matter, especially in a review of this nature. We have actually used your comments to improve other papers in this series as some of them apply across the board. Thank you very much! We really appreciate the time that you took to make these detailed comments.

Comment 3: Lines 67-70: Please refer to the transporter in TAL by the name it is more typically referred to "sodium potassium chloride co-transporter" although I recognize that the paper wishes to stress potassium. Also, NKCC2 is a transporter not a channel. Please correct.
Reply 3: You are absolutely right to suggest using the standardised name. This, as well as calling it a transporter and not a channel, has been done on lines 95-96. Thank you.

Comment 4: It would be helpful to name the K-secretory channel in the DCT/principal cell: ROMK, renal outer medullary channel (this is a channel).
Reply 4: Although we have shown and defined ROMK in figure 2, we completely agree that reference to this in the text would be useful. We have added this on lines 97-98. Thank you.

Comment 5: While recognizing the likely emphasis that the H/K are going in opposite directions, the proton/potassium transporter in collecting duct is an ATPase not technically an antiporter.

Reply 5: The word ‘channel’ has been replaced with ‘transporter’ on line 99 to reflect that this movement requires energy input from ATP and is not passive. Thank you.

Comment 6: Fig. 2: Along with the above, please amend legend to read “major ion channels and transporters” in the kidney.
Reply 6: This has been changed. Thank you.

Comment 7: Line 84: Hyperkalemia is not the most common electrolyte disturbance if we consider all populations; would just say it is “common” rather than “most common.”
Reply 7: You are completely right, apologies for this inaccuracy. This has now been changed on line 113. Thank you.

Comment 8: Line 115: Would qualify “haemolysis” as hyperkalemia due to haemolysis within the blood stream may lead to actual hyperkalemia. Please clarify or refer to lines 155ff as you discuss this there.
Reply 8: Thank you for picking up on this as this certainly has the potential to be misunderstood. We are referring to in vitro haemolysis here but never stated this to make it clear. This has now been changed on line 146, and we have added some more information on lines 146-147 in brackets to highlight this difference to avoid this technical inaccuracy.

Comment 9: Elevated WBC may also lead to artifactual hyperkalemia if the tube is left standing and the cells undergo necrosis. This can occur with leukemias. (Noted that the pseudohypokalemia due to uptake of metabolically active WBC post phlebotomy is addressed later in lines 333ff)
Reply 9: We included the specific circumstances that can cause pseudohyperkalaemia (including high WBCs as you pointed out) in the pseudohyperkalaemia algorithm (figures 5a and 5b). We actually originally had a lot of text to explain each contributing factor, but we found that we had to get rid of it due to the word count which is why we decided to make an algorithm for it instead (and is also why this section is relatively short compared to the pseudohypokalaemia section, despite there being a lot more to talk about). However, we are happy to expand the pseudohyperkalaemia section text in addition to the information in figures 5a and 5b if you believe that this will benefit the readers understanding? We just did not want to push it with the word count.

Comment 10: Line 118: There should be a statement made regarding the urgency of the hyperkalemic changes on EKG that would necessitate life saving treatment rather than implying cessation of medications that may induce hyperkalemia is sufficient and just monitor. Something to the effect of “determine the urgency of hyperkalemia and need for treatment…once addressed then embark on the diagnostic and pathophysiological underpinnings” or something to that effect.
Reply 10: This is a very valid point that we discussed when planning these articles. We wanted to steer clear from mentioning treatments as much as we could as practice varies so widely across the world. However, we agree that in this context, and due to the

objectivity of its urgency, we should expand this as you have suggested. We have added a statement at the start of the drug assessment section (lines 153-157) to the effect of what you have kindly suggested: 'After exclusion of possible pseudohyperkalaemia, it is essential to determine the urgency of the clinical situation. If ECG changes associated with hyperkalaemia (figure 4) are present (which in practice should be determined before consideration of pseudohyperkalaemia), it is likely that urgent treatment is required (follow local guidelines) in order to stabilise the patient before a more thorough investigation of the cause can commence.'. We have added a similar statement to hypokalaemia in lines 383-387 as this is important. We hope that this addresses the potential clinical urgency in a more appropriate way. Thank you for this fantastic point.

Comment 11: Line 49: Mineral acidosis (normal anion gap acidosis) causes redistribution of K; organic acidosis do not (e.g., the hyperkalemia of diabetic ketoacidosis is primarily due to the osmotic change causing K to exit the cell rather than the pH itself and/or hypoinsulinemia or insulin resistance).
Reply 11: This is a good technical point. As there is limited word count, and the acid base articles within this series addressed this in more detail, we have changed lines 62-63 to avoid being too inclusive of all acidoses by saying 'Changes in physiological states including **some presentations** of acid base disturbances'. We hope that this is more accurate without having to specifically explain the differences as this is done in the other articles. Thank you.

Comment 12: Line 181: Would add "positive urine dipstick for blood but without RBC on sediment…"
Reply 12: Excellent clarification point. This has been added on line 217. Thank you.

Comment 13: Lines 201ff: Although urine K concentration may be of limited value, it should be > 40 mmol/L in hyperkalemia. A value < 20 mmol/L is inappropriately low.
Reply 13: We initially avoided including this as ruling out CKD and AKI before urine potassium assessment (as per algorithm) would usually mean that this would not often be seen. However, this is still useful information and helps with the understanding, therefore we have included this on lines 241-244. Thank you.

Comment 14: The TTKG is only valid if the urine osmolality is > plasma (some would say 2x plasma). Thus, TTKG is acute kidney injury where Uosm is similar to plasma is not valid. This is why the TTKG is not as accurate in humans as this issue is often forgotten or ignored.
Reply 14: This is also an important and valid point. We have added a statement to lines 248-249 – 'and it is only valid when the urine osmolality is greater than the plasma osmolality (which may not be the case during AKI)' – to address this point. We have also added lines 257-260 to mention the TTKG's utility in differentiating mineralocorticoid deficiency from resistance.

Comment 15: Lines 228: A comment that hyperkalemia is itself a direct stimulus of

aldosterone is warranted and is even more temporally acute and powerful stimulus than angiotensin. This is discussed later (lines 254ff) but a comment here or referring to the paragraph later in the paper would be good.
Reply 15: We agree that it is certainly important to mention hyperkalaemia as a stimulator by its self here. We have added this to lines 269-270. Thank you.
Comment 16: Line 261: Hyperkalemia suppresses renin independently of blood pressure as shown many times by Churchill et al in vitro in renal slices. Would delete lines 260-264.
Reply 16: This is a fair point. I think that we may have possibly overcomplicated this bit of physiology so have deleted these lines as suggested. Thank you.

Comment 17: Line 282ff: These caveats are very important!
Reply 17: We completely agree! These are also frequently overlooked, and in our experience, are often explanations of confusing results. Thank you.

Comment 18: Line 301: “and” should be “or”…do nto need both mutations.
Reply 18: Good spot. This has been changed. Thank you.

Comment 19: Line 420: Hypomagnesemia may lead to increased urinary K excretion as low intracellular K leads to increased open probability of ROMK (secreting K). Low intracellular magnesium also regulated the Na,KATPase which raises intracellular K and permits more K to be secreted as intracellular K rises.
Reply 19: We have explained this mechanism in slightly more detail than the original manuscript (lines 453-456) as suggested, and have included an extra reference for readers to refer to if more information is required. Thank you for this.

Comment 20: Line 446: The losses of K during vomiting are from increased urinary excretion of K. There is no K in gastric fluid; any K in the emesis would be from the salivary glands or due to an incompetent sphincter with biliary juices being lost in the emesis.
Reply 20: Apologies for this, you are right. We think that some notes with other articles in this series may have got confused. Thank you for this great spot. This has been changed on lines 480-481.