

The Challenge of Hyponatremia

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ABSTRACT

Treatment of hypotonic hyponatremia often challenges clinicians on many counts. Despite similar serum sodium concentrations, clinical manifestations can range from mild to life threatening. Some patients require active management, whereas others recover without intervention. Therapeutic measures frequently yield safe correction, yet the same measures can result in osmotic demyelination. To address this challenge, we present a practical approach to managing hyponatremia that centers on two elements: a diagnostic evaluation directed at the pathogenesis and putative causes of hyponatremia, the case-specific clinical and laboratory features, and the associated clinical risk; and a management plan tailored to the diagnostic findings that incorporates quantitative projections of fluid therapy and fluid losses on the patient's serum sodium, balances potential benefits and risks, and emphasizes vigilant monitoring. These principles should enable the clinician to formulate a management plan that addresses expeditiously three critical questions: Which of the determinants of the serum sodium are deranged and what is the underlying culprit? How urgent is the need for intervention? What specific therapy should be instituted and which are the associated pitfalls?

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Hypotonic hyponatremia, the most common and relevant form of the disorder, often challenges clinicians. Little information might be available at presentation about the patient and the prevailing hyponatremia other than its severity. One or several predisposing conditions might participate in the generation of hyponatremia. Clinical manifestations can vary widely despite similar serum sodium concentrations. Some patients require active management, whereas others recover without intervention. Therapeutic measures frequently yield safe correction, yet the same measures can result in osmotic demyelination. The challenge to the clinician is commonly heightened by major comorbidities such as hepatic encephalopathy or potassium depletion.

Recent developments in hyponatremia, including epidemiologic insights, newly

recognized adverse effects, and the introduction of vaptans (vasopressin receptor antagonists), have rekindled physician interest in the disorder and could improve its management.^{1–9} Notwithstanding, current medical care frequently proves suboptimal resulting in adverse consequences of either hyponatremia or its treatment both in adults and children.^{10–17} Relowering the serum sodium has been introduced to address the not uncommon overcorrection of hyponatremia.^{18–20} Even preventive administration of desmopressin, a hormone that can actually aggravate hyponatremia, has been proposed to counter the risk of overcorrection.^{21,22}

We contend that confronting the challenge of hyponatremia requires a two-pronged approach. First, a diagnostic evaluation is aimed at identifying the

pathogenesis and putative cause(s) of hyponatremia, the case-specific clinical and laboratory features, and the associated clinical risk. Second, a management plan is tailored to the diagnostic findings that incorporates quantitative projections of prescribed fluid therapy and ongoing fluid losses on the patient's serum sodium, balances potential benefits and risks, and emphasizes vigilant monitoring. Here we present a practical approach to managing hyponatremia that centers on these principles.

DIAGNOSTIC EVALUATION

Estimating the State of the Determinants of the Decreased Serum Sodium

The serum sodium concentration is approximated by the sum of the exchangeable (osmotically active) portions of the body's sodium and potassium content divided by total body water (Edelman equation; Figure 1).^{23,24} Maintenance of serum sodium occurs as a by-product of matching the intake of sodium, potassium, and water with the corresponding losses. The Edelman equation establishes that hypotonic (or dilutional) hyponatremia represents an excess of water relative to

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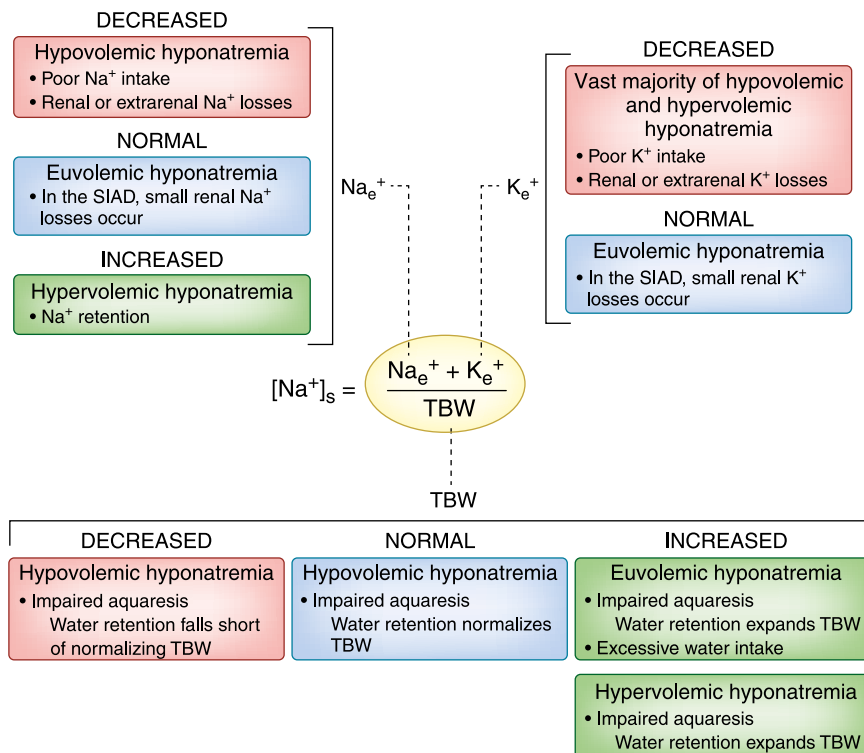


Figure 1. Pathogenesis of hypotonic hyponatremia as derived from the Edelman equation. Hypotonic hyponatremia represents an excess of water relative to the body's sodium and potassium stores. In that context, patients with hypotonic hyponatremia can feature decreased, normal, or increased Na_e^+ ; decreased or normal K_e^+ ; and decreased, normal, or increased TBW. Na_e^+ , exchangeable sodium; K_e^+ , exchangeable potassium; TBW, total body water.

the sodium and potassium stores. Water retention usually results from impairment of renal excretion of electrolyte-free water (aquaresis); less commonly, it is caused by excessive intake of water while excretory capacity is normal or nearly normal.²⁵

In hyponatremia caused by water retention, sodium and potassium stores remain essentially unchanged but body water is increased; these patients exhibit euvolemic hyponatremia, including the syndrome of inappropriate antidiuresis (SIAD) and some endocrinopathies.^{25–27} Renal or extrarenal fluid losses deplete sodium, potassium, and water stores; subsequent water retention results in hyponatremia. These patients exhibit extracellular fluid volume contraction. Conversely, retention of sodium and water in edematous disorders can also be associated with hyponatremia, which reflects a disproportionate increase in

body water. Loss of potassium depletes intracellular stores, leading to transfer of sodium from the extracellular to the intracellular fluid and generating hyponatremia coupled with hypokalemia. Not infrequently, all three determinants might contribute to decreasing serum sodium. The clinician must collect the relevant clinical information and laboratory data to infer the state of these determinants in the individual case of hyponatremia.

Unraveling the Predisposing Condition and the Effector of Hyponatremia

Generation of hypotonic hyponatremia occurs as a by-product of unmatching the electrolyte (sodium and potassium) and water content of all intake and output such that a net gain of electrolyte-free water relative to the body's sodium and potassium stores ensues (Figure 2).

Numerous conditions can impose an aquaretic defect and thus predispose to hyponatremia.^{25,28} Notwithstanding, an effector must be superimposed that would result in a positive electrolyte-free water balance. Typically, the effector is intake of electrolyte-free water in amounts that exceed the composite of renal and extrarenal electrolyte-free water losses. The medical history should provide clues about the predisposing conditions, including an underlying acute or chronic disease, as well as fluid and electrolyte intake and losses, protein intake, changes in body weight, medications (thiazides, selective serotonin reuptake inhibitors), and previous diagnosis of hyponatremia. Physical examination allows assessment of extracellular fluid volume status and identification of signs characteristic of predisposing conditions. Ancillary tests may include serum electrolytes, BUN, creatinine, uric acid, serum and urine osmolality, serum cortisol and thyroid panel, and radiologic studies (head computed tomography scan or magnetic resonance imaging).

Measuring urine electrolytes and computing the urine/serum (U/S) electrolyte ratio, which is the sum of the urinary concentrations of sodium and potassium divided by the serum sodium, can point to the effect of the urine output on the level of serum sodium at the time of evaluation (Figure 3). If the ratio is approximately 1, the urine output is not affecting the serum sodium; if >1 , the urine contributes to lowering the serum sodium; and if ≤ 0.5 , it indicates that one-half or more of the urine volume amounts to electrolyte-free water and thus the urine contributes to raising the serum sodium.^{26,29} The larger the urine output, the greater the effect of a U/S electrolyte ratio $\neq 1$ on serum sodium.

Establishing the Clinical Risk of Hyponatremia

The level of serum sodium correlates inversely with clinical risk, with levels <120 mEq/L being regarded as severe hyponatremia. Clinical manifestations are dependent on the severity and acuteness of the hypotonic state.^{25,30,31} Acute

hyponatremia results in brain swelling and intracranial hypertension; it can progress to life-threatening neurologic complications, including seizures, coma, brain-stem herniation, and respiratory arrest, which can lead to permanent brain damage or death. Such progression can occur suddenly and rapidly. Symptomatic and potentially life-threatening cerebral edema is characteristically observed in euvolemic hyponatremia, including that associated with psychogenic polydipsia, the postoperative state, intracranial pathology, endurance exercise, recent administration of thiazides, induction of delivery with oxytocin, use of ecstasy (3,4-methylenedioxymphetamine), and water drinking contests.^{12,27,31–33} Young women and children are particularly vulnerable to hyponatremic brain damage.^{12,31} Noncardiogenic pulmonary edema can occur in acute hyponatremia and the resulting hypoxemia can worsen the severity of brain edema. Fortunately, adaptive processes partially restore brain volume within a few hours, with essential normalization within 2 days. As a result, hyponatremia that develops or persists over days (chronic hyponatremia) generally exhibits only modest symptomatology, including cognitive deficits, gait disturbance, and propensity to falls and fractures.^{5,6,8,31} When extreme, usually <110 mEq/L, it can manifest confusion, delirium, and rarely seizures, but not the other life-threatening complications of severe acute hyponatremia.^{30,31,34} Beneficial as it is in terms of symptoms, brain adaptation markedly increases the risk of osmotic demyelination.^{15,17,27}

The vast majority of hyponatremic patients exhibit the chronic form of the disorder, arbitrarily defined as >48 hours in duration. However, the duration of hyponatremia is commonly unknown, hyponatremia of shorter duration has already mounted substantial brain adaptation, and an acute decrease in serum sodium can be superimposed on chronic hyponatremia. When the time frame of hyponatremia cannot be established with confidence, it is safer to conclude that the hypotonic state is chronic.

THERAPEUTIC PRINCIPLES

Treating Actual or Impending Life-Threatening Complications

Severely symptomatic hyponatremia and hyponatremia in association with neurologic or neurosurgical disease of the brain represent medical emergencies; in these settings, even mild augmentation of the cerebral edema can prove catastrophic. Immediate intervention might include anticonvulsants, laryngeal intubation, oxygen administration, and ventilator support. The gravity of the condition mandates correction of the serum sodium by 4–6 mEq/L within 4–6 hours; this degree of correction can repair cerebral edema and is sufficient to reverse the most ominous complications of hyponatremic encephalopathy. This goal can be achieved with a continuous infusion of hypertonic saline (3% NaCl). Intravenous furosemide (20 mg) reduces the volume expansion resulting from the hypertonic saline.^{25–28} Instead of a continuous infusion, a 100-ml bolus of this solution, with up to two additional boluses given at 10-minute intervals depending on clinical manifestations, has been proposed.³¹ Although this strategy might be warranted under certain circumstances (severely symptomatic exercise-induced hyponatremia or impending herniation), we caution against its indiscriminate use. Administration of up to 300 ml of hypertonic saline can cause overcorrection of hyponatremia in small-sized individuals, especially if aquaresis is ongoing. Vaptans should not be prescribed in hyponatremic emergencies.

Considering the common uncertainty about the duration of hyponatremia and that overcorrection can lead to osmotic demyelination, we recommend that total correction does not exceed 6–8 mEq/L in any 24-hour period; this cutoff applies to both acute and chronic hyponatremic patients, regardless of clinical presentation and method of treatment, including active management and spontaneous correction. This is not a target of therapy, but rather a therapeutic threshold that should not be crossed. This limit ensures effective management of the most serious consequences of hyponatremic

encephalopathy, while providing a margin of protection from osmotic demyelination, a condition that can occasionally develop after correcting serum sodium by only 9–10 mEq/L in 24 hours. Although the likelihood of demyelination caused by overcorrection of acute hyponatremia is low, no clinical advantage is derived from exceeding this cutoff.^{25,27,31}

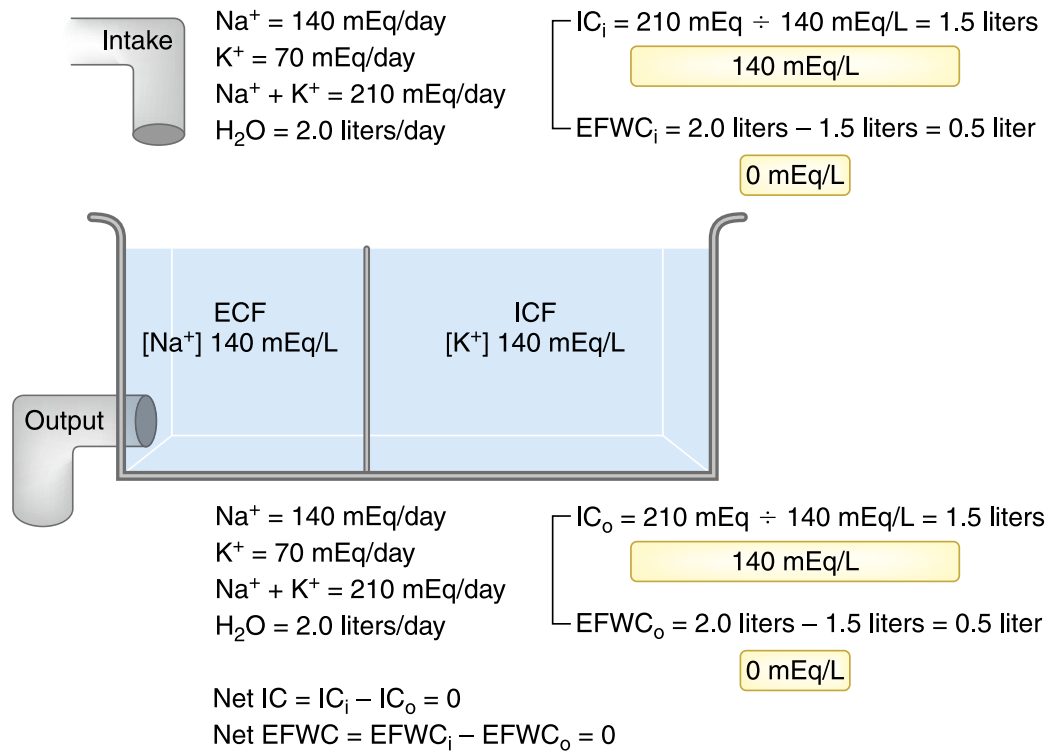
Utmost Vigilance for Preventing Osmotic Demyelination

Osmotic demyelination is a most serious demyelinating disorder typically involving the central pons (central pontine myelinolysis), but often extending into extrapontine structures (extrapontine myelinolysis).^{15,17,35,36} The root cause of this complication is overcorrection of hyponatremia that has undergone substantial brain adaptation. Its clinical manifestations, including hyperreflexia, pseudobulbar palsy, quadriparesis, parkinsonism, locked-in syndrome, and even death, arise 1–7 days after overcorrection of hyponatremia. Two or more weeks from the initial neurologic manifestations might elapse before diagnostic findings on brain magnetic resonance imaging and computed tomography become evident.

Conditions posing high risk for this dreaded complication include chronic hyponatremia of <110 mEq/L, alcoholism, hepatic failure, orthotopic liver transplantation, potassium depletion, and malnutrition.^{15,25,27,31,37} In the presence of these conditions, correction of serum sodium should not exceed 6 mEq/L in any 24-hour period. Fear of inducing osmotic demyelination from overcorrection of hyponatremia caused by excessive aquaresis has prompted the recommendation of treating severe hyponatremia with the combination of hypertonic saline and desmopressin.^{21,22,31}

We do not support this approach for several reasons. High levels of vasopressin prevail in the vast majority of hyponatremic patients and in most, this abnormality is irreversible; administering desmopressin to these patients strikes us as inappropriate and risky. Those patients with reversible SIAD (drug-induced) would be better served by close monitoring instead of perpetuating the

Normal state



	Net IC	Net EFWC	Na_e^+	K_e^+	TBW	$[\text{Na}^+]_s$
Normal State	0	0	NORMAL	NORMAL	NORMAL	NORMAL
Heart failure						
Early phase	Positive	0	INCREASED	NORMAL	INCREASED	NORMAL
Late phase	0	Positive	INCREASED	DECREASED	INCREASED	DECREASED
Diarrhea						
Early phase	Negative	0	DECREASED	DECREASED	DECREASED	NORMAL
Late phase	0	Positive	DECREASED	DECREASED	DECREASED	DECREASED
SIAD	0	Positive	NORMAL	NORMAL	INCREASED	DECREASED
Primary polydipsia	0	Positive	NORMAL	NORMAL	INCREASED	DECREASED
Potassium depletion	Negative	Positive	NORMAL/ INCREASED	DECREASED	NORMAL	DECREASED

Figure 2. Generation of hypotonic hyponatremia as a by-product of unmatching the electrolyte and water content of all intake and output. Maintenance of serum sodium occurs as a by-product of matching the electrolyte and water content of all intake and output, denoted by the subscripts i and o, respectively. Both intake and output can be viewed as composed of two components: An isotonic component (IC), which contains all the Na^+ and K^+ content distributed in a volume of water sufficient to attain a concentration identical to that of serum sodium, as well as an electrolyte-free water component (EFWC), which comprises water free of Na^+ and K^+ . The latter is computed by subtracting the corresponding IC from the total volume of water intake or output. When the IC is smaller than the total volume, the difference represents the EFWC; if larger, there is negative EFWC. In the normal state, the net IC ($\text{IC}_i - \text{IC}_o$) is zero and the net EFWC ($\text{EFWC}_i - \text{EFWC}_o$) is also zero so that $[\text{Na}^+]_s$ remains stable. When net IC becomes positive, volume expansion occurs, whereas if negative, volume contraction ensues. When net EFWC is positive, serum sodium decreases, whereas if negative, serum sodium increases. The deviations of net IC and net EFWC

[Na ⁺ + K ⁺] _u mEq/L	[Na ⁺] _s mEq/L	U/S electrolyte ratio [Na ⁺ + K ⁺] _u / [Na ⁺] _s	Impact on [Na ⁺] _s	Estimated change in [Na ⁺] _s per liter of urine		Clinical examples
				70-kg man	50-kg woman	
120	120	1.0	↔	None	None	Thiazide treatment
180	120	1.5	↓	-1.6	-2.5	SIAD
60	120	0.5	↑	1.6	2.5	Furosemide administration in heart failure
20	120	0.17	↑↑	2.7	4.2	Withholding water in primary polydipsia

Figure 3. Effect of urine electrolyte concentration on serum sodium level in hypotonic hyponatremia. Estimated change in [Na⁺]_s per liter of urine is obtained using the fluid-loss formula (Table 1) and total body water (TBW) in liters calculated as a fraction of body weight (0.55 in men and 0.5 in women). As an example, the 50-kg woman with a tumor-induced SIAD has TBW equal to 25 L; thus, the Δ [Na⁺]_s is obtained by subtracting the sum of urinary sodium and potassium from the serum sodium (120 – 180 = –60) and dividing by TBW minus 1 L (25 – 1 = 24), *i.e.*, –60 ÷ 24 = –2.5 mEq/L. Note that if the U/S electrolyte ratio is approximately 1, the urine output is not affecting the serum sodium; if >1, the urine contributes to lowering the serum sodium; and if ≤0.5, it indicates that one-half or more of the urine volume amounts to electrolyte-free water and thus the urine contributes to raising the serum sodium. The larger the urine output, the greater the effect of the U/S electrolyte ratio ≠1 on serum sodium.

antidiuresis with desmopressin. The combined strategy of hypertonic saline and desmopressin substantially increases the risk of aggravation of hyponatremia from retention of prescribed (medication diluents or tube feedings) or unprescribed hypotonic fluids. Furthermore, the sodium and water retention resulting from this strategy can cause pulmonary edema and hypoxemia, especially in elderly patients.

Repairing the Abnormal State of the Determinants of Hyponatremia

Most patients exhibit hyponatremia of indeterminate duration and variable symptomatology that deserves treatment but does not represent a medical emergency. Fluid restriction (up to <800 ml/d) must be prescribed in all patients, excluding those with ongoing aquaresis.^{26,30} For any level of fluid restriction, the lower the dietary sodium and potassium, the

higher the electrolyte-free water intake, thereby decreasing the effectiveness of this maneuver (Figure 2). Moreover, low solute intake (protein, sodium, and potassium) impairs aquaresis predisposing to hyponatremia.³⁸ In euvolemic and hypervolemic hyponatremia, fluid restriction should be complemented by a loop diuretic, which promotes aquaresis by reducing the hypertonicity of the renal medulla. The stringency of fluid restriction can be lessened with the use of vaptans, agents that antagonize the effect of vasopressin, thereby promoting aquaresis. These drugs can be administered intravenously (conivaptan, for up to 4 hospital days) or orally (tolvaptan, treatment must be initiated in the hospital) in euvolemic or hypervolemic hyponatremia of mild to moderate severity but not in hypovolemic hyponatremia.^{9,39–43} Because the aquaresis response to these drugs is variable, close vigilance of the trend of serum sodium is required. The introduction of vaptans generated great expectations, yet concerns about safety and cost currently limit the utility of these promising drugs for long-term management of hyponatremia.^{44–48} In SIAD, conventional treatment with fluid restriction combined with plentiful sodium intake and loop diuretics has limited success.²⁵ Urea has been used as an effective alternative, but unpalatability has hindered its wide application.⁴⁹ In hypervolemic hyponatremia, measures to optimize the underlying disease should complement fluid and sodium restriction, and administration of loop diuretics.^{25,27,31}

depicted in the figure occur during the generation of disturbances of extracellular volume or serum sodium; should net IC and net EFWC return to zero, a new steady state is established. Generation of hypotonic hyponatremia occurs as a by-product of unmatching the electrolyte and water content of all intake and output that results in a net gain of electrolyte-free water relative to the body's sodium and potassium stores. As examples, at an early phase of heart failure, renal retention of sodium and water causes volume expansion but no hyponatremia; at a late phase, impaired aquaresis combined with decreased dietary sodium and potassium intake and use of diuretics generate hyponatremia and potassium depletion. Fluid losses caused by diarrhea cause volume contraction and potassium depletion but no hyponatremia (early phase); actually, absent sufficient water intake, hypernatremia will develop, because the diarrheal losses are hypotonic (Table 2). As diarrhea continues and electrolyte losses are not replenished (late phase), impaired aquaresis will lead to water retention and hyponatremia but usually will fall short of normalizing total body water. In potassium depletion, the deficit of cellular potassium triggers cells to gain sodium from the extracellular fluid (to maintain volume and tonicity), generating hyponatremia coupled with hypokalemia. Potassium depletion also promotes renal sodium retention, thereby increasing exchangeable sodium. Net EFWC is positive as a result of decreased potassium intake or increased potassium loss. Excluding severe potassium depletion, water balance and thus total body water remain normal.

The hyponatremia resulting from sodium depletion is commonly managed with an infusion of isotonic saline (0.9% NaCl) at rates of 1–3 ml/kg per hour and fluid restriction. Close observation is required to avoid an overly rapid correction of serum sodium upon nearing restitution of the extracellular fluid volume. Patients with milder cases can be managed as outpatients by increasing sodium ingestion. When the extracellular fluid volume estimate is equivocal, a 1- to 2-L challenge of isotonic saline can aid diagnosis and treatment.

Potassium depletion poses a vexing challenge to managing hyponatremia. Failure to consider the effect of potassium replacement on the level of serum sodium has caused many cases of osmotic demyelination.^{11,31} Prudent management requires that the clinician first focus on potassium replacement. Considering that 1 mEq of retained potassium affects serum sodium as much as 1 mEq of retained sodium (Figure 1), even partial correction of potassium depletion can cause an excessive rise in serum sodium without sodium administration. Depending on clinical circumstances, potassium can be administered orally, intravenously, or by both

routes. Recall that potassium depletion predisposes to osmotic demyelination and it frequently coexists with additional risk factors for this complication. Retention of only 3 mEq/kg of potassium is sufficient to raise serum sodium by as much as the daily threshold of 6 mEq/L (for total body water of 50% body weight).

Trend of Serum Sodium Concentration

Repair of hypovolemia, discontinuation of thiazides or other medications inducing SIAD, and cortisol or thyroxine replacement can each rapidly reverse the defect in water excretion, and thus cause brisk aquaresis and rapid correction of hyponatremia (autocorrection). These patients might require measures to limit the pace of correction or terminate correction altogether. Infusion of 5% dextrose in water at rates guided by the urine output, administration of desmopressin (1–5 μ g at 6- to 8-hour intervals), or both can achieve this goal.^{18,27,31} Should overcorrection occur, these measures must be applied promptly to relower serum sodium below the specified cutoff for the corresponding time point.^{18–20} If signs suggestive of osmotic demyelination appear in the course of

treatment of hyponatremia, immediate relowering of the serum sodium should be accompanied by administration of steroids. Experimental studies and limited human observations are in support of this approach.^{19,20} Animal data suggest that minocycline and myoinositol can prevent or ameliorate the course of osmotic demyelination.^{50–52}

Estimating the Effect of Infusates and Fluid Losses on Serum Sodium

Implementation of case-specific therapeutic measures requires information derived from the quantitative projections of prescribed fluid therapy and ongoing fluid losses on the patient's serum sodium, while maintaining a sharp focus on anticipated benefits and potential pitfalls. Easily applicable formulas based on the Edelman equation allow estimation of the effect of infusates (infusate formula) and fluid losses (fluid-loss formula) on the serum sodium, and have gained popularity among clinicians (Table 1).^{25,53,54} These formulas represent auxiliary instruments to facilitate implementation of a quantitative approach to fluid therapy (Table 2).^{55–57} Concomitant fluid and electrolyte losses, if substantial, can result

Table 1. Formulas for estimating the effect of infusates and fluid losses on $[\text{Na}^+]_s$

Infusate Formula	Fluid-Loss Formula
$\Delta[\text{Na}^+]_s = \frac{[\text{Na}^+ + \text{K}^+]_{\text{inf}} - [\text{Na}^+]_s}{\text{TBW} + 1}$	$\Delta[\text{Na}^+]_s = \frac{[\text{Na}^+]_s - [\text{Na}^+ + \text{K}^+]_{\text{fl}}}{\text{TBW} - 1}$
Projects the effect of gaining 1 L of any infusate (inf) on the patient's $[\text{Na}^+]_s$	Projects the effect of losing 1 L of any fluid (fl) on the patient's $[\text{Na}^+]_s$
Derivation	Formulas are based on the Edelman equation. ²³ Note that in the infusate formula, the patient's $[\text{Na}^+]_s$ is subtracted from the electrolyte composition of the infusate and 1 L is added to TBW. By contrast, in the fluid-loss formula, the electrolyte composition of the fluid is subtracted from the patient's $[\text{Na}^+]_s$ and 1 L is subtracted from TBW.
Clinical Utility	Formulas aid clinicians in making quantitative projections of the effect of prescribed fluid therapy and ongoing fluid losses on patient's serum sodium. Adjustments in fluid therapy over time are facilitated by applying the two formulas as often as needed utilizing the intercurrent data of the patient. Utilization of fluid-loss formula in the management of hyponatremia is only required when ongoing fluid losses (renal and extrarenal) are substantial (>1 L/d); in that case, the effect of the fluid loss on the patient's $[\text{Na}^+]_s$ should be included in the computation of prescribed fluid therapy. If the fluid-loss formula predicts correction of hyponatremia at an inappropriately rapid rate, a hypotonic infusate (e.g., 0.45% NaCl, 5% dextrose in water) must be used at a rate determined by the infusate formula.
Limitations	Reliability of projections depends on utilizing a reasonable approximation of TBW. A substantial overestimate of TBW would decrease the projected effect of infusates and fluid losses on $[\text{Na}^+]_s$, risking overcorrection of hyponatremia.

The estimated TBW (in liters) is calculated as a fraction of body weight. This fraction is 0.6 in children, 0.55 in men, and 0.5 in women.^{25,55,56} TBW, total body water.

Table 2. Estimated effect of infusates and fluid losses of different electrolyte composition on $[Na^+]_s$ ^a

	Infusate			Fluid Loss	
	$[Na^+ + K^+]$ (mEq/L)	Effect on $[Na^+]_s$ per 1 L (mEq/L)		$[Na^+ + K^+]$ (mEq/L)	Effect on $[Na^+]_s$ per 1 L (mEq/L)
3% NaCl	513	↑ 13.0	Aquaresis (e.g., primary polydipsia)	20	↑ 3.1
0.9% NaCl	154	↑ 1.4	Natriuresis (e.g., furosemide)	55	↑ 1.9
0.9% NaCl + 30 mEq KCl per L	184	↑ 2.4	Viral/bacterial diarrhea	90	↑ 0.7
Ringer's lactate	135	↑ 0.8	Osmotic diarrhea	40	↑ 2.4
0.45% NaCl	77	↓ 1.1	Gastric fluid	70	↑ 1.4
5% dextrose	0	↓ 3.5			

(1) SIAD with moderately severe neurologic symptoms and oliguria. Retention of 1 L of 3% NaCl is projected to increase $[Na^+]_s$ by 13 mEq/L ($(513 - 110)/(30 + 1)$). For a targeted increase in $[Na^+]_s$ of 4 mEq/L over 6 hours, 308 ml of 3% NaCl ($(1000/13) \times 4$), or 51 ml/h (308/6) is required. (2) Primary polydipsia with severe neurologic symptoms and large aquaresis (500 ml/h; $[Na^+ + K^+]$ is 20 mEq/L). Loss of 1 L of urine is estimated to increase $[Na^+]_s$ by 3.1 mEq/L ($(110 - 20)/(30 - 1)$). A targeted increase in $[Na^+]_s$ of 4 mEq/L requires 1.3 L of urine (4/3.1) and will be achieved in 2.6 hours (1.3/0.5). At the 3-hour mark $[Na^+]_s$ is 115 mEq/L. To prevent overcorrection of hyponatremia, desmopressin is prescribed. (3) Hypovolemic hyponatremia with mild neurologic symptoms and oliguria. $[K^+]_s$ is 3.0 mEq/L. Retention of 1 L of 0.9% NaCl + 30 mEq of KCl is projected to increase $[Na^+]_s$ by 2.4 mEq/L ($(184 - 110)/(30 + 1)$). After administration of this infusate at 250 ml/h for 6 hours, $[Na^+]_s$ is 114 mEq/L and $[K^+]_s$ is 3.4 mEq/L. Urine output has increased and at the 6-hour mark is 150 ml/h; urine $[Na^+ + K^+]$ is 20 mEq/L. Loss of 1 L of such urine is estimated to increase $[Na^+]_s$ by 3.2 mEq/L ($(114 - 20)/(30 - 1)$). To prevent overcorrection of hyponatremia, the infusate is changed to 0.45% NaCl.

^aCalculations are made for initial $[Na^+]_s$ of 110 mEq/L in a 60-kg woman with an estimated total body water of 30 L (60×0.5) using the formulas for infusates and fluid losses, as appropriate (Table 1). Application of the formulas to the management of this patient under three clinical scenarios is presented in lower portion of this table. The electrolyte compositions of fluid losses are averages of clinically encountered values.^{25,57} In the absence of actual measurements, these estimates can be used in clinical practice.

in a sizable deviation of the actual level of serum sodium from that projected simply by applying the infusate formula.

A large series confirmed the clinical utility of the infusate formula in patients free of aquaresis.^{58,59} Subsequent studies further corroborated the predictive accuracy of the infusate formula in such patients, but expectedly not in those undergoing substantial aquaresis.^{21,22,60,61} Our experience indicates that concomitant application of the fluid-loss formula extends the utility of the infusate formula to those with substantial aquaresis or extrarenal fluid losses (Table 2).

Monitoring and Prescription Reassessment

Successful management of hyponatremia with actual or impending life-threatening complications requires vigilant observation in an intensive-care setting, especially during the initial 24–48 hours. Monitoring should be conducted every 2–4 hours and include vital signs, neurologic status, serum electrolytes, fluid balance, and urine electrolytes if applicable. During this early phase, the underlying pathophysiology can be dynamic, thereby necessitating frequent prescription reassessment, particularly if the rate of correction of serum sodium is overly slow or excessive (Table 2). Commensurate with

the patient's progress, the monitoring interval can be extended to every 6–8 hours and subsequently to every 12–24 hours.^{25,27,31}

Hyponatremic patients without severe symptomatology can be managed on the general medical floor or as outpatients. In all patients, the need for a long-term follow-up depends on the pathogenesis and risk factors of hyponatremia.

MEETING THE CHALLENGE

The preceding diagnostic and therapeutic principles would enable the clinician to formulate a case-specific management plan. Such formulation centers on expeditiously addressing the following three questions.

Which of the Determinants of the Serum Sodium Are Deranged and What Is the Underlying Culprit?

Proper evaluation should reveal the prevailing state of sodium content, potassium content, and total body water, and in the process, unravel the predisposing condition and the effector of hyponatremia. A plan for correction of each of the deranged determinants must be formulated. Uncertainty about the patient's volume status justifies a limited trial of

isotonic saline infusion. At times, the predisposing condition can be removed (discontinuation of a drug) or controlled (hemodynamic improvement). In other cases, this may not be feasible (SIAD secondary to cancer) and measures to counter chronically the aquaretic defect are required. Severe restriction of electrolyte intake predisposes to hyponatremia; moderating this restriction aids correction of the disorder.^{25,38}

How Urgent Is the Need for Intervention?

The vast majority of hyponatremic patients do not require urgent management. Conversely, patients with severely symptomatic hyponatremia and those with neurologic or neurosurgical conditions at risk of worsening intracranial hypertension represent medical emergencies.

When violation of the correction threshold appears likely, urgent measures to slow or halt further correction are required.⁶² Overcorrection should be treated as a medical emergency; prompt relowering of the serum sodium concentration is in order.^{18–20} Urgent intervention might also be required for coexisting conditions that do not emanate from the hyponatremia itself. As examples, severe volume depletion might have caused circulatory shock and AKI, whereas severe hypokalemia can

lead to cardiac arrhythmias and neuromuscular manifestations.

What Specific Therapy Should Be Instituted and Which Are the Associated Pitfalls?

Implementation of case-specific therapeutic measures can be aided by formula-based quantitative projections and should maintain a sharp focus on anticipated benefits and potential pitfalls. Fluid restriction remains the cornerstone of managing oligosymptomatic patients with euvolemic or hypervolemic hyponatremia. Although variably effective, fluid restriction does not pose a risk as long as the aquarectic defect persists. On the other hand, repair of the aquarectic defect can lead to overcorrection and thus risk development of osmotic demyelination. Prescription of stringent sodium restriction in patients with liver cirrhosis or heart failure helps control volume overload but counters correction or even aggravates hyponatremia.^{25,38}

Hypertonic saline is required for patients with severe hyponatremic encephalopathy and concentrated urine. In view of the high potential for overcorrection, its prescription should be based on a quantitative approach guided by a simple formula (Table 2). The commonly coadministered furosemide can augment correction of hyponatremia.

Isotonic saline will correct volume depletion and the associated hyponatremia. However, great vigilance is required to prevent overcorrection, because brisk diuresis can ensue when extracellular fluid volume nears restitution. Isotonic saline is unsuitable for correcting the hyponatremia of the SIAD, culminating in worsening of the serum sodium.^{25,27}

Hyponatremia associated with potassium depletion requires prompt but cautious repletion. Prescribing multiple doses of potassium without close monitoring of both serum potassium and sodium values is fraught with risk for hyperkalemia and osmotic demyelination. Catastrophic overcorrection of the serum sodium is well documented in such settings, especially because potassium depletion is a risk factor for osmotic demyelination.¹¹

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H.J.A. has served on an advisory board for Astellas Pharma and Otsuka America Pharmaceutical. N.E.M. has served as a consultant for Astellas Pharma and Otsuka America Pharmaceutical.

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