Appendix 7 | External Review

1. Review by Kidney Health Australia – Caring for Australasians with Renal Impairment (KHA-CARI)

1.1. Comment on recommendation 8.1.3.1.
Topic original statement: We recommend defining ‘moderately symptomatic’ hyponatraemia as any biochemical degree of hyponatraemia where the patient has any of the signs as listed in Table 6.

Comment: Mild degree of hyponatraemia is common in elderly patients and it is difficult to establish the causal relationship between symptoms and mild hyponatraemia with a degree of certainty. I think this recommendation cannot be easily implemented in clinical practice.

Response
In chapter 8.1, we wanted to set separate definitions for hyponatraemia based on biochemical severity, time of development and symptoms such that their meaning would be unambiguous throughout the document. We did not mean the definitions to have direct diagnostic or therapeutic implications, but merely wanted to provide a vocabulary to work with in further chapters. To distinguish between these definitions from actual recommendations, we reframed the statement to:

We define ‘moderately symptomatic’ hyponatraemia as any biochemical degree of hyponatraemia in the presence of moderately severe symptoms of hyponatraemia (Table 5).

1.2. Comment on recommendation 8.2.2.1.
Topic original statement: Exclude hyperglycaemic hyponatraemia by measuring serum glucose and relating that to the expected degree of hyponatraemia. (Not graded)

Comment: I suggest rewording this recommendation: Exclude hyperglycaemic hyponatraemia by measuring serum glucose and calculate corrected serum sodium level

Response
The guideline development group agreed that the wording of this statement could be improved for reasons of clarity. In the final document the statement was changed to:

We recommend excluding hyperglycaemic hyponatraemia by measuring the serum glucose concentration and correcting the measured serum sodium concentration for the serum glucose concentration if the latter is increased.

1.3. Comment on recommendation 8.3.1.4.
Topic original statement: We suggest accepting low effective arterial volume if urinary sodium is < 30 mmol/L. (2D)

Comment: I do not agree with this recommendation. A recent study by Titze revealed sodium levels fluctuate over weekly or monthly cycles. Body stores sodium in interstitial tissues and hence urine sodium levels can be low in the presence of euvolaemic state and vice versa.

Response
We agree with the referee that urine sodium concentrations may (sometimes) be low in case of
euvolaemia. We accept that classifying hyponatraemia based on urine osmolality may lead to misclassification, due to less than perfect diagnostic accuracy of the test. While sensitivities are high for detecting low effective arterial blood volume, specificities are variable and will lead to false positive diagnoses. Nevertheless, urine sodium concentration performs better than any of the alternative tests, including clinical evaluation of fluid status. Hence, it will more often lead to a correct diagnosis than if not used. We acknowledge the uncertainty and tried to express it by formulating a weak recommendation with an indication to merely ‘accept’ low effective arterial blood volume for classification purposes. It is important to understand that this guidance should cover the majority of cases, and that it is nearly impossible to cover all potential exceptions without making the recommendation highly complex.

1.4. Comment on recommendation 9.4.3.1.
Topic of original statement: In moderate or profound hyponatraemia, we suggest restricting fluid intake as first-line treatment. (2D)

Comment: There is often confusion about the type of fluid restriction. Is it just water restriction or all type of fluids? I think we should recommend pure water restriction.

Response
The reviewer is of course right by stating that the final goal is to reduce “free water intake”. However, the guideline group considers that the actual details of “fluid restriction” should be discussed with individual patient based on the individual case. For some the advice not to drink "additional" fluids might suffice, others need to be instructed to limit fluids to a certain amount. The guideline group considers that with regard to the type of fluid to be restricted, this should also be discussed with the patient on an individual basis: some would prefer to reduce real liquids, other maybe to restrict maybe on foods containing a lot of water (e.g. yoghurt …)

2. Review by Endocrine Society of Australia (ESA)

2.1. Comment on Definition 8.1.1.2.
Topic original statement: We define ‘moderate’ hyponatraemia as a biochemical finding of a sodium concentration between 125-129 mmol/L as measured by ion specific electrode in serum or plasma; and definition 8.1.1.3. We define ‘profound’ hyponatraemia as a biochemical finding of a sodium concentration < 125 mmol/L as measured by ion specific electrode in serum or plasma.

Comment: We suggest to change the definition to 120-129 mmol/L and <120 mmol/L respectively. This often depends on the rapidity of the fall however. "Profound" should be an indication of when to consider hypertonic saline, and I would generally not use that if the Na is not <120 mmol/L

Response
In chapter 8.1. we wanted to set separate definitions for hyponatraemia based on biochemical severity, time of development and symptoms such that their meaning would be unambiguous throughout the document. We did not mean the definitions to have direct diagnostic or therapeutic implications, but merely to provide a vocabulary to work with in further chapters.

2.2. Comment on recommendation 9.1.2.7.
Topic original statement: In treatment for moderately symptomatic hyponatraemia: We suggest checking the serum sodium concentration after one, 6 and 12 hours. (2D)
Comment: The management depends not only on if "moderate" symptoms are present but also the absolute Na level – i.e. more likely to use the 150 mL over 20 min if Na was 118 compared to 124. No need to aim for a 1 mmol/L increase, using the formula and aiming for 0.5 mmol/L/h, realising that it often corrects more quickly. I think a repeat blood test at 1 hour is too soon, unless the 150 mL starting dose is used. If the calculation is correct and you are aiming to correct between 0.5 to 1 mmol/L/h, a check at 1h might be within the error of the measurement. Suggest 2h.

Response
It is true that symptoms of hyponatraemia are very aspecific and often due to concomitant disorders rather than the hyponatraemia itself. The lower the serum sodium concentrations the more likely symptoms are caused by the hyponatraemia and the more likely you will be prompted to infuse hypertonic saline. The recommendation does not contradict this idea. We strongly recommend cause-specific treatment and only weakly suggest a single hypertonic saline infusion, because we believe the risk of brain oedema is less imminent and acknowledge symptoms are frequently caused by concomitant problems as hyponatraemia is less pronounced. We purposefully abstained from including biochemical thresholds because these can never be absolute and are linked to the clinical setting. We wanted the guideline to be practical and wanted to avoid ambiguity or excessive complexity. For this reason also, we introduced the same measurement interval for moderately symptomatic and severely symptomatic hyponatraemia, but acknowledge this comes at the cost of being less situation-specific.

We will in the future produce case vignettes to further clarify the application of the recommendations in clinical practice.

2.3. Comment
Topic of the original statement: on management of patients with inappropriate antidiuresis.
Recommendation 9.4.3.5: We recommend against using vasopressin receptor antagonists in patients with profound hyponatraemia. (1C)

Comment: These agents are not available in Australia so we have no clinical experience in using them, and I note the committee's concerns re rapid overcorrection. However, might they have a place used in the inpatient setting where fluid restriction alone is not working and there are no symptomatic indications for 3% saline?

Response
Although vasopressin receptor antagonists do increase serum sodium, the guideline development group judged that based on current evidence these drugs cannot be recommended. Indeed, the risk benefit ratio seems to be negative: there is no proven outcome benefit aside from increase in serum sodium concentrations, while there are increasing concerns on safety. The most prominent safety-related factor is the increased risk for overly rapid correction of hyponatraemia. As this risk is greatest in patients with profound hyponatraemia, the guideline development group wanted to recommend against the use of vasopressin receptor antagonists in this specific patient group. In addition, our concern around the toxicity profile of these compounds was increased by reports from the U.S. Food and Drug Administration warning for hepatotoxicity associated with the use of high tolvaptan doses in autosomal dominant polycystic kidney disease. However, guidelines should never be interpreted as absolute. The guideline group can imagine that in exceptional cases the risk-benefit ratio of prescribing a vasopressin receptor antagonist can be considered positive by individual physicians for individual patients, and this after careful informing the patient of the potential risks (osmotic demyelination syndrome) and the lack of proof of benefit in terms of mortality.
2.4. Comment
Topic of the original statement: what to do in case hyponatraemia is corrected too rapidly?
Recommendation 9.5.1.3 and 9.5.1.4. We recommend consulting an expert and discuss the appropriateness of:
a. starting an infusion of 10 mL/kg body weight of electrolyte-free water over 1 hour under strict monitoring of urinary output and fluid intake. (1D)
b. adding desmopressin 2µg IV, with the understanding that this should not be repeated more frequently than every 8 hours. (1D)

Comment: This is quite different to that recommended in other management guidelines, where 6 mL/kg over 2h and desmopressin 6 hourly is recommended.

Response
The guideline group considered that the risk of rapid overcorrection outweighs the risk of a too slow correction. In this regard, the choice for 10 mL/kg over an hour can be defended.