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UNDERSTANDING THE DISEASE

Hypernatremia in the critically Ill: beyond free water replacement

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Sodium accounts for approximately 90% of extracellular fluid osmolality. Plasma [Na^+] reflects the balance between sodium and water intake and excretion. Hypernatremia develops when there is a net gain of sodium, a deficit of free water, or a combination of both, and is invariably associated with hyperosmolality.

Regulation of sodium and water homeostasis

Osmoreceptors in the hypothalamus detect rising plasma osmolality and trigger two compensatory responses: release of antidiuretic hormone (ADH) from the posterior pituitary and activation of the thirst mechanism. ADH increases water permeability of the cortical and medullary collecting tubules, thereby promoting water reabsorption. Hypovolemia independently stimulates ADH release, whereas increased effective blood volume mildly suppresses it. ADH secretion begins when plasma osmolality exceeds approximately 275–285 mOsm/kg, while the threshold for triggering thirst is slightly higher [1]. Even when maximal urinary osmolality has been achieved, the kidneys cannot compensate for insensible water losses without additional water intake, highlighting the critical importance of an intact thirst response.

Hypernatremia is defined as a [Na^+] exceeding 145 mmol/L. Importantly, laboratory measurements reflect [Na^+] in whole plasma. However, since only about 93% of plasma volume is water, the physiologically active [Na^+] in plasma is slightly higher than the reported laboratory value. Importantly, in hyperglycemia, osmotic water shifts from the intracellular to the extracellular compartment dilute plasma sodium which can mask the true degree of hypernatremia.

Hypernatremia in critical illness

ICU-acquired hypernatremia is common, affecting 6 to 47% of patients, depending on definition, time of diagnosis and clinical settings [2], and independently associated with mortality across multiple cohorts [3]. The principal causes encompass free water deficit due to reduced intake or excessive losses, and positive sodium balance due to sodium administration and/or impaired sodium excretion.

Decreased water intake

The inability to respond to thirst due to sedation, intubation and impaired consciousness, creates a dysregulated loop. Elderly patients are particularly vulnerable as aging is associated with a higher osmotic threshold for thirst and reduced baroreceptor sensitivity.

Increased water loss

Non-renal water losses include vomiting, diarrhea, insensible losses, and losses via surgical drains. Renal water loss may result from osmotic diuresis driven by non-reabsorbed solutes such as glucose (e.g. hyperglycemia or SGLT2 inhibitor therapy), mannitol, or urea, or from impaired urinary concentrating ability in case of diabetes insipidus, tubular dysfunction, ongoing or recovering acute kidney injury (AKI), and diuretic therapy.

Urea-mediated osmotic diuresis is an underrecognized contributor to ICU-acquired hypernatremia. Increased urea generation associated with burn injury, sepsis, polytrauma, high-protein feeding, or recovery from

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AKI contributes to urine osmolality and may increase electrolyte-free water losses. Exogenous glucocorticoid administration can also promote free water loss through enhanced urea-mediated osmotic diuresis and possible suppression of ADH secretion.

Decreased sodium excretion

Inappropriate renal sodium retention may result from mineralocorticoid excess, including exogenous glucocorticoid therapy [4]. In case of shock, the expected suppression of the renin–angiotensin–aldosterone system in response to hypernatremia may be blunted by hemodynamic instability and sympathoadrenergic activation, thereby perpetuating renal sodium retention [5]. Interestingly, reduced urinary sodium and chloride excretion has been observed before the development of ICU-acquired hypernatremia [6], suggesting that impaired natriuresis may precede hypernatremia.

Increased sodium intake

All sodium-containing intravenous fluids contribute to the daily sodium load, irrespective of tonicity. Therapeutic hypertonic saline can rapidly increase serum sodium. Less recognized contributors include antibiotics (e.g. fosfomycin), citrate anticoagulation during continuous renal replacement therapy (mostly when using trisodium-citrate), sodium bicarbonate, enteral and parenteral nutrition, and drug-dilution fluids prepared in 0.9% saline. Moreover, potassium administration, especially during correction of major potassium deficits, may lead to an increase in serum sodium concentration, due to intracellular water shifts [7].

Physiological consequences of hypernatremia

Hypernatremia impairs insulin-mediated glucose uptake and glucagon-dependent glucose release, contributing to hyperglycemia. Hyperosmolality exerts broad systemic effects. In the central nervous system, osmotic fluid shifts from the intracellular to the extracellular compartment can cause cerebral cell shrinkage and vascular damage potentially leading to neurological deficits or delirium. Experimental data suggest that hyperosmolality may also impair myocardial contractility via induction of proinflammatory cytokines [8].

Diagnostic approach to hypernatremia

A thorough assessment of volume status and urine production is essential (Fig. 1). Calculation of the free water deficit and free water clearance serve to determine the appropriate volume and rate of fluid replacement. In critically ill patients, estimation of electrolyte-free water clearance may more accurately reflect ongoing water losses than conventional free water clearance, particularly when urea- or glucose mediated osmotic diuresis is suspected.

Formulas:

$$\begin{aligned} &\textit{Free Water Deficit} = \textit{Total Body Water} \\ &\times \left[{\left(Na^{+}_{current} - 140 \right)}/{140} \right] \end{aligned}$$

$$\textit{Free Water Clearance} = \textit{Urine Volume} \times \left(1 - \frac{P_{osm}}{U_{osm}} \right)$$

$$\begin{aligned} &\textit{Electrolyte Free Water Clearance} \\ &= \textit{Urine Volume} \times \left(1 - \frac{U_{Na} + U_{K}}{P_{Na}} \right) \end{aligned}$$

Treatment

Management focuses on identifying the underlying cause, correcting free water deficits safely and estimating anticipated fluid losses. The route of free water administration depends on gastrointestinal function. The classic medical teaching to correct hypernatremia at a rate of < 0.5 mmol/L/hr has been challenged by an analysis showing that a faster rate may be safe and result in shorter duration of hospitalization and decreased mortality [9].

Hypovolemic hypernatremia

Volume resuscitation with isotonic fluids is prioritized before free water replacement. Once hemodynamically stable, free water can be administered to correct hypernatremia.

Euvolemic or hypervolemic hypernatremia

In euvolemic or hypervolemic patients with adequate urine output, formal quantification of the daily sodium load is essential. Replacing 0.9% sodium chloride–based drug solvents (containing 154 mmol/l sodium) with glucose-based solutions, adopting low-sodium maintenance fluid strategies and adopting strategies to limit fluid creep have been shown to lower the incidence of hypernatremia [10–12]. Drug compatibility and stability constraints need to be considered when modifying diluents.

Hydrochlorothiazide has been explored as an adjunct therapy for euvolemic or hypervolemic ICU-acquired hypernatremia, but evidence remains limited to a single small randomized controlled trial (RCT) that demonstrated no significant effect [13]. A RCT of 40 ICU patients with fluid overload showed that the addition of indapamide to furosemide, led to larger natriuresis (210

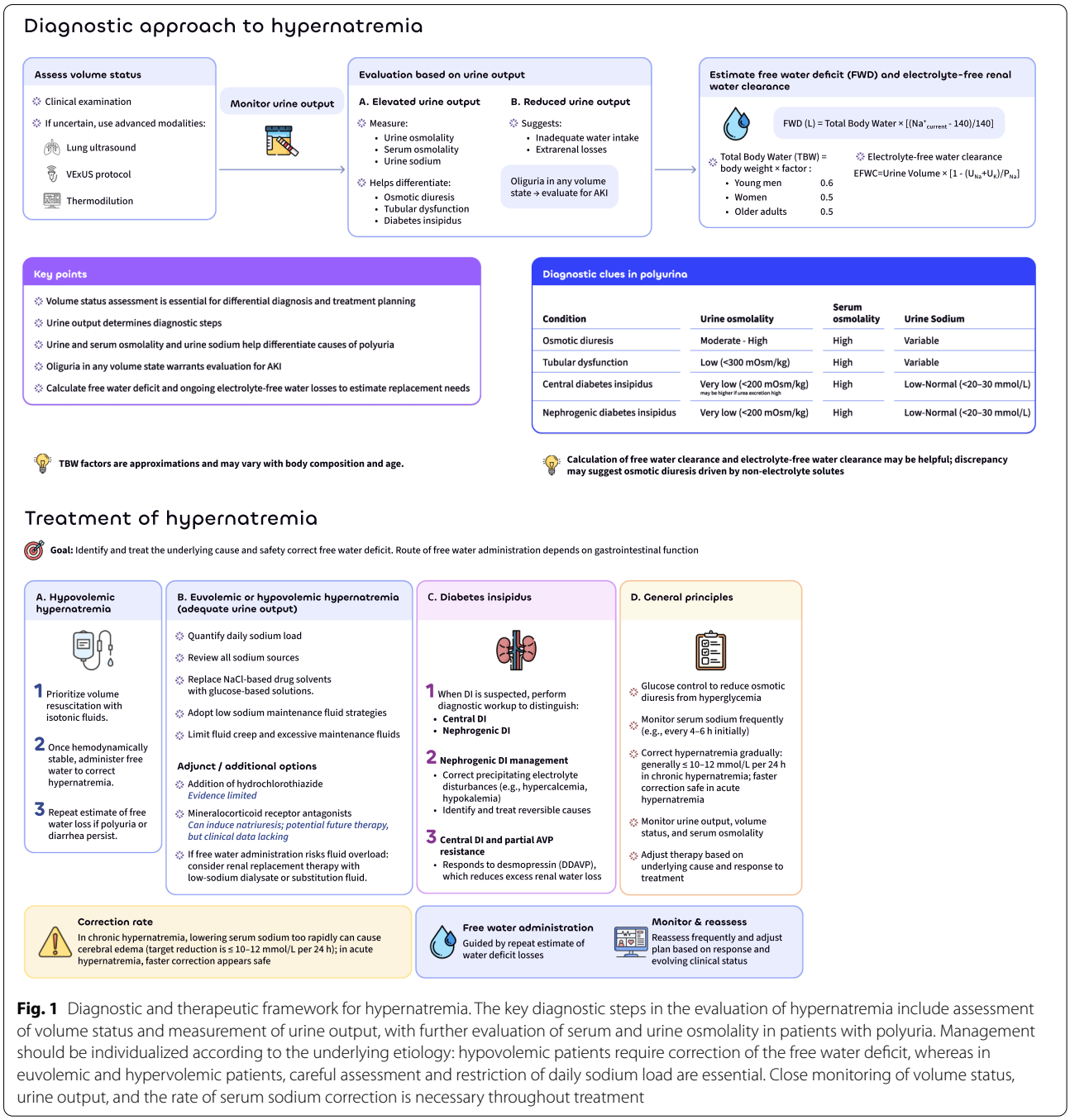

Fig. 1 Diagnostic and therapeutic framework for hypernatremia. The key diagnostic steps in the evaluation of hypernatremia include assessment of volume status and measurement of urine output, with further evaluation of serum and urine osmolality in patients with polyuria. Management should be individualized according to the underlying etiology: hypovolemic patients require correction of the free water deficit, whereas in euvolemic and hypervolemic patients, careful assessment and restriction of daily sodium load are essential. Close monitoring of volume status, urine output, and the rate of serum sodium correction is necessary throughout treatment

vs 119 mmol of sodium) but similar urine volumes [14]. The furosemide only group had an increase in serum sodium after 24 h of treatment, which was not seen in the indapamide plus furosemide group. Mineralocorticoid receptor antagonists can induce natriuresis and represent a potential therapy, though clinical data are lacking.

In addition to diuretics, free water administration might be required to facilitate sodium removal [15]. In case this risks fluid overload, renal replacement therapy may be an option.

Diabetes insipidus

Management of diabetes insipidus depends on the etiology. Nephrogenic diabetes insipidus is managed by correcting precipitating electrolyte disturbances and identifying reversible causes whereas central diabetes insipidus typically responds to desmopressin therapy.

Conclusion

Hypernatremia is relatively common in critically ill patients and associated with increased mortality. A thorough evaluation of fluid status, electrolytes and urine chemistry and understanding of the underlying physiology are paramount to guide management.

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