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REVIEW

Hyponatraemia and hypernatraemia: Disorders of Water Balance in Neurosurgery

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Abstract

Disorders of tonicity, hyponatraemia and hypernatraemia, are common in neurosurgical patients. Tonicity is sensed by the circumventricular organs while the volume state is sensed by the kidney and peripheral baroreceptors; these two signals are integrated in the hypothalamus. Volume is maintained through the renin-angiotensin-aldosterone axis, while tonicity is defended by arginine vasopressin (antidiuretic hormone) and the thirst response. Edelman found that plasma sodium is dependent on the exchangeable sodium, potassium and free-water in the body. Thus, changes in tonicity must be due to disproportionate flux of these species in and out of the body. Sodium concentration may be measured by flame photometry and indirect, or direct, ion-sensitive electrodes. Only the latter method is not affected by changes in plasma composition. Classification of hyponatraemia by the volume state is imprecise. We compare the tonicity of the urine, given by the sodium potassium sum, to that of the plasma to determine the renal response to the dysnatraemia. We may then assess the activity of the renin-angiotensin-aldosterone axis using urinary sodium and fractional excretion of sodium, urate or urea. Together, with clinical context, these help us determine the aetiology of the dysnatraemia. Symptomatic individuals and those with intracranial catastrophes require prompt treatment and vigilant monitoring. Otherwise, in the absence of hypovolaemia, free-water restriction and correction of any reversible causes should be the mainstay of treatment for hyponatraemia. Hypernatraemia should be corrected with free-water, and concurrent disorders of volume should be addressed. Monitoring for overcorrection of hyponatraemia is necessary to avoid osmotic demyelination.

Keywords Hyponatraemia · Hypernatraemia · SIADH · Cerebral salt wasting · Diuretics · Diabetes insipidus

Introduction

Disorders of water balance ("dysnatraemias") are common. In addition to substantial economic and resource burdens [18], dysnatraemias are a preventable cause of secondary brain injury and can worsen outcome and increase mortality [9]. Individuals with a plasma sodium concentration ($[Na^+]_p$) < 130 mmol/L have a mortality rate 59-fold (11.2% vs 0.19%) that of normonatraemic individuals. The severity of the hyponatraemia also correlates with mortality; those with a $[Na^+]_p$ < 120 mmol/L have greater than 2.5-fold the mortality (25% vs 9.3%) of those with a $[Na^+]_p$ between 120 and 130 mmol/L. Hyponatraemia in individuals with subarachnoid haemorrhage (SAH) is associated with increased rates of delayed cerebral ischemia (DCI) [52, 140] and worse outcome [106], while severe hypernatraemia ($[Na^+]_p$ > 160 mmol/L) is an independent predictor of poor outcome in general neurosurgical patients [6].

Physiology of sodium and water balance

Disorders of volume, hypervolaemia (oedema) and hypovolaemia, are disorders of sodium balance. Disorders of

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water balance, hyponatraemia (water overload) and hypernatraemia (water depletion), may occur independently or coexist with disorders of volume.

Osmoles are a measure of solute within a solution and may be described by osmolarity (solute per unit volume) or osmolality (solute per unit weight). Tonicity is the summed strength of the effective osmoles, that is, osmoles that cannot easily cross cellular membranes and thus influence water distribution. Ineffective osmoles include urea, alcohols (ethanol, methanol, ethylene glycol) and acetone; these substances can confound laboratory results and they contribute to measured plasma osmolarity without influencing the distribution of water [109]. Tonicity, not osmolarity, is the key to water balance.

The body is a reservoir that exquisitely balances influx and efflux of free-water and solute (Fig. 1). Even with maximal urine concentration (~1200mosm/L), approximately 500 ml/day of free-water is required to excrete the approximately 10 mosm/kg/day of waste solute. Conversely, if effective osmole intake is low compared to water intake, even maximal urinary dilution (50–100 mosl/L) can be insufficient to excrete ingested water. Exceptionally, urea can be excreted in nonlinear fashion to facilitate constant nitrogen balance despite varying water [44]:

$$Urine\ Volume = \frac{Solute}{Urine\ Concentration}$$

Regulation of plasma tonicity is achieved by alterations in water balance through the central arginine vasopressin (AVP, antidiuretic hormone) axis, while regulation of plasma volume is through the renal renin-angiotensin-aldosterone (RAA) axis. RAA activity leads to retention of volume (solute and solvent together) and is independent of changes in tonicity when intravascular haemodynamics are normal (Fig. 2).

The organum vasculosum of the lamina terminalis (OVLT) is the primary tonicity-receptor, though other circumventricular organs (devoid of a blood-brain barrier) as well as the median preoptic nucleus (MPN) and magnocellular neurons of the neurohypophysis itself are intrinsically tonicity-sensitive. At these regions converge other regulators of AVP release, including angiotensin II which activates neurons of the subforniceal organ, OVLT and MPN. In response to an increase in plasma tonicity or angiotensin II release due to hypovolaemia, projections from the circumventricular organs to the MPN activate the magnocellular neurons of the neurohypophysis. Converging on these magnocellular neurons are projections from the nucleus tractus solitarius and ventrolateral medulla which relay baroreceptor signals. Thus, tonicity and volume signals integrate at the site of AVP release, the magnocellular neurons of the neurohypophysis. AVP acts on the kidney to stimulate free-water resorption, thus concentrating urine. AVP also upregulates urea transport proteins in the collecting duct, improving the concentrating capacity of the medullary loops.

AVP is secreted when tonicity increases above an individual's osmostat set point, generally 280–285mosm/kg,

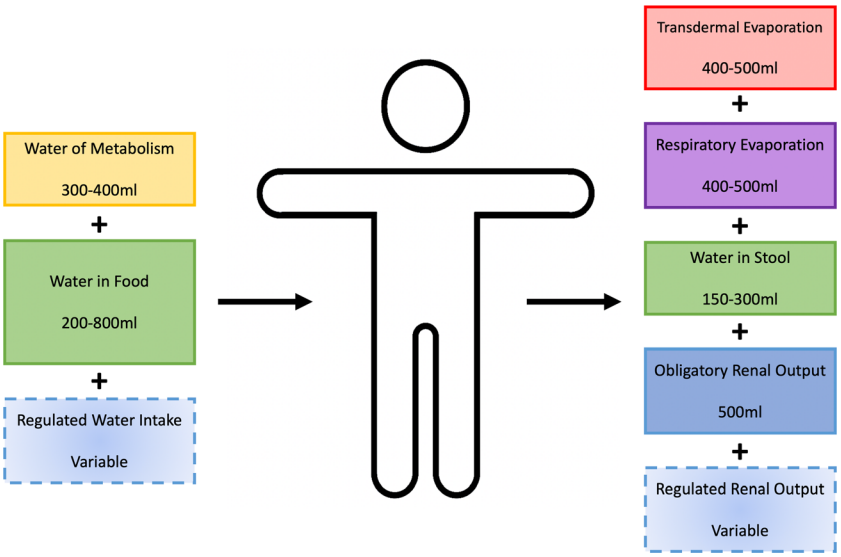

Fig. 1 Summary of the daily flux of free-water in an average individual. Each flux may be obligatory (unregulated) or regulated. Influx of free-water and solute is mostly dietary (obligatory) and metabolic (water liberated from oxidation of carbohydrates), while regulated intake of water also occurs via the thirst response and hedonistic/social intake. Obligatory water excretion occurs through "insensible losses" (trans-epidermal diffusion, sweat, airway humidification and gastrointestinal output; totaling approximately 10–12 ml/kg/day) and that required to eliminate excess solute and metabolic waste through the kidney. The water content of food varies with diet while the regulated water intake varies with societal norms, diet and thirst. Transdermal and respiratory evaporative losses may vary with environmental temperature and activity, while regulated renal losses relate to regulated water intake. Patients inhaling pre-humidified air, such as those receiving mechanical ventilation, high-flow nasal cannulae or pressure support, will have reduced respiratory losses

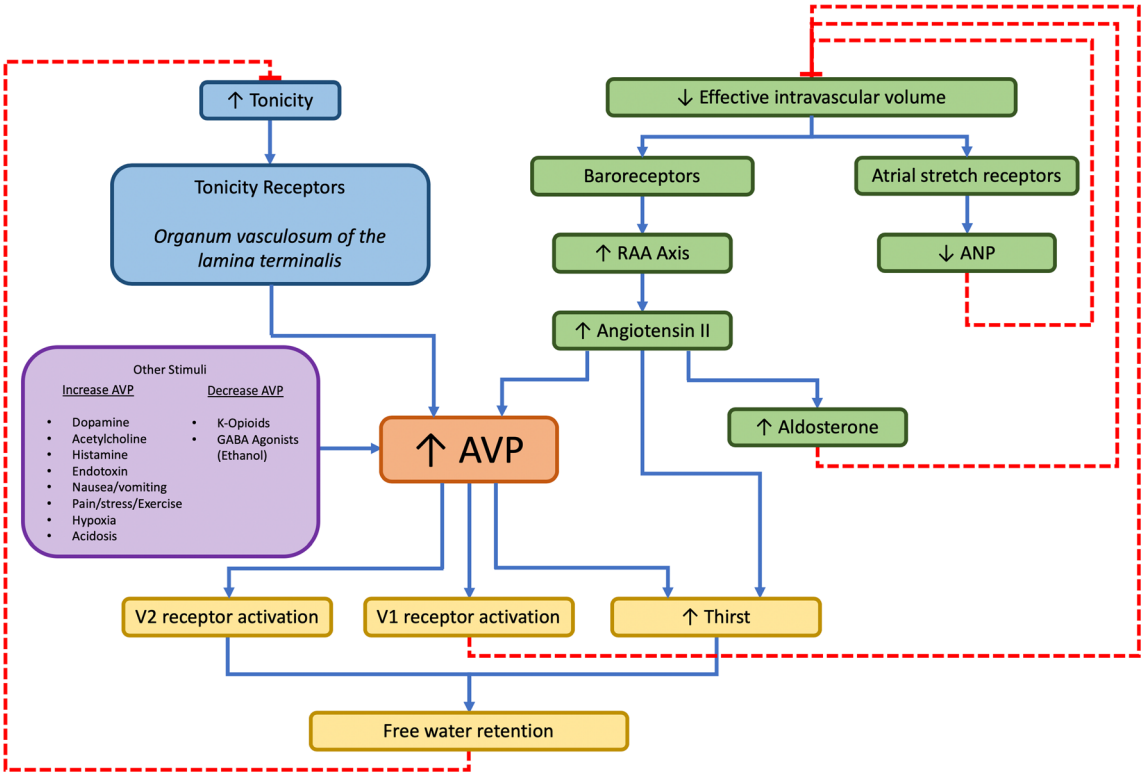

Fig. 2 Summary of water and volume homeostasis. AVP is the primary mediator of tonicity regulation, controlled by tonicity receptors and volume signalling. Negative feedback is shown in red (broken) lines. The thirst response and free water absorption in the collecting duct (V2 receptor mediated) lead to reduction in plasma tonicity. Sodium retention, mediated by aldosterone and decreased ANP, increases the volume state. ANP, atrial natriuretic peptide; AVP, arginine vasopressin (antidiuretic hormone); RAA, renin angiotensin aldosterone

although significant interindividual variability is seen [109, 110, 117]. Moreover, the set point may drift, often to become more sensitive, with age, pregnancy, medications and fluctuations in serum ionized calcium [69, 77, 142]. The circumventricular organs are exquisitely sensitive to changes in tonicity; perturbations as small as 1% cause changes in AVP release. The tonicity at which healthy adults first report a conscious desire to drink (thirst threshold) is the same as, or a few milliosmoles greater than, the osmostat set point [59, 132]. In those with primary polydipsia, the thirst threshold is much lower than this osmostat set point.

Maximal free-water resorption is reached at approximately 294 mosm/Kg, corresponding to an AVP concentration of approximately 5 pg/ml [109]. Further increases in tonicity lead to further AVP release, although concentrating activity is maximal, to bolster the thirst mechanism. As a result, hypernatraemia will almost only occur in the setting of an impaired thirst mechanism, damage to the neurohypophysis or inadequate access to free-water.

The volume state interacts with AVP secretion in two ways: Firstly, independent of changes to tonicity, a marked decrease (≥ 8–10%) in the volume state stimulates AVP release. Secondly, changes to the volume state alter the set point and gain of the AVP response to tonicity. Hypovolaemia leads to more AVP secretion for a given tonicity and shifts the threshold for secretion to a lower tonicity (Fig. 3). Although the threshold for hypovolaemia stimulating AVP release is much greater than for tonicity, the AVP response to volume depletion is exponential and stronger, though diminishes with age [69].

The Edelman equation

In 1958, Edelman demonstrated that $[Na^+]_p$ is related to the total exchangeable sodium (Na^+_e), total exchangeable potassium (K^+_e) and total body water (TBW) (Fig. 4) [35, 100]:

$$[Na^+]_p = 1.11 \cdot \frac{Na^+_e + K^+_e}{TBW} - 25.6$$

For simplicity, however, the Edelman equation can be reduced to:

$$[Na^+]_p \propto \frac{Na^+_e + K^+_e}{TBW}$$

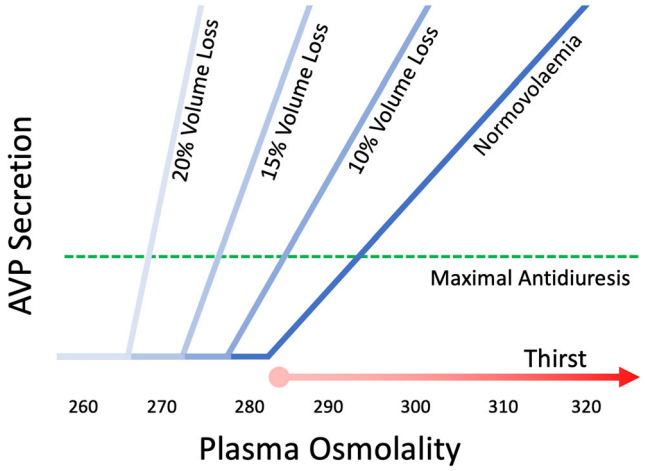

Fig. 3 Relationship between AVP, thirst and plasma osmolarity is modified by the volume state. Increasing degrees of hypovolaemia shift the threshold for thirst and AVP release to lower osmolalities. The gain is also increased by hypovolaemia, with more AVP secreted per unit increase in osmolality. AVP, arginine vasopressin (antidiuretic hormone)

Thus, the main effective osmoles in the body, sodium and potassium, determine the $[Na^+]_p$. From this, we extrapolate that perturbations in $[Na^+]_p$ are due to altered flux of effective osmoles and free-water in and out of the body. Conversely, ineffective osmoles do not have any effect on $[Na^+]_p$. Urea contributes to osmolarity but not tonicity:

$$Osmolality_{Calculated} = 2 \cdot \left([Na^+]_p + [K^+]_p \right) + [Glucose]_p + [Urea]_p$$

Other effective osmoles (besides sodium and potassium) affect $[Na^+]_p$. In health, plasma glucose is tightly controlled between 4 and 11 mmol/L. However, the neurosurgical perioperative period is often not healthful; patients with acromegaly and Cushing's disease are prone to hyperglycaemia, as are those on perioperative steroids. At higher concentrations, glucose, mannitol and other effective osmoles cause a shift of TBW into the ECF, reducing $[Na^+]_p$. This translocational hyponatraemia is physiologically necessary to maintain normal plasma tonicity. Translocation has been quantified as a 1 mEq/L drop in $[Na^+]_p$ for every 3.5 mmol/L increase in $[glucose]_p$ above normal (6.7 mmol/L). Correction of $[Na^+]_p$ for $[Glucose]_p$ separates this translocational effect from concurrent disorders of water balance. A large discrepancy (e.g. > 10 mmol/L) between calculated and measured osmolality suggests an unmeasured osmole is present. Translocational hyponatraemia (hyperosmolar hypertonic hyponatraemia) occurs with high levels of glucose, mannitol and contrast agents,

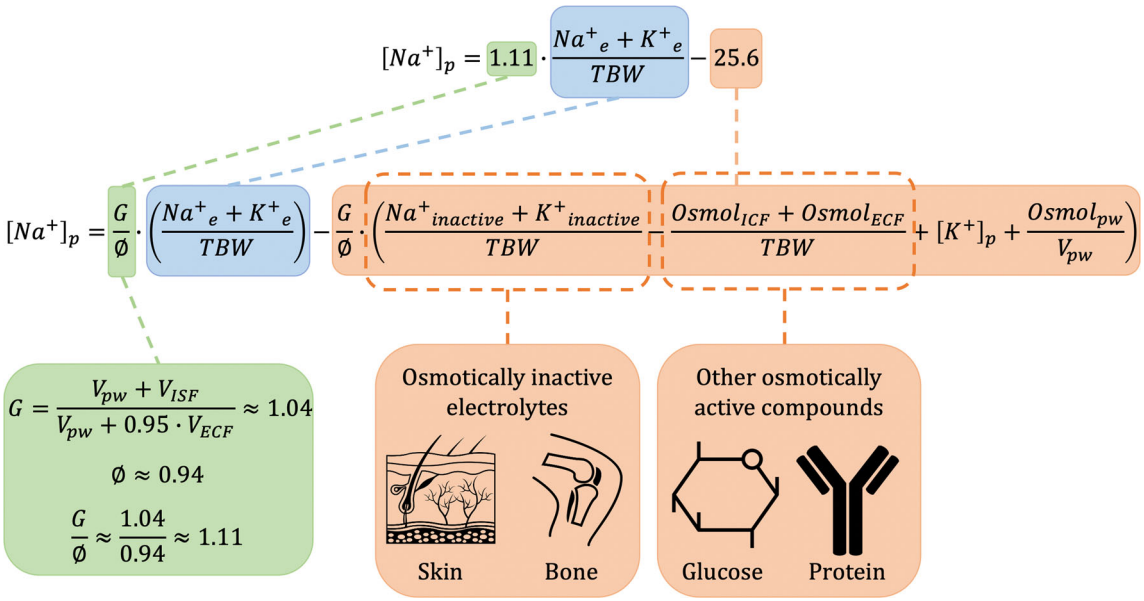

Fig. 4 The Edelman and Nguyen-Kurtz equations. The Edelman equation (top) and its corresponding coefficients in the Nguyen-Kurtz equation (bottom). The gradient (1.11) is the ratio of the coefficient of the Gibbs-Donnan effect (GDE) (G = 1.04) and the average osmotic coefficient of sodium salts (Ø = 0.93–0.94). The GDE is due to the higher concentration of large, anionic plasma proteins intravascularly that cannot cross the endothelium/glycocalyx barrier, thus attracting further sodium cations to the vascular space to balance their electromagnetic charge. The *Y*-intercept is related to the other osmotically effective species in the ICF ($Osmol_{ICF}$), ECF ($Osmol_{ECF}$) and plasma water ($Osmol_{pw}$); the plasma water volume (V_{pw}) and potassium concentration ($[K^+]_p$); and the inactive/bound sodium ($Na^+_{inactive}$) and potassium salts ($K^+_{inactive}$). The components of the Nguyen-Kurtz equation that represent osmotically inactive stores of exchangeable sodium and potassium (such as stored in the skin, interstitial spaces and bone) as well as the other osmotically active components of plasma (glucose and plasma proteins) are shown in dotted boxes. Several important lessons can be gleaned from these equations. Firstly, the main effective osmoles in the body, sodium and potassium determine the $[Na^+]_p$. From this, we extrapolate that perturbations in $[Na^+]_p$ are due to altered flux of effective osmoles and free-water in and out of the body. Secondly, ineffective osmoles do not have any effect on $[Na^+]_p$. Urea contributes to osmolarity but not tonicity

and removal of the osmole will generally ameliorate the hyponatraemia. Conversely, with high levels of ineffective osmoles (urea, alcohols), a hyperosmolar hypotonic hyponatraemia can develop. In this latter situation, the cause of the hyponatraemia still requires investigation as usual.

Neurosurgical and neurological dysnatraemias

Syndrome of inappropriate antidiuresis

The syndrome of inappropriate antidiuresis describes AVP secretion inappropriate from the plasma tonicity and intravascular volume state. SIAD is a diagnosis of exclusion but should be considered when known precipitants of SIAD are present (Fig. 5) [125, 136]. High levels of AVP increase free-water resorption in the collecting duct, thus increasing TBW leading to plasma dilution and ECF volume expansion. The expansion of the ECF leads to a pressure natriuresis which restores the normal ECF volume but leads to effective osmole loss that worsens the hyponatraemia. Given the RAA axis is unimpaired, and thus renal salt handling is intact, euvolemia is the norm.

AVP may be secreted inappropriately in response to cerebral pathology [74]. Classically, these are associated with AVP in the high normal range but not responsive to changes in tonicity. This is in contrast to grossly elevated AVP levels, typical for ectopic secretion from neuroendocrine tumours [39].

Anti-epileptics, namely, carbamazepine and its derivative oxcarbazepine, may cause a syndrome similar to SIAD, due to increased renal sensitivity to AVP and possibly a shift of the osmostat "set point" [135]. Hyponatraemia occurs in 26% of those taking carbamazepine and 46% on oxcarbazepine [15]. It is especially common in elderly patients [60], is dose dependent [85] and is more likely in those with a history of hyponatraemia and on concomitant diuretics.

Cerebral-renal salt wasting

Intracerebral catastrophes may be associated with ECF depletion, high urine sodium losses, hypovolaemia and an ensuing hyponatraemia. Traditionally termed cerebral salt wasting syndrome, we prefer this association to be termed cerebral-renal salt wasting (CRSW) [88]. Classically described in SAH [64, 139], it has been described in other neurosurgical diseases including TBI [71, 86], aneurysm clipping [98], vault reconstruction for craniosynostosis [45, 75] and infection [123]. CRSW has been variably attributed to natriuretic peptide release, alterations of sympathetic outflow to the kidney which downregulate the RAA axis and directly impair proximal tubular sodium resorption, and hypothalamic-pituitary-adrenal axis dysfunction (Fig. 6) [103]. The differentiation of CRSW and SIAD, and even the concept of CRSW itself, has been the subject of much debate. As the ECF is depleted in the early stages of CRSW, baroreceptor signalling causes increased secretion of AVP, leading to hyponatraemia. Urinary sodium concentration (which is often a critical step in differentiating the aetiology of hyponatraemia) is not helpful in differentiating between CRSW and SIAD. The only clinical difference is the ECF status (deplete in CRSW and replete in SIAD), which is often difficult to measure clinically [25, 93]. Neurosurgical studies utilizing (gold standard) radioisotope dilution methods demonstrate that there is a subset of hyponatremic patients with depleted ECF better explained by CRSW than SIAD [98, 139].

Central diabetes insipidus

Diabetes insipidus (DI) is caused by interruption of the AVP axis leading to inappropriate free-water excretion and hypernatraemia. Central DI is the most common type and most relevant to neurosurgical patients, often seen after sellar surgery or head trauma. Damage to 80–90% of hypothalamic magnocellular neurons is necessary before symptoms arise [54]; transient DI and permanent DI are seen after 10-20% and 2% of pituitary surgeries, respectively [55, 99]. The risk of DI after surgery increases with intraoperative CSF leak; specific pathologies include craniopharyngioma, Rathke cleft cysts, and Cushing's disease; young age; extrasellar expansion; and the extent of superior resection [55, 79, 99]. Sectioning above the median eminence generally causes permanent DI, as the probability of Wallerian degeneration of the magnocellular neuron is proportional to the proximity of the axotomy from the soma (located in hypothalamic nuclei). More superior damage to the circumventricular organs, specifically the SFO and OVLT, such as after anterior communicating artery aneurysm (AComA) clipping and craniopharyngioma resection [28], may lead to central DI with adipsia [133].

Occult AVP deficiency may be masked by concurrent ACTH deficiency and only after glucocorticoid replacement therapy has been administered do the symptoms DI appear. Firstly, cortisol induces resistance of the V_2 receptor (or at a post-receptor level) to AVP; thus in states of glucocorticoid deficiency, the effects of AVP are amplified [118]. Secondly, corticotrophin-releasing hormone (CRH) stimulates ACTH and AVP release; as glucocorticoid deficiency upregulates CRH, thus AVP release is increased [23]. Lastly, hypocortisolaemia results in renal sodium loss and volume depletion, potent stimulators for increased (but "appropriate") AVP release. As such, when glucocorticoid deficiency is ameliorated, these compensatory mechanisms fail, and DI ensues. Thus, assessment of AVP function both before and after

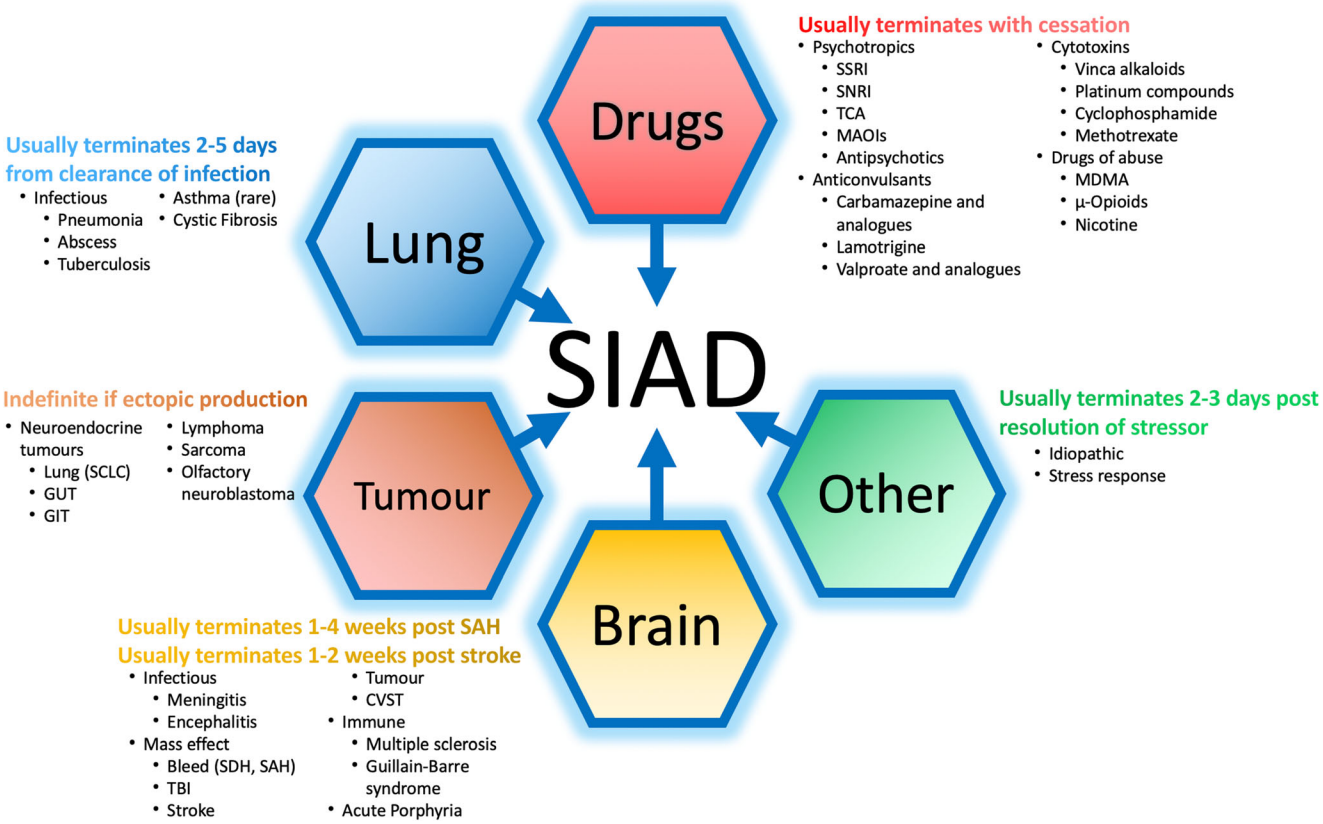

Fig. 5 Common causes of the syndrome of inappropriate antidiuresis. Typical duration of SIAD caused by each aetiology is shown in grey. AIDS, acquired immunodeficiency syndrome; AVP, arginine vasopressin (antidiuretic hormone); CVST, cerebral venous sinus thrombosis; GIT, gastrointestinal tract; GUT, genitourinary tract; MAOIs, monoamine oxidase inhibitors; MDMA, 3,4-methylenedioxy methamphetamine; SAH, subarachnoid haemorrhage; SCLC, small cell lung carcinoma; SDH, subdural hematoma; SIAD, syndrome of inappropriate antidiuresis; SNRI, serotonin noradrenaline reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TBI, traumatic brain injury; TCA, tricyclic antidepressant

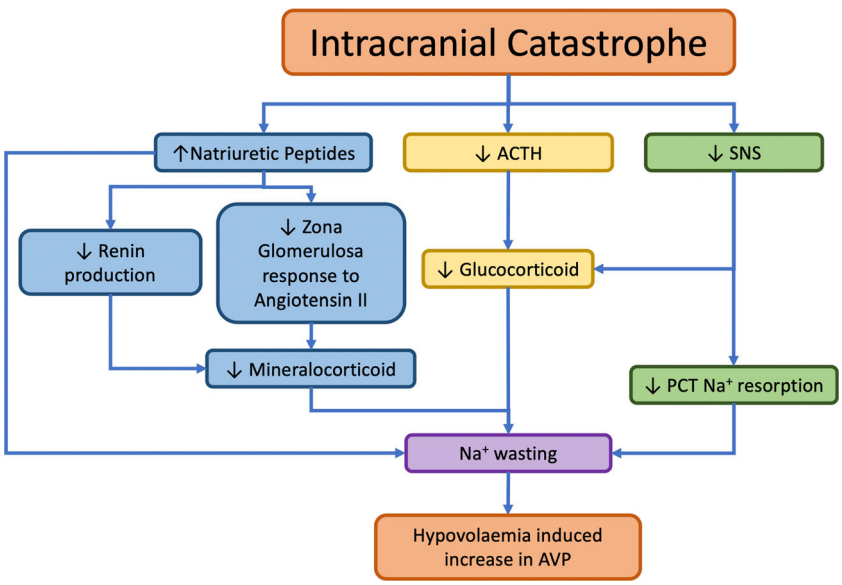

Fig. 6 Pathophysiology of the cerebral-renal salt wasting after intracranial catastrophe. CRSW has been variably attributed to natriuretic peptide release, alterations of sympathetic outflow to the kidney which downregulates the RAA axis and directly impairs proximal tubular sodium resorption, and hypothalamic-pituitary-adrenal axis dysfunction. This culminates in ECF depletion, and consequent baroreceptor signalling causes increased secretion of AVP, leading to hyponatraemia. ACTH, adrenal corticotropic hormone; PCT, proximal convoluted tubule; SNS, sympathetic nervous system

glucocorticoid replacement appears to increase the sensitivity for diagnosis of DI [19].

Central DI is a rare presenting feature of pituitary adenomas and other slow-growing lesions of the sella. As AVP synthesis occurs in the hypothalamus and not the neurohypophysis, slow destruction of the latter damages only the magnocellular nerve terminals, allowing the site of secretion to migrate superiorly to the stalk or hypothalamus [24]. Given the substantial reserve of magnocellular neurons, sellar lesions causing DI are often fast growing and highly destructive, such as metastases, carcinoma or apoplexy. It should also be noted that conditions affecting stalk (e.g. Langerhans cell histiocytosis, sarcoidosis and autoimmune hypophysitis) may cause DI early in their course.

In a patient with new central DI, MR imaging of the sellar region is paramount to exclude a structural lesion in the absence of trauma or surgery. Idiopathic central DI is a diagnosis of exclusion in the setting of a normal MRI and is likely autoimmune [24]. MRI may demonstrate absence of the posterior pituitary bright spot, but this is not specific [26]. Antivasopressin cell antibodies are present in the majority of cases [89], while DI associated with adipsia is seen with autoantibodies to the circumventricular organs [57]. The presence of a thickened pituitary stalk (> 2–3 mm) is generally pathological, and the combination of a thickened stalk and absent bright spot demands thorough investigation for neoplastic and infiltrative lesions of the hypothalamus and pituitary [24].

Dysnatraemias following pituitary surgery

Given the proximity of tonicity receptors and magnocellular neurons to the adenohypophysis, dysnatraemias are relatively common after sellar surgery. Dysnatraemias also represent the most common cause for delayed unplanned re-admission following pituitary surgery, accounting for 70% of cases [17]. Risk factors for dysnatraemias after pituitary surgery include male gender, younger age, larger tumours (macroadenomas), greater extent of resection, suprasellar extension, reoperation, CSF leak, non-adenoma lesions (Rathke's cleft cyst and craniopharyngioma), Cushing's disease, and microscopic (c.f. endoscopic) approaches [7, 27, 80, 99, 116, 141]. The initiation of DI may be delayed after Rathke's cleft cyst surgery, as the cyst contents incite sterile inflammation of the stalk which may present weeks to months postoperatively [53]. Furthermore, those with surgically managed Cushing's disease are at increased risk of fluctuating serum sodium due to the opposing effects of relative glucocorticoid deficiency and central DI; indeed up to 70% exhibit some abnormality in sodium and water balance postoperatively [55].

Post-traumatic and post-surgical patients may exhibit fluctuations in AVP secretion termed "biphasic" and "triphasic" responses (Fig. 7). Immediately after surgery, DI may develop due to interruption of axons and axoplasmic flow in the magnocellular osmoregulatory system. This may arise from surgical manipulation of the stalk or neurohypophysis, or excision [121]. An increase in serum sodium of 4.5 mmol/L from preoperative to first postoperative testing is 91% specific and has a positive predictive value of 57% for DI, while a postoperative serum sodium of > 145 mmol/L is 98% specific [116]. After some time, generally 5–7 days, stored AVP may be released from Herring bodies of the neurons distal to the site of axonal injury leading to a transient SIAD. Finally, after partial damage to magnocellular neurons, the remaining neurons and regenerating axons begin to secrete AVP, and normal osmoregulation reinstated (biphasic response). However, if damage is severe, all magnocellular cells may degenerate, and once AVP stores are exhausted, chronic DI persists (triphasic response).

Hyponatraemia following pituitary surgery is usually SIAD [29]. It is generally delayed, with a nadir 7–9 days postoperatively [113, 114], and is associated with larger tumours, younger age and reoperation [126]. This SIAD likely represents an "isolated second phase" of the triphasic response. Initial trauma to the stalk is incomplete, with persisting neurons sufficient to defend plasma tonicity. However, degeneration of damaged neurons continues, and delayed release of stored AVP produces a transient SIAD. Once these stores are exhausted, the remaining neurons again resume to maintain normal tonicity [105].

Dysnatraemias following SAH

Hyponatraemia following SAH is common, occurring in up to 56% of patients [50, 122]. Risk factors include increased age, aneurysmal aetiology [122], current smoking [119], AComA aneurysms [115], post-SAH hydrocephalus, rebleeding [84], high SAH grade, large clot volume [90] and surgical or endovascular intervention. Generally, SIAD is considered more common than CRSW, but this is contentious [122]; both have a similar morbidity and mortality [64]. Atrial, brain and dendroaspis [65] natriuretic peptides are increased after SAH [14, 36, 61, 63, 130, 134], are associated with hypovolaemia [33] but may not specifically cause hyponatraemia [50, 130]. Aldosterone levels are generally suppressed despite normal renin levels [14]. AVP (and a by-product of its formation, copeptin) levels are greater in patients with DCI independent of plasma tonicity [41]. Total glucocorticoid levels are commonly low after SAH [66, 67, 104]. However, as cortisol is highly protein bound, simultaneous "negative acute-phase" changes in carrier protein concentration may dictate that free cortisol levels are actually normal [47, 68]. Concentrations of albumin and corticosteroid-binding globulin should be considered before renal salt wasting is attributed to glucocorticoid deficiency. Importantly, hypervolaemic hyponatraemia and hyponatraemia due to inappropriate fluid replacement are also seen after SAH [50, 122]. The severity of the hyponatraemia

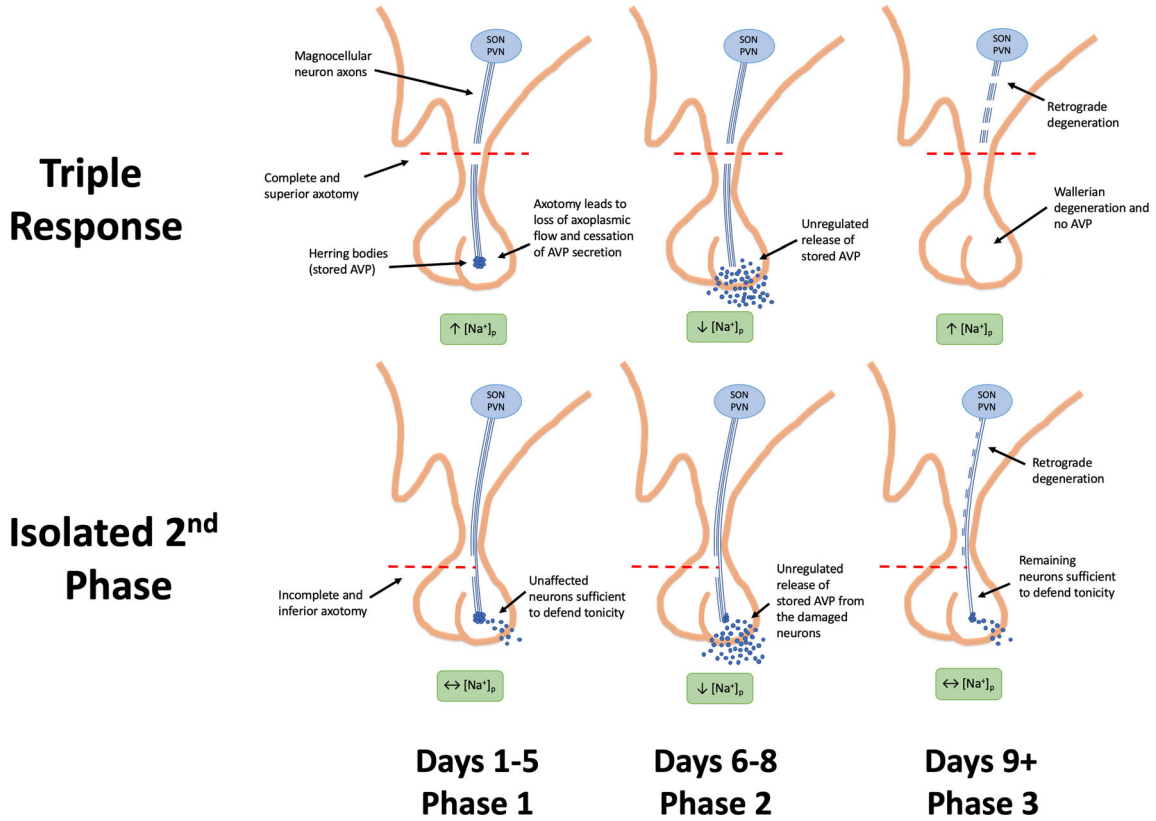

Fig. 7 Pathophysiology of the triple response to magnocellular injury after pituitary surgery. Immediately after surgery DI may develop due to interrupted axoplasmic flow in the magnocellular neurons. After a variable amount of time, generally 5–7 days, AVP stored in Herring bodies located at the terminal part of the magnocellular axon is released, leading to a transient SIAD. Once the AVP stores are exhausted, degeneration of the damaged neurons leads to chronic DI. When damage is less severe, the spared neurons are sufficient to defend body tonicity, but unregulated release of stored AVP in the affected neurons still causes a transient SIAD around days 5–9 (isolated second phase). *SON* supraoptic nucleus; PVN, paraventricular nucleus; AVP, arginine vasopressin

and its trajectory are independent risk factors for poor outcome after SAH [34, 91], length of hospital stay [91, 122] and the development of DCI [34]; however, the overall impact of hyponatraemia on outcome is small [106, 138].

DI is uncommon after SAH [106, 131]. It is generally transient but may persist in some patients [5]. DI is associated with AComA aneurysms and is particularly important to recognize and treat given the risk of DCI with hypovolaemia. Adipsic DI may complicate surgical clipping of AComA aneurysms [124].

Dysnatraemias following traumatic brain injury

Hyponatraemia commonly complicates traumatic brain injury (TBI), occurring in approximately 13% of cases [108], and is associated with longer hospital stays and poorer outcome [95]. The incidence correlates with radiological severity [82], the majority of cases are due to SIAD [3] and complete recovery is the norm [4]. CRSW may also complicate TBI, with an incidence of 0.8–34.6% [73], greater in those with more severe injury. Late-onset hyponatraemia, in the second week post-injury, tends to resemble CRSW more than SIAD [51]. Although uncommonly the sole cause for hyponatraemia, concomitant hypothalamic-pituitary-adrenal axis dysfunction may complicate post-TBI hyponatraemia [49].

The frequency of DI following TBI correlates with clinical and imaging severity, occurs in over 20% of individuals acutely and persists in approximately one-quarter of these cases [3]. Initially, oedema, ischemia or direct neuronal injury to the hypothalamus and stalk causes DI that presents within 2–3 days of injury [2], correlating with maximal post-traumatic oedema. Resolution of oedema leads to resolution of DI in the majority; however, with direct injury to magnocellular neurons, DI may present earlier and be permanent. Concomitant injury to the thirst centres leads to adipsic DI, which carries a worse prognosis [124]. The presentation of post-traumatic DI may be delayed and may occur in the absence of acute-phase DI. All individuals with resolved post-traumatic acute DI should have a screening post-acute phase water deprivation test, while those without a history of acute post-traumatic DI

that are asymptomatic (no ongoing thirst, polyuria or nocturia) and have normal urine output (< 3 L/day) require no further assessment [3].

Common "medical" dysnatraemias

The reset osmostat

The reset osmostat, common in pregnancy, is a shift of the osmostat set point where AVP secretion begins to increase significantly [10]. The diagnosis should be considered in those with mild hyponatraemia or hypernatraemia that is stable over long time periods despite varying solute and water intake. Importantly, AVP secretion will alter appropriately after water and salt loads to maintain tonicity at this new set point.

Hypovolaemic hyponatraemia

Intravascular hypovolaemia is a potent stimulus for AVP secretion. As such, free-water is retained in states of whole-body salt and water depletion (hypovolaemia). This is not SIAD; secretion will normalize when intravascular haemodynamics are restored.

Diuretic-induced hyponatraemia

Thiazides are the primary offender in diuretic-associated hyponatraemia [56]. Thiazides impair diluting ability of the nephron, stimulate AVP release and increase water resorption in the inner medullary collecting duct independent of AVP [20]. The combination of water retention and renal salt wasting begets hyponatraemia. Because thiazides impair urinary dilution, those that require maximally dilute urine to maintain water balance (e.g. those with poor solute intake, psychogenic polydipsia or "beer potomania") are especially vulnerable. Discontinuation of thiazides may lead to dangerously prompt correction of serum sodium, with the risk of osmotic demyelination augmented by the concurrent hypokalaemia induced by thiazides.

Loop diuretics (e.g. frusemide), although more prevalent than thiazides in hospitalized patients with hyponatraemia [46], seldom cause hyponatraemia themselves. They disrupt the countercurrent concentrating mechanism of the nephron and lead to an increase in free-water clearance. Hypovolaemia-induced hyponatraemia from overzealous loop diuresis is possible, but uncommon. More commonly, patients with another cause for their hyponatraemia, such as heart failure or renal failure, are also on a loop diuretic, and the latter is wrongly ceased. Potassium-sparing diuretics (e.g. spironolactone) do mildly reduce serum sodium [21] but are unlikely to cause hyponatraemia in isolation.

Hypervolaemic hyponatraemia

In states of whole-body hypervolaemia, but reduced effective intravascular volume, such as heart failure or cirrhosis, intravascular depletion stimulates AVP release and thus hyponatraemia. Normalization of intravascular dynamics may improve hyponatraemia, although hyponatraemia is an independent risk factor for mortality in these patients [16, 70, 72, 112].

Sodium measurement and pseudohyponatraemia

Methods of measuring $[Na^+]_p$ include flame photometry (FP); the indirect ion-sensitive electrode (I-ISE), used for "formal" pathology tests; and the direct ISE (D-ISE), used in point-of-care analysers [76] (Table 1). FP and I-ISE may produce spurious results in the setting of elevated or decreased plasma solid phase, termed pseudohyponatraemia and pseudohypernatraemia, respectively. The D-ISE is not influenced by the solid phase composition of plasma [30, 32, 42, 129] (Fig. 8).

A physiology based approach to dysnatraemia

Traditionally, dysnatraemias were classified by the apparent volume state of the individual. The clinical utility of such a classification is hampered by the difficulty of accurately measuring the volume state [25, 92]. Indeed, clinicians perform worse than the flip of a coin in differentiating between hypovolaemia and euvolemia in individuals with hyponatraemia [6]. Our approach to dysnatraemia is centred around the flux of effective osmoles and water entering and exiting the body. Simply, if more effective osmoles are excreted than ingested, or more free-water is gained than lost, $[Na^+]_p$ will fall. Conversely, if more effective osmoles are ingested than excreted, or more free-water is lost than gained, $[Na^+]_p$ will rise. As such, we have categorized the common causes of hyponatraemia and hypernatraemia by free-water and effective osmole flux (Tables 2 and 3). Additionally, medications are an often-overlooked sodium burden (Table 4) [137].

Our approach to diagnosis of dysnatraemia (Figs. 9 and 10) begins by measurement of the excreted effective osmoles in comparison to the serum effective osmoles. This is simplified (initially) to the comparison of urinary sodium and potassium to $[Na^+]_p$, correcting the latter for $[Glucose]_p$ if hyperglycaemia is present (Figs. 11 and 12). We measure urinary losses first as they represent the body's attempt to rectify the dysnatraemia. Dichotomisation based on urinary effective osmole concentrations classifies pathologies into those due to renal loss or other

Table 1 Summary of clinically relevant methods to measure sodium in a solution

Device	Method		Advantages	Disadvantages
Flame photometry	Alkali metal salts are ionized by a flame and emit light as electrons return to the ground state. The wavelength determines the metal species while the intensity determines the concentration		Does not need to be calibrated regularly	Subject to spurious results "psuedohyponatraemia" in the setting of hyperlipidaemia, hyperproteinaemia or any other state of altered plasma water to plasma ratio "Psuedohypernatraemia" may also occur in altered plasma water to plasma ratio (usually hypoproteinaemia)
Ion-specific electrode	An electrode permeable to a specific species allows a potential gradient to form across it, which is proportional to the activity of that ion as per the Nernst equation. Activity must then be converted to concentration*			
	Indirect ion-specific electrode	A sample of whole plasma is diluted with a relatively large volume of buffer of high ionic strength, so that the activity coefficient is constant	Result similar to flame photometry	Same as flame photometry
	Direct ion-specific electrode	The activity of a sample of whole plasma is converted to a concentration assuming constant activity coefficients for the standards, calibrators and samples	Not effected by states of altered plasma water to plasma ratio as measures electrolyte content in the plasma water (mmol/kg H_2O)	The electrochemical activity of the ions in the water is converted to the readout concentration by a fixed (ion-specific) multiplier. This is only accurate for a given ionic strength, usually chosen to equal 160 mmol/L for plasma, and thus is less accurate at extremes of sodium concentration

*= Activity is the product of concentration and the activity coefficient (which is defined by the Debye-Huckel equations). *ISE* ion-sensitive electrode

means. Note that the interpretation of plasma and urinary tonicities required for diagnosis and treatment differ slightly.

When urinary tonicity is less than plasma tonicity (i.e. $([Na^+]_u + [K^+]_u) < [Na^+]_p$), the kidney is expelling net free-water from the body. In the setting of hyponatraemia, if AVP is fully supressed (the appropriate response to low plasma tonicity), urinary tonicity shoud be much less than plasma tonicity (i.e. ([Na+]u + [K+]u) << [Na+]p)). If urinary tonicity is not supressed, even if it lower but similar to plasma, this response is considered abnormal, as the physiological response to hyponatraemia is maximally dilute urine. In the setting of hypernatraemia, a low urinary tonicity is inappropriate for plasma tonicity. When urinary tonicity is high $([Na^+]_u + [K^+]_u) > [Na^+]_p$), the kidney is retaining net free-water from the body. In the setting of hyponatraemia, this is inappropriate, while in hypernatraemia, it is appropriate for plasma tonicity. The same caveat applies such that a urinary tonicity just above that of plasma in hypernatraemia is still inappropriate, as urine should be maximally concentrated. A futher caveat is if a previously renally driven process resolves prior to testing, only the restorative phase may be capturedbiochemically, thus obscuring the diagnosis (but not effecting treatment).

Although we present a dichotomous approach, clinical application is often more blurred, and clinical reasoning is key. The thresholds presented should not be seen as absolutes, but as guides (see Appendix 1).

Free-water clearance as a guide to management

Calculation of the (electrolyte) free-water clearance (EFWC) of the kidney can be helpful to conceptualize the physiology underlying the treatment of dysnatraemias (Fig. 13). Urine volume (V_{urine}) is described as being comprised of two components, one that is isotonic to plasma, and another that is (electrolyte) free-water. When EFWC is positive, this is volume of free-water being excreted per unit time (e.g. per day) by the kidney; when negative, it is the volume of free-water being retained [101]:

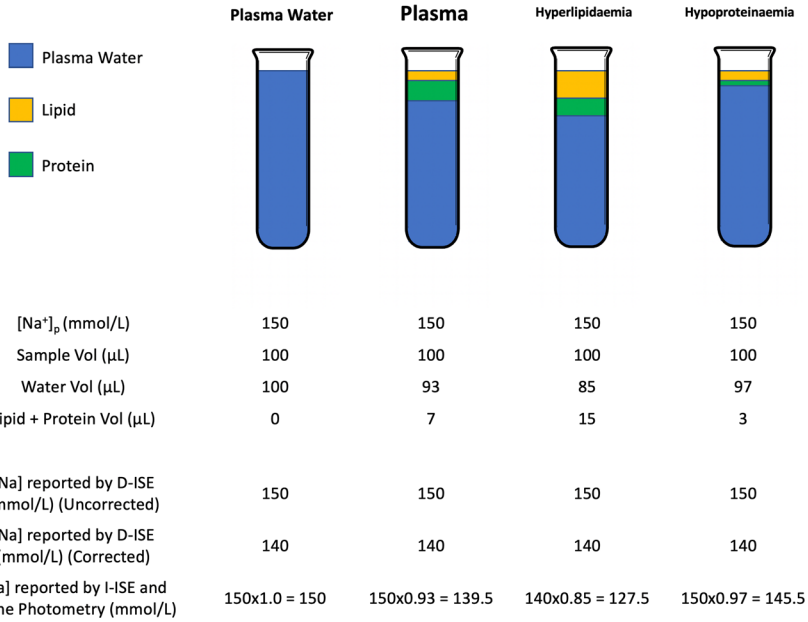

Fig. 8 Comparison of the methods of calculating sodium concentration in plasma with different compositions. Plasma is generally composed of 93% water, with proteins and lipids (together the "solid phase") accounting for the remaining 7%. The D-ISE measures the thermodynamic activity of sodium in plasma water, which generally follows its concentration, although other species in the plasma, namely, chloride, may alter this. The thermodynamic activity of sodium is then divided by an activity coefficient to yield the concentration of sodium in plasma water. Finally, this value is corrected to match the values produced by I-ISE and FP methods, assuming the plasma contains 7% solid phase. I-ISE and FP require dilution prior to sampling, which introduces dilutional error. Moreover, the I-ISE and FP methods, by virtue of this dilution step, measure the sodium concentration in whole plasma, as opposed to the sodium concentration in plasma water measured by D-ISE. Importantly, the former may produce spurious results in the setting of elevated or decreased plasma solid phase. Spuriously low values are seen in states where the lipid or protein component of plasma is increased, the so-called pseudohyponatraemia, and spuriously high values in the setting of hypoproteinaemia. D-ISE measurements are not affected by changes in plasma solid phase. Modified from Fortgens P, Pillay TS. Pseudohyponatraemia revisited: a modern-day pitfall. Arch Pathol Lab Med. 2011;135:516. ©2010 College of American Pathologists

Table 2 Causes of hyponatraemia classified by free-water and effective osmole flux

Hyponatraemia	
Increased free-water intake	Decreased effective osmole intake
Polydipsia	Malnutrition
Hypotonic fluids*	
Surgical irrigation	
Decreased free-water output	Increased effective osmole output
SIAD	Renal losses
Physiologically appropriate increase in AVP (states of decreased effective intravascular volume, e.g. HF, CLD, sepsis, hypothyroidism)	Diuretics (primarily thiazides)
	CRSW
	Hypocortisolaemia
	Hypoaldosteronaemia
	Hypothyroidism
	Salt losing nephropathy
	Non-renal losses
	Bleeding
	GIT losses with high effective osmolarity (e.g. secretory diarrhoea)
	Burns

*= Note any fluid with an effective osmolar concentration less than the average of the effective osmolar concentrations of all excretions will lower the serum sodium. Remember to consider the osmotic coefficient of the solute in the fluid

HF heart failure, *CLD* chronic liver disease, *AVP* arginine vasopressin (antidiuretic hormone), *SIAD* syndrome of inappropriate antidiuresis, *CSWS* cerebral-renal salt wasting, *GIT* gastrointestinal tract

Table 3 Causes of hypernatraemia classified by free-water and effective osmole flux

Hypernatraemia	
Decreased free-water intake	Increased effective osmole intake
No access to water	Medications (see Table 4)
NPO	Hypertonic fluids*
Loss of thirst drive (e.g. hypothalamic lesions)	Salt poisoning
Increased free-water output	Decreased effective osmole output
Renal losses	Rarely a cause of clinically important hypernatraemia
DI (central and nephrogenic)	
Osmotic diuresis (e.g. hyperglycaemia, mannitol, urea)	Hyperaldersteronaemia
Reduced renal concentrating capacity (e.g. myeloma, ATN, TIN)	Hypercortisolaemia
	Glucocorticoids
Non-renal losses	
Sweating	
Osmotic diarrhoea	
Respiratory losses (e.g. high flow oxygen without humidifier)	

*= Note any fluid with an effective osmolar concentration greater than the average of the effective osmolar concentrations of all excretions will increase the serum sodium. Remember to consider the osmotic coefficient of the solute in the fluid

NPO nil per Os, *DI* diabetes insipidus, *ATN* acute tubular necrosis, *TIN* tubulointerstitial nephritis

$$EFWC \approx V_{urine} \cdot \left(1 - \frac{([Na^+]_u + [K^+]_u)}{[Na^+]_p}\right)$$

Table 4 Common medications with a high sodium load

Drug (route)	Sodium per dose (mmol)
Piperacillin/tazobactam 4 g/500 mg (IV)	9.4
Ampicillin 2 g (IV)	5.7
Ceftriaxone 2 g (IV)	7.2
Meropenem 1 g (IV)	3.9
Ceftazidime 2 g (IV)	4.7
Omeprazole 40 mg (PO)	13.2
Macrogol 3350 (Movicol®) (1 sachet)	65
1000 ml of 0.9% NaCl	154
100 ml of 3% NaCl	51
20 ml of 23.4% NaCl	80
1000 ml of compound sodium lactate	130

PO per oral, *IV* intravenous

Sodium per dose is given as the intrinsic sodium for the dose of antibiotic only. Additional sodium may be present when administered in a "ready to use" pack or when reconstituted in saline. Note that many intravenous medications are administered in 100–250 ml solutions of 0.9% saline, which increases their sodium load. For example, QID dosing of piperacillin/tazobactam 4 g/500 mg reconstituted in 100 ml 0.9% sodium chloride equates to ~ 100 mmol of sodium

Insensitive losses (trans-epidermal and respiratory) must also be considered in the clearance pathways of free-water. Sweat and gastrointestinal losses also contribute; however, they contain variable amounts of solute.

Electrolyte free-water intake (EFWI) is conceptually similar to EFWC, being the amount of free-water entering the body:

$$EFWI \approx V_{intake} \cdot \left(1 - \frac{([Na^+]_{intake} + [K^+]_{intake})}{[Na^+]_p}\right)$$

Production of metabolic water is an additional source of free-water.

Electrolyte free-water balance (EFWB) has therefore been defined as the difference between EFWI and EFWC [9, 10]:

$$EFWB = EFWI + Metabolic\ Water - EFWC - Insensible\ Losses$$

The clinical consequences of these equations are that in the setting of hyponatraemia:

When EFWC is positive, the kidneys are expelling free-water. If EFWI can be made less than EFWC (e.g. by restriction of free-water intake), hyponatraemia should resolve (see Supplemental content 1).

When EFWC is negative, the kidneys are retaining free-water. Here, EFWC may be increased by AVP

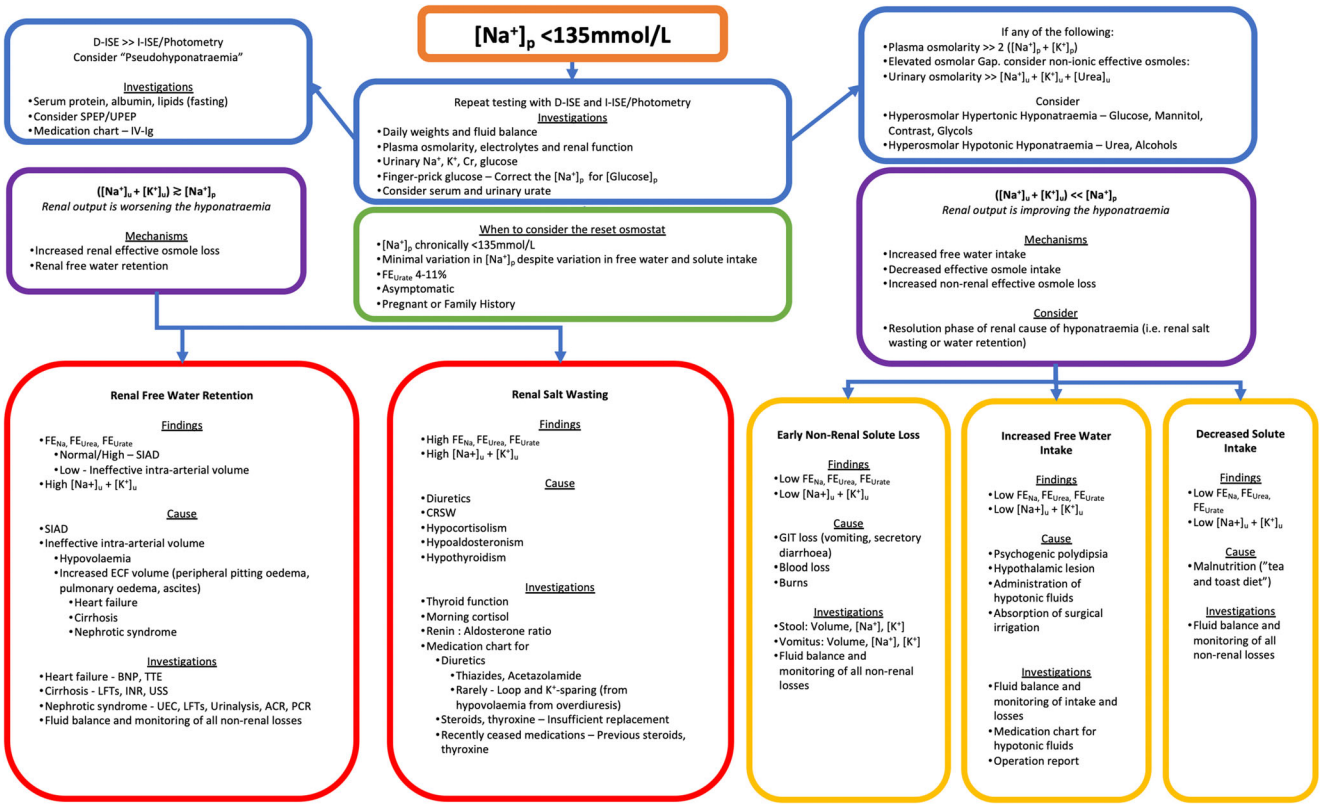

Fig. 9 An approach to the diagnosis of hyponatraemia. ACR, albumin/creatinine ratio (urine); BNP, brain natriuretic peptide; BSL, blood sugar level; CRSW, cerebral renal salt wasting; D-ISE, direct ion-sensitive electrode; DKA, diabetic ketoacidosis; ECF, extracellular fluid; FE_{Na}, fractional excretion of sodium; FE_{Urate}, fractional excretion of urate; GIT, gastrointestinal tract; HHS, hyperglycaemic hyperosmolar; I-ISE, indirect ion-sensitive electrode; INR, international normalized ratio; IV-Ig, intravenous immunoglobulin; LFTs, liver function tests; PCR, protein/creatinine ratio (urine); SIAD, syndrome of inappropriate antidiuresis; SPEP, serum protein electrophoresis; TTE, transthoracic echocardiogram; UEC, urea, electrolytes and creatinine; UPEP, urine protein electrophoresis; USS, ultrasound

antagonism or EFWI may be made negative by restriction of free-water intake and prescription of hypertonic substances (e.g. salt tablets, 3% saline).

Differentiating the cause of increased AVP in hyponatraemia

Both hypovolaemia and SIAD demonstrate elevated AVP. Differentiation is complex, reliant on the amalgam of clinical history, physical signs and response to treatment. Physiologically, the difference lies in the state of the RAA axis, normal in SIAD and upregulated in hypovolaemia (Fig. 14). Differentiation is critical as volume replacement will improve hyponatraemia in hypovolaemia, but worsen it in SIAD. Conversely, free-water restriction below EFWC will lead to improvement in SIAD but not in hypervolaemia, as the primary stimulus has not been addressed.

Several markers have been proposed to assess the RAA axis in hyponatraemia, but none has proved effective in isolation. A low $[Na^+]_u$ (< 20 mmol/L) is common in hypovolaemia and, if present, permits volume replacement without risk of worsening hyponatraemia. However, $[Na^+]_u$ may be elevated (> 40 mmol/L) in hypovolaemia and renal salt wasting: *not all elevated $[Na^+]_u$ is SIAD.*

Tubular handling of different solutes can be estimated using their fractional excretion, the percentage of the filtered solute that is lost in the urine:

$$FE_{Solute}(\%) = 100 \cdot \frac{[Solute]_{urine} \cdot [Cr]_{plasma}}{[Solute]_{plasma} \cdot [Cr]_{urine}}$$

A low fractional excretion of sodium (FE_{Na}) (< 0.5%) is one sign the RAA is upregulated and the kidney is retaining most of its filtered sodium. In small studies, a $FE_{Na} < 0.5\%$ predicted improvement of hyponatraemia with saline administration [96, 97]. When glomerular filtration rate is high and sodium intake is low, FE_{Na} may also be suppressed, even in the absence of hypovolaemia. The addition of a low (< 55%) fractional excretion of urea (FE_{Urea}) or a low (< 12–17%) fractional excretion of uric acid (urate) (FE_{UA}) to an $FE_{Na} < 0.5\%$ improves specificity for saline responsiveness [38, 96, 97].

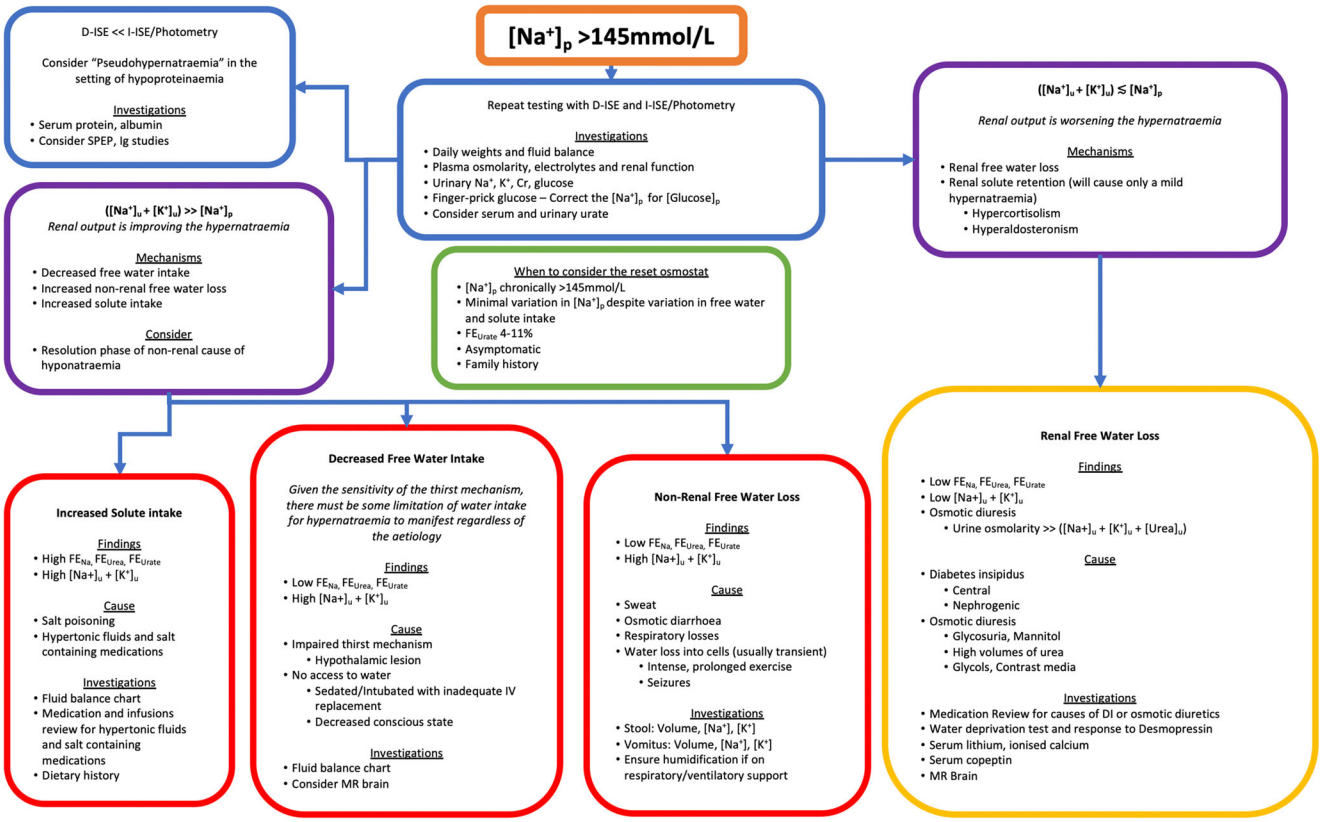

Fig. 10 An approach to the diagnosis of hyponatraemia. DI, diabetes insipidus; D-ISE, direct ion-sensitive electrode; ECF, extracellular fluid; FE_{Na}, fractional excretion of sodium; FE_{Urate}, fractional excretion of urate; I-ISE, indirect ion-sensitive electrode; MR, magnetic resonance imaging; SPEP, serum protein electrophoresis

Tracking of FE_{Na} and $[Na^+]_u$ after a volume loading can also be useful, as SIAD is associated with an increase in FE_{Na} but persistently elevated $[Na^+]_u$.

Differentiation between SIAD and CRSW using FE_{Na} or FE_{UA} unfortunately can only be performed retrospectively after correction of serum sodium (FE_{urate} corrects in SIAD, while is persistently elevated in CRSW), limiting its clinical utility [87, 88]. Non-specific markers of the volume depletion of CRSW (cf. SIAD) include an elevated urea/creatinine ratio and haematocrit.

Symptoms of dysnatraemia

Cerebral symptoms in dysnatraemias [43] (Fig. 15) are related to the degree of dysnatraemia and the tempo at which it developed, with more acute and severe changes associated with worse symptoms [13].

Management of hyponatraemia

Treatment of hyponatraemia (Fig. 16) depends on clinical context. Those with cerebral symptoms should be treated urgently with hypertonic solutions. After SAH, volume restriction increases the risk of DCI and alternative treatments are required [140]. In individuals with hypovolaemic hyponatraemia with renal salt wasting (CRSW or other), free-water restriction must be employed in concert with volume replacement to avoid worsening hypovolaemia. In most other clinical contexts, free-water restriction should be considered first-line therapy. Additional therapies include increasing effective osmole intake and possibly increasing EFWC using loop diuretics or antagonists of the AVP axis. These should be used judiciously and only employed when EFWC is low (< 500 ml/day) or negative. Given that the equations predicting the response of $[Na^+]_p$ to treatment are not accurate [48, 78], we suggest monitoring of serum and urinary electrolytes every 1–2 h during active treatment and twice daily when treating with free-water restriction alone.

Symptomatic hyponatraemia

Symptomatic hyponatraemia should always be treated by intravenous hypertonic fluid (e.g. 3% saline). The goal is to rapidly increase $[Na^+]_p$ by 4–6 mmol/L to prevent progression of cerebral oedema and herniation [128]. The guidelines recommend infusion of 150 ml of 3% saline over 20 min, followed by a repeat infusion once a repeat plasma sample has been

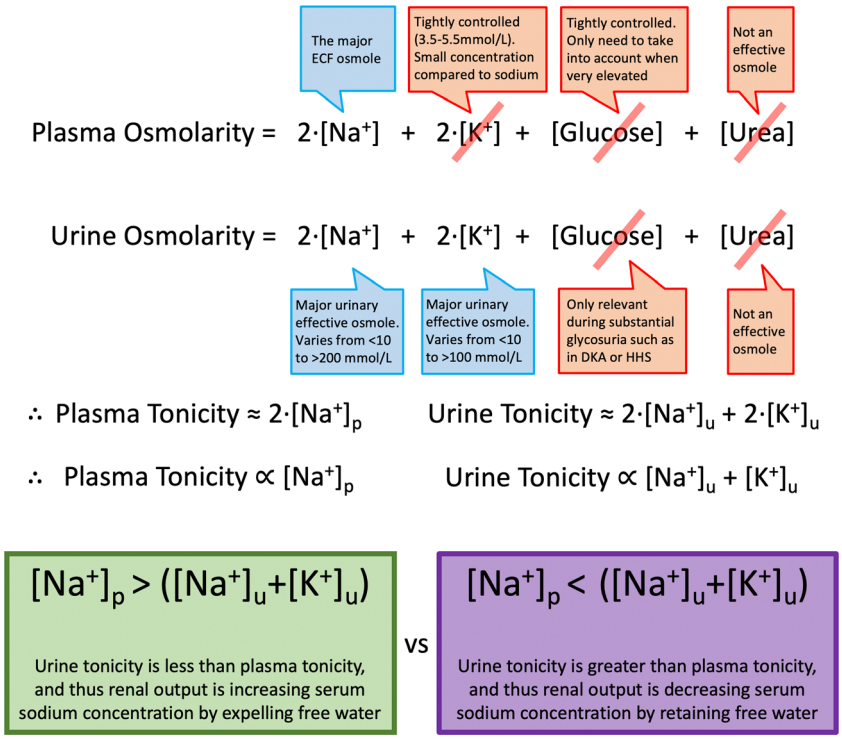

Fig. 11 Derivation of plasma and urine tonicity. The osmolarity of both plasma and urine differs from their tonicity by the inclusion of urea, which is an ineffective osmole. Plasma tonicity can be simplified to twice the sodium concentration given that potassium and glucose levels are highly regulated within a narrow range. Urine tonicity can be approximated to twice the sodium potassium sum, as substantial glycosuria occurs only in the setting of profound hyperglycaemia or a Fanconi syndrome. We can halve these approximations to more easily compare urinary tonicity ($[Na^+]_p$ and $[K^+]_p$) to plasma tonicity $[Na^+]_p$. DKA, diabetic ketoacidosis; ECF, extracellular fluid; HHS, hyperglycaemic hyperosmolar syndrome

taken [125]. This process should be repeated until a 5 mmol/L rise in $[Na^+]_p$ has been achieved. Infusion of 3% saline should then be continued until symptoms resolve or a 10 mmol/L rise in plasma sodium has been achieved, aiming for a rise of 1 mmol/L/h.

Hyponatraemia in the setting of intracranial catastrophe

Volume restriction in the presence of intracranial catastrophe is associated with poor outcome [140], and the treatment for hyponatraemia in these settings is salt. The volume state should be maintained with isotonic (0.9%) saline, and all efforts should be made to limit the administration of hypotonic fluids (such as reconstituting medications in saline as opposed to dextrose solutions). Free-water should be restricted as much as possible. If EFWC is substantially negative, or $[Na^+]_p$ continues to decline, second-line agents include salt tablets, continuous, slow infusion of 3% saline (e.g. 20 ml/h) and mineralocorticoids (fludrocortisone) [107]. The latter has not been shown to improve outcome after SAH [94, 120] and may increase the risk of hypokalaemia.

Free-water restriction

Restriction of free-water intake reduces EFWI and thus EFWB, therefore ameliorating hyponatraemia. Restriction of free-water intake is often all that is required to treat hyponatraemia when the volume restriction can reasonably be made lower than EFWC. The restriction of free-water intake must be lower than EFWC to be effective in isolation; thus, in those with low (e.g. < 500 ml per day) or negative EFWC, an additional strategy is commonly employed.

Intravenous volume replacement

When volume depletion is driving AVP secretion, intravenous crystalloid volume replacement facilitates physiological suppression of AVP secretion. Those with a reduced $FE_{Na/UA/Urea}$ have an upregulated RAA axis and will likely respond to volume replacement. Those with a normal or elevated $FE_{Na/UA/Urea}$ may be renally salt wasting (respond to volume replacement) or have SIAD (worsen with fluid administration). Because differentiation is impossible biochemically, volume replacement should only be trialled after free-water restriction alone is unsuccessful and clinical suspicion of SIAD is low, as hyponatraemia from SIAD may worsen with crystalloid.

Increasing effective osmole intake

Effective osmoles (salt tablets or hypertonic saline infusion) can be conceptualized as decreasing EFWI (and EFWB). These are particularly useful in individuals with negative EFWC, where free-water restriction alone is insufficient. In the asymptomatic, salt tablets or high-dose urea [31] provide a noninvasive method of increasing effective osmole intake, so long as the dose is great enough to saturate urea transport

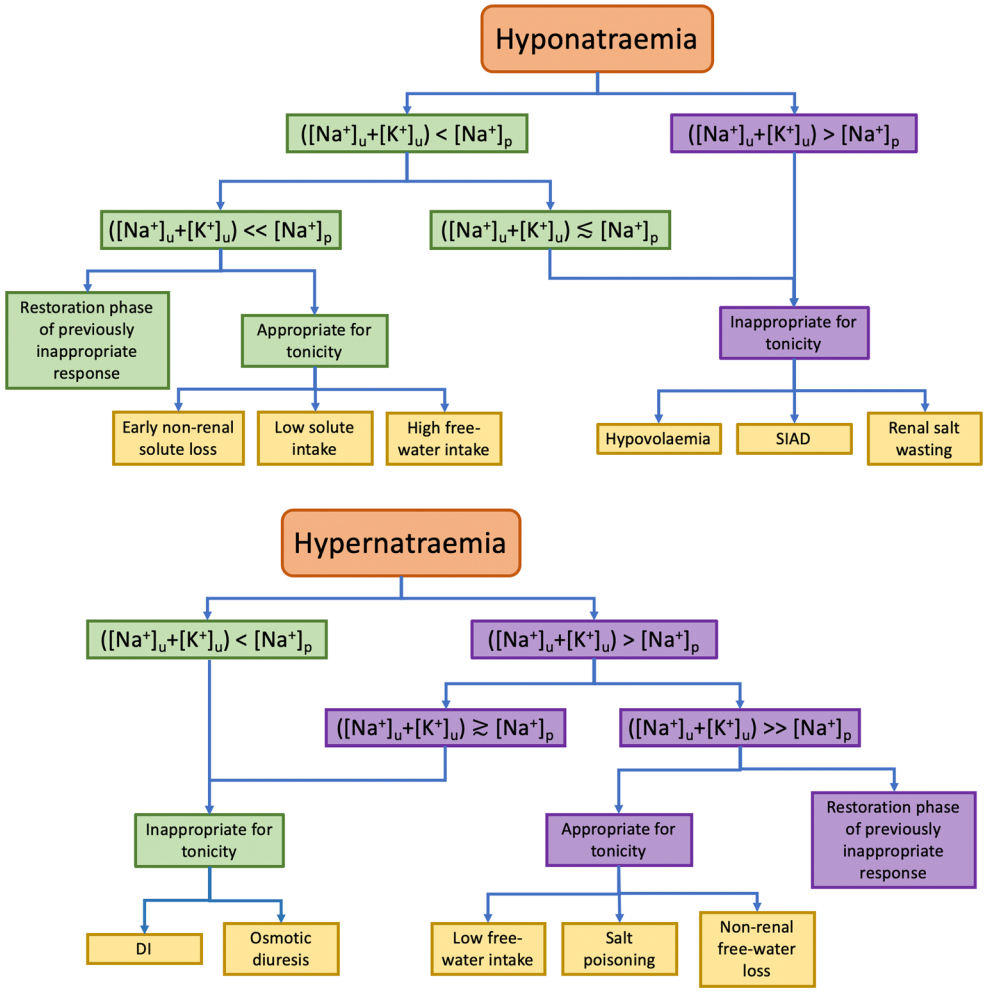

Fig. 12 Using the urinary sodium potassium sum to classify dysnatraemias. When the urinary sodium ($[Na^+]_u$) potassium ($[K^+]_u$) sum is greater than the serum sodium (i.e. $([Na^+]_u + [K^+]_u) > [Na^+]_p$) (purple boxes), renal output is causing free-water to be retained and AVP levels are high. In the setting of hyponatraemia, whether this elevated AVP is an appropriate physiological response to a decreased effective volume state or is non-physiological (i.e. SIAD) requires further investigation. Furthermore, a urinary sodium potassium sum that is slightly less than the serum sodium in a hyponatraemic individual is still grossly abnormal, as ADH should suppress completely, and points towards renal free-water retention (see Appendix 1). In the setting of hypernatraemia, this is the appropriate physiological response and the cause of the hypernatraemia is likely non-renal. The caveat is a previously renally driven process that resolves prior to testing, where only the restorative phase is captured biochemically. Conversely, when the urinary sodium potassium sum is less than the serum sodium (i.e. $([Na^+]_u + [K^+]_u) < [Na^+]_{pw}$) (green boxes), renal output is causing excretion of free-water, and AVP levels are low (or the kidney is not responding appropriately to circulating AVP, i.e. nephrogenic DI). In the setting of hyponatraemia, this suppressed AVP is an appropriate physiological response and the cause is likely non-renal (with the same caveat as above). In the setting of hypernatraemia, this lack of AVP effect is pathological and points to a lesion along the AVP axis, from hypothalamus to kidney

mechanisms in the collecting duct [40]. Salt tablets and urea have both successfully been used in chronic SIAD resistant to fluid restriction [81]. Of interest, high-dose urea (15 g) has been shown to simultaneously reduce intracranial pressure (ICP) and raise $[Na^+]_p$ in hyponatraemic patients with intracranial catastrophe [11]. Crucially, salt tablets or other effective osmoles are not appropriate in hypervolaemic hyponatraemia. Here, there is adequate (if not surplus) total body effective osmoles; they are just not in the intravascular space. Management here relies on improvement of haemodynamics through vasomediators, albumin and diuretics.

Increasing urinary free-water clearance

Loop diuretics, by virtue of interfering with the countercurrent concentrating mechanism of the nephron, ameliorate the fixed urinary diluting capacity seen with increased AVP. Thus, when combined with increased solute intake, they can augment treatment in SIAD. Importantly, they also increase kaliuresis, and serum potassium should be monitored throughout therapy.

EFWC can be increased by V2-antagonists ("-vaptans"), useful in those with a negative EFWC but dangerous in those with hypovolaemic hyponatraemia. The role of vaptans in

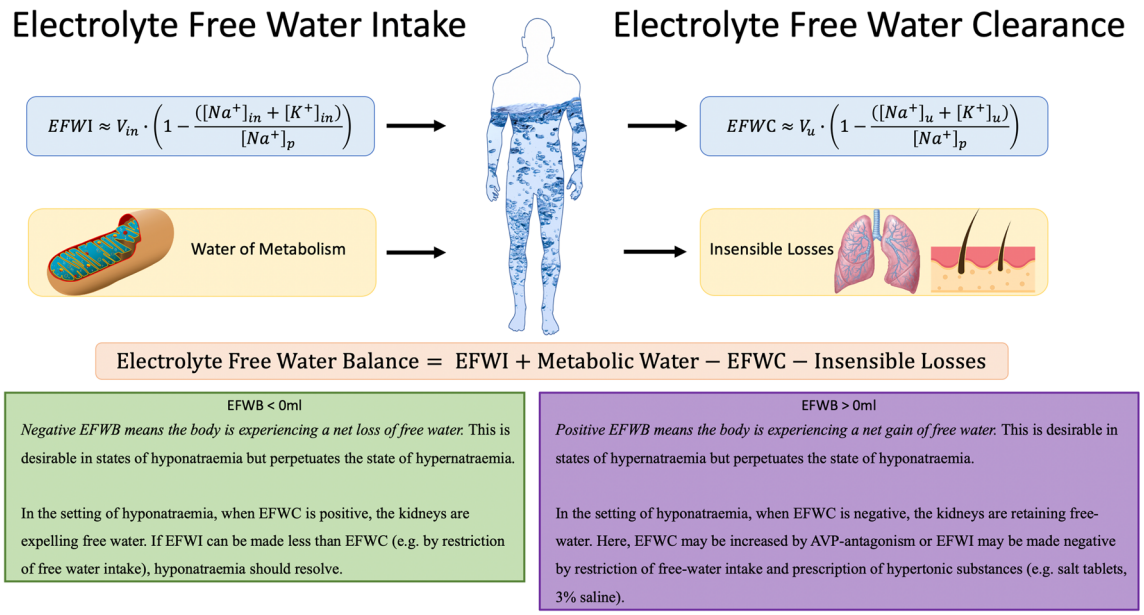

Fig. 13 Electrolyte free-water balance. The fluids that enter and exit the body can be described as being comprised of two components, one that is isotonic to plasma, and another that is (electrolyte) free-water. This is true for urine volume (V_{urine}) where the free-water component is termed the electrolyte free-water clearance (EFWC). When EFWC is positive, this is the volume of free-water being excreted per unit time (e.g. per day) by the kidney; when negative, it is the volume of free-water being retained by the kidney. Insensitive losses (trans-epidermal and respiratory) must also be considered in the clearance pathways of free-water. Sweat and gastrointestinal losses also contribute; however, they contain variable amounts of solute. Electrolyte free-water intake (EFWI) is conceptually similar to EFWC, being the amount of free-water entering the body through the volume of food and drink intake (V_{in}). Production of metabolic water is an additional source of free-water. Electrolyte free-water balance (EFWB) has therefore been defined as the difference between EFWI and EFWC

acute symptomatic hyponatraemia has not been established as this has been an exclusion criterion in all clinical trials. In a meta-analysis of 14 studies [111], vaptans increased serum sodium by 5.27 mEq/L (95% CI: 4.27–6.26) and EFWC by 67.8 ml/h (95% CI: 50.2–85.4) over the first 3–7 days; however, there was significant heterogeneity between studies ($I^2 = 70\%$ and 35%, respectively). Resistance to vaptans may be observed with excessive free-water intake, high AVP levels, diminished distal renal tubular flow and activating mutations of the V2-receptor [62]. Inhibition of endothelial V2

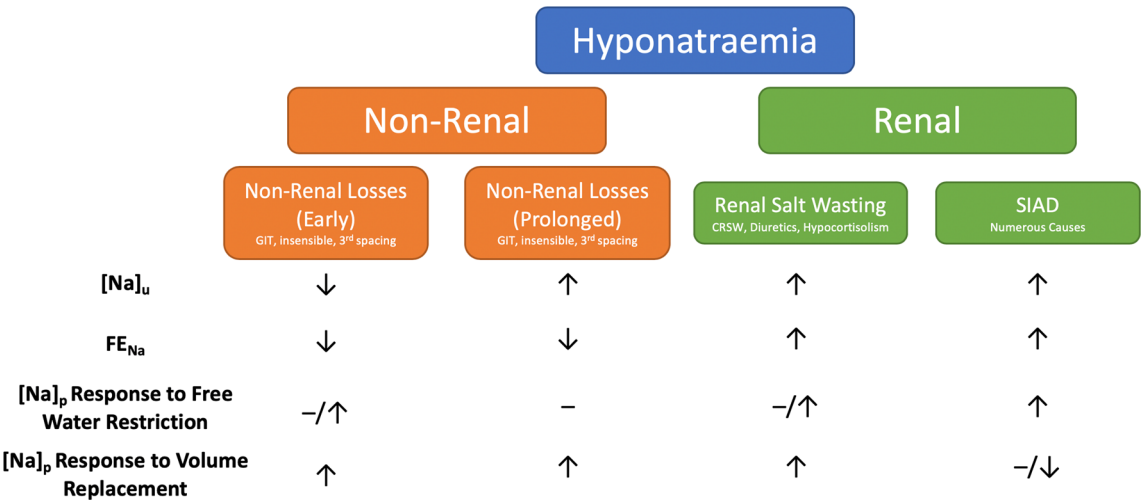

Fig. 14 Differentiating the common causes of hyponatraemia based on FE_{Na} and response to therapy. Prolonged and severe hypovolaemia can cause a high urinary sodium due to very high levels of AVP. A low FE_{Na} predicts a good response to volume replacement. CRSW, cerebral renal salt wasting; FE_{Na}, fractional excretion of sodium; GIT, gastrointestinal tract; SIAD, syndrome of inappropriate antidiuresis

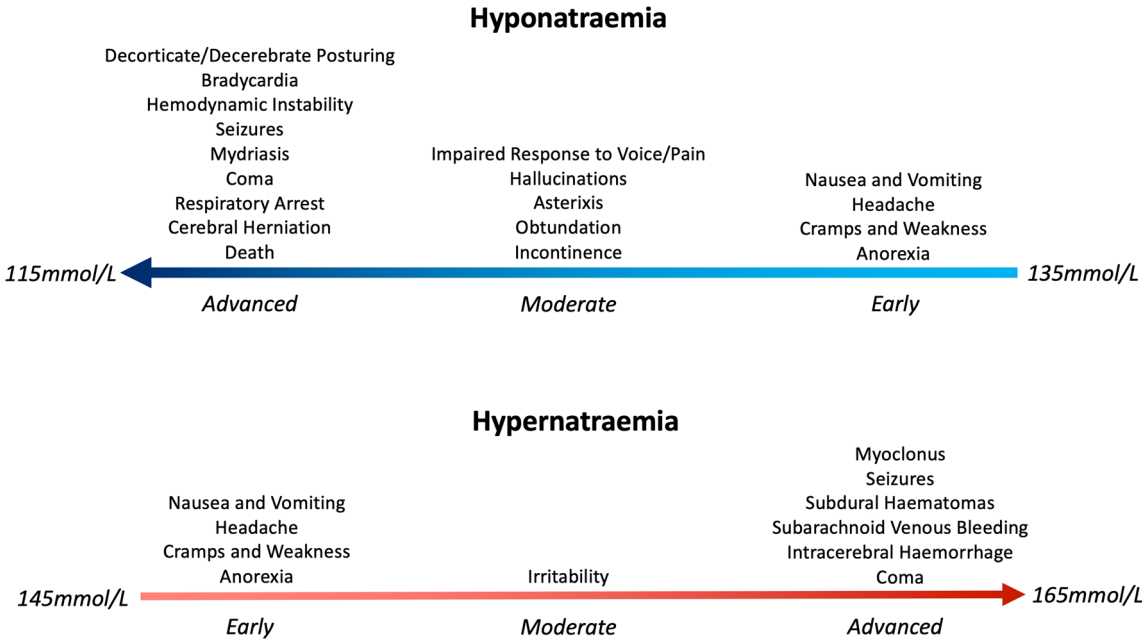

Fig. 15 Symptoms of hyponatraemia and hyponatraemia. Note that acute changes in tonicity generally present with earlier, more severe symptoms. Cerebral symptoms of dysnatraemias generally occur in those in whom a precipitous drop in $[Na^+]_p$ occurred within 48 h, as it is thought that this is the length of time neurons and glia require to alter their intracellular tonicity to match that of the ECF. In a study of 65 individuals with $[Na^+]_p < 128$ mmol/L, all those in whom the hyponatraemia developed within 48 h were symptomatic. For those in whom the hyponatraemia was chronic (present for >48 h), symptomatic individuals had a mean $[Na^+]_p$ of 115 mmol/L (cf. 122 mmol/L in the asymptomatic). All individuals in whom seizures developed had a $[Na^+]_p < 121$ mmol/L. Precipitous rises in plasma sodium concentration are associated with a rapid decrease in brain volume leading to rupture of cerebral vessels and consequently intracerebral, subdural and subarachnoid haemorrhages, as well as osmotic demyelination

may promote bleeding [1], and conivaptan, which also inhibits the V1a receptor, may particularly promote bleeding given the role of the V1a receptor in platelet aggregation [58]. Given their variable efficacy and potential for uncontrolled aquaresis, "vaptans" are not recommended for routine use in hyponatraemia.

Management of hypernatraemia

Our approach to the treatment of hypernatraemia (Fig. 17) depends on clinical context. Those with cerebral symptoms due to hypernatraemia must be treated urgently with free-water and consideration of DDAVP. In asymptomatic individuals, slow correction (< 6 mmol/L/day) is associated with greater morbidity [8] while overzealous correction (> 24 mmol/L/day) may be associated with cerebral oedema [37]. The volume state is more often deranged than in hyponatraemia and thus should be corrected simultaneously.

Acute, symptomatic hypernatraemia

Acute hypernatraemia due to DI or salt intoxication may be symptomatic. Free-water in the form of intravenous 5% dextrose should be given, and an initial rate of 4–6 ml/kg/h is reasonable. Because of the time required for cerebral adaptation, $[Na^+]_p$ may be rapidly normalized with impunity. DDAVP may be required as an adjunct in those with central DI.

Free-water

The thirst mechanism will generally maintain plasma tonicity within a narrow range, and thus hypernatraemia is seen primarily in individuals who cannot experience or respond to thirst normally; this may be exacerbated by diuretics, vomiting or diarrhoea [102]. In asymptomatic individuals with adequate mentation, free oral water is appropriate. Five percent of dextrose is equivalent to free-water and may be given intravenously at a rate of 1–1.5 ml/kg/h. Hyperglycaemia is a potential complication of large dextrose loads and may cause a transient fluid shift that obfuscates the true severity of the hypernatraemia. Plasma glucose should be measured at the same intervals as electrolytes, and 5% dextrose may be replaced with pure water infused directly into the right atrium in refractory hyperglycaemia.

AVP analogues

AVP analogues should be utilized in central DI when it is difficult to match urinary losses with oral intake, such as with impaired mentation or large urinary losses, especially

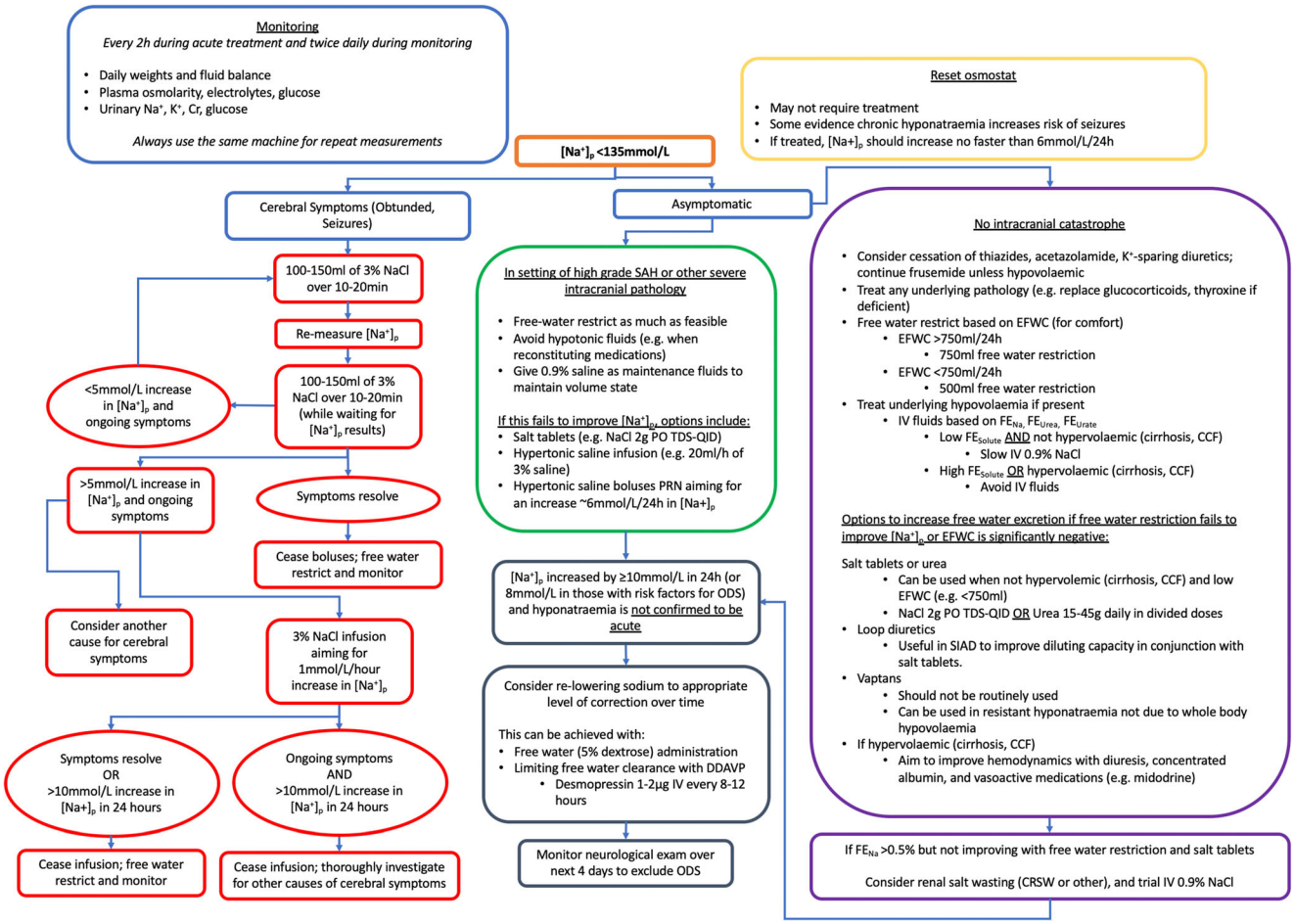

Fig. 16 An approach to the management of hyponatraemia. Note the early and important distinction between those with acute and symptomatic hyponatraemia and those with chronic and asymptomatic hyponatraemia. Those with cerebral symptoms should be treated urgently with hypertonic solutions. After SAH or other intracranial catastrophes, free-water restriction increases the risk of DCI and alternative treatments are required. In individuals with hypovolaemic hyponatraemia with renal salt wasting (CRSW or other), free-water restriction must be employed in concert with volume replacement to avoid worsening hypovolaemia. In most other clinical contexts, free-water restriction should be considered first-line therapy. Additional therapies include increasing effective osmole intake and possibly increasing EFWC using loop diuretics or antagonists of the AVP axis. These should be used judiciously and only employed when EFWC is low (< 500 ml/day) or negative. CCF, congestive cardiac failure; CRSW, cerebral renal salt wasting; DDAVP, desmopressin; EFWC, effective free-water clearance; FE_{Na}, fractional excretion of sodium; IV, intravenous; ODS, osmotic demyelination syndrome; PO, per oral; PRN, as needed; SAH, subarachnoid haemorrhage; SIAD, syndrome of inappropriate antidiuresis; TDS, three times a day; QID, four times a day

overnight. Desmopressin is the most common agent, available as a tablet, nasal spray and injectable. Duration of effect depends on dose and route of administration with moderate inter-individual variability.

Effective osmole restriction and effective osmole excretion

Less commonly, hypernatraemia may occur due to excessive effective osmole intake. This hypernatraemia can only be sustained if accompanied by either impaired access to free-water or renal dysfunction because of hypovolaemia or concentrating defect. Here, treatment consists of reduction of unnecessary effective osmole intake, provision of free-water and creation of negative cation balance using thiazides or, if necessary, renal replacement therapy.

Complications of dysnatraemia management

Osmotic demyelination syndrome

If the magnitude and rapidity of correction of chronic hyponatraemia (present for > 48 h) is too great, pontine and extrapontine myelinolysis occur, presenting as rapidly progressive paraparesis or tetraparesis with pseudobulbar findings, usually delayed 2–6 days after correction (Fig. 18). An increased risk of ODS is seen in those with substantial hyponatraemia ($[Na^+]_p < 105$ mmol/L), hypokalaemia,

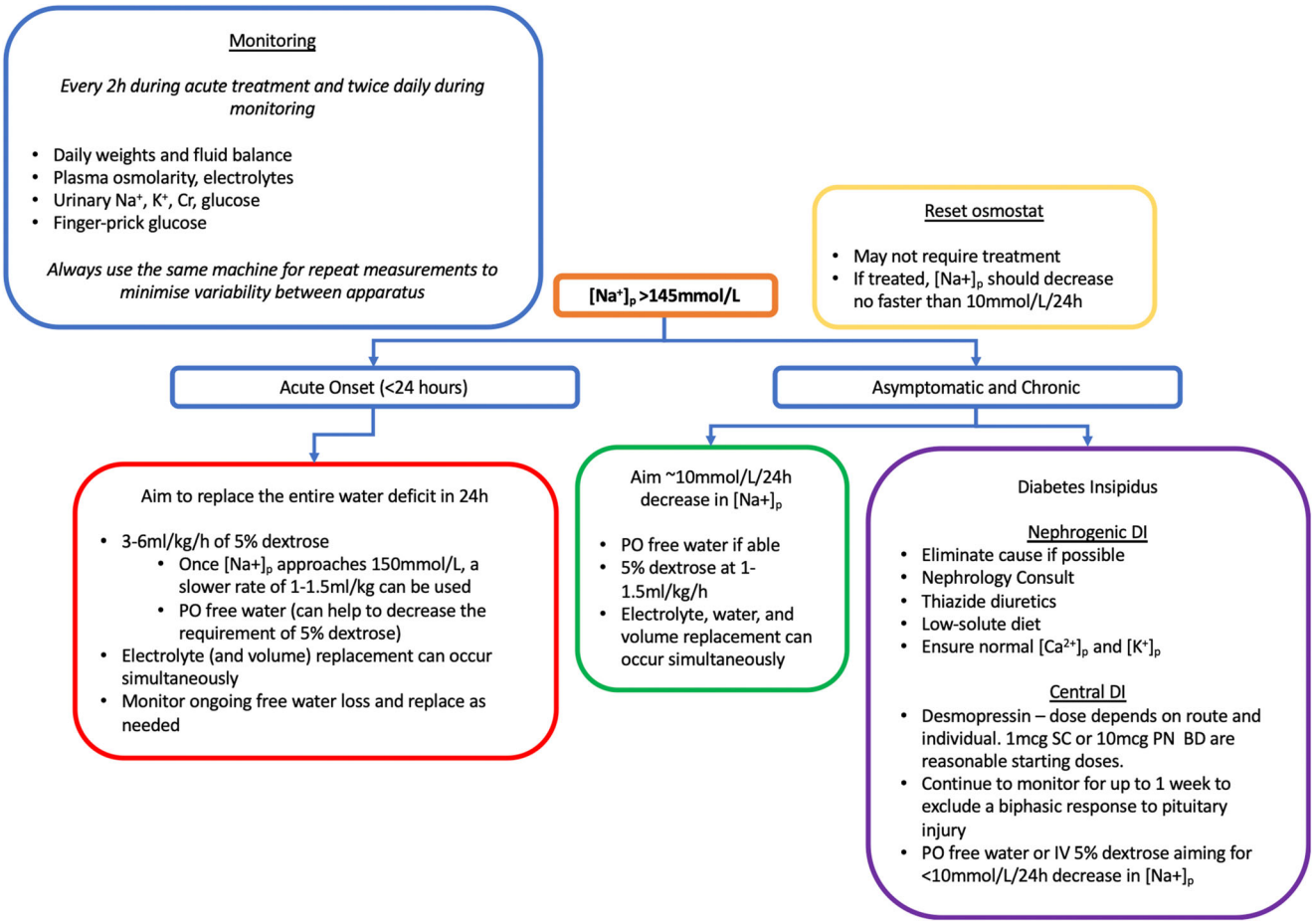

Fig. 17 An approach to the management of hypernatraemia. DI, diabetes insipidus; IV, intravenous; PO, per oral

alcoholism, malnutrition and cirrhosis [136]. Generally, ODS does not occur unless $[Na^+]_p$ rises by > 10 mmol/L in 24 h or > 18 mmol/L in 48 h [83]; however, in asymptomatic individuals, there is no benefit in raising the serum sodium at > 6 mmol/L/24 h [12]. Thus, for asymptomatic individuals, we avoid a rise in $[Na^+]_p$ by > 10 mmol/L/24 h, while in high risk groups (vide supra) a more conservative goal (e.g. < 6–8 mmol/L/24 h) is appropriate. Overcorrection of $[Na^+]_p$ can be promptly reversed with 5% dextrose or DDAVP. These individuals should be managed in an intensive care unit with endocrinologist and intensivist input.

Cerebral oedema

Cerebral oedema occurs if the magnitude and rapidity of correction of chronic, generally severe (> 155 mmol/L) hypernatraemia, are too great and relative reduction in tonicity results in cellular swelling. Unlike hyponatraemia, there is no clear evidence in adults for limiting the rate of correction [127]. Indeed, correction at a rate of > 0.5 mmol/L/h (> 12 mmol/L/day) produced similar outcomes to more conservative sodium lowering [22]. If signs of increased ICP do occur, a hypertonic saline bolus can be administrated.

Conclusion

A summary of the take-home points regarding the diagnosis and management of disorders of water balance in neurocritically ill patients is given below.

Normal physiology

- The renal renin-angiotensin-aldosterone axis (RAA) is the primary mechanism of volume (combined solute and solvent) homeostasis. Increased RAA activity leads to volume retention with no substantial change in free-water balance as both solute and solvent are retained concurrently.
- The central AVP axis is the primary mechanism of free-water homeostasis. AVP secretion causes free-water retention and thus an altered balance of solute to solvent, leading to decreased plasma sodium (solute) concentration.
- AVP maintains tonicity unless substantial (> 10%) hypovolaemia occurs. Then, defence of tonicity is sacrificed for the defence of volume, and the body must tolerate hypotonicity to maintain euvolaemia.
- Sodium, potassium and free-water flux are the primary determinants of the serum sodium concentration.

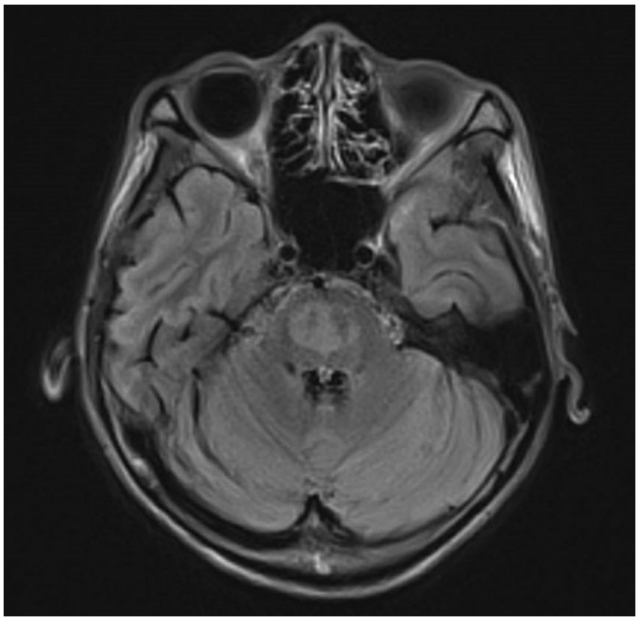

Fig. 18 Typical appearance of pontine osmotic demyelination. This patient presented with a $[Na^+]_p$ of 107 mmol/L in the setting of malnutrition and primary polydipsia. Over the course of 24 h, $[Na^+]_p$ rose 18 mmol/L, and in 48 h it had normalized. Three days after presentation, the patient became comatose, and MR imaging (T2-FLAIR sequence shown) demonstrated pontine myelinolysis

- Urea is not an effective osmole and thus urinary osmolarity does not correlate well with urinary tonicity. The latter is the clinically important variable

Pathological states

- Hyponatraemia is a disorder of too much free-water; hypernatraemia is a disorder of too little free-water. Thus, plasma sodium concentration is an effective marker of total body free-water.
- Hypernatraemia will only occur in the setting of an impaired thirst mechanism or inadequate access to free-water.

Analysis

- The sodium concentration in the blood is slightly greater than that of the interstitial fluid due to the pull of plasma proteins (Gibbs-Donnan effect). This is negated by compensatory underestimation of plasma water sodium by measurement devices.
- In states of hyperlipidaemia, hyperproteinaemia or hypoproteinaemia, sodium values reported on formal pathology may be spuriously low or high, respectively, due to alteration of the ratio of plasma water to solid phase.
- Psuedohyponatraemia and pseudohypernatraemia should *not* be considered when analysing results from point-of-care analysers ("blood-gas machines").
- Effective osmoles in large concentrations, such as glucose, mannitol and glycols, may produce translocational hyponatraemia or hyperosmolar hyponatraemia.
- Always correct the serum sodium for the glucose concentration in the setting of hyperglycaemia.

Clinical points

- In the absence of overt volume overload (peripheral pitting and/or alveolar oedema) or overt hypovolaemia (hypotension, postural hypotension and tachycardia), the volume state is very difficult to discern clinically.
- Medications and fluid losses other than urine are often overlooked causes of hyponatraemia.
- All hyponatraemias should be presumed to be chronic unless these is biochemical evidence of its acuity (i.e. a normal serum sodium within the last 48 h).

Assessment

- Dysnatraemias can be classified by the flux of water and solute and by the renal response to dysnatraemia.

  When $([Na^+]_u + [K^+]_u)$ exceeds $[Na^+]_p$, renal output is causing free-water to be retained.
  When $([Na^+]_u + [K^+]_u)$ is less than $[Na^+]_p$, renal output is causing excretion of free-water.
  When $([Na^+]_u + [K^+]_u)$ is much less than $[Na^+]_p$, absolute (or functional) AVP levels are low.
  When ([Na+]u + [K+]u) appraoches or exceeds $[Na^+]_p$, AVP is being secreted

- When EFWC is negative, the kidney is retaining free-water, lowering the serum sodium concentration. Conversely, when EFWC is positive, the kidney is excreting free-water.
- If free-water intake is greater than EFWC and the balance of insensate losses and metabolic water, serum sodium will fall. Thus, free-water restriction should be based on EFWC and, when substantial, GI losses.
- AVP activation is seen in severe hypovolaemia (renal and non-renal salt wasting) and SIAD and is associated with an elevated $[Na^+]_u$.

Management

- As a rule of thumb, the volume state can be controlled with normal saline, while water balance can be controlled with free-water restriction or salt (salt tables, hypertonic saline).
- Individuals with intracranial catastrophe and moderate/severe hyponatraemia should be treated with salt and volume replacement, as volume restriction is associated with poor outcome.

- Patients with cerebral symptoms (decreased conscious state or seizures) due to hyponatraemia should be treated with hypertonic saline.
- Those with asymptomatic hyponatraemia should be initially treated with free-water restriction.
- Options when free-water restriction alone fails to improve hyponatraemia include adding salt (salt tables, hypertonic saline), loop diuresis or AVP antagonism (in descending order of safety).
- Those in which hypovolaemia is thought to be driving AVP secretion in hypontraemia should receive volume replacement. This can be safely administered when [Na+]u is low (e.g. <20). When [Na+]u is elevated (e.g. >40), hypovolaemia may still be driving the hyponatraemia, but SIAD needs to be considered. If volume replacement is trialled, [Na+]p should be monitored closely.
- Those with obvious hypervolaemia and hyponatraemia should be free-water restricted and the volume state corrected as possible.
- Overcorrection of sodium in patients with chronic hyponatraemia (present > 48 h), defined as > 10 mmol/L in 24 h or > 18 mmol/L in 48 h, introduces the risk of osmotic demyelination syndrome. Patients with hypokalaemia, alcoholism, malnutrition and cirrhosis are at increased risk, and a target of 6–8 mmol/L/day is presumed to be safest.
- Hypernatraemia should be treated with free-water, preferably orally if tolerated. AVP analogues can be used when oral intake cannot match urinary losses.
- Evidence for limiting the rate of correction in hypernatraemia is lacking in adults. However, limits from studies in the paediatric population are commonly applied to adults (e.g. < 12 mmol/L/day).

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Compliance with ethical standards

Conflict of interest The authors have no conflicts of interest to disclose.

Ethics approval Not applicable.

Consent to participate Not Applicable.

Consent for publication Not applicable.

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