



Management of Hyponatremia in the ICU

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Hyponatremia is common in critical care units. Avoidance of neurologic injury requires a clear understanding of why the serum sodium (Na) concentration falls and why it rises, how the brain responds to a changing serum Na concentration, and what the goals of therapy should be. A 4 to 6 mEq/L increase in serum Na concentration is sufficient to treat life-threatening cerebral edema caused by acute hyponatremia. In chronic (> 48 h), severe (< 120 mEq/L) hyponatremia, correction by > 8 to 10 mEq/L/d risks iatrogenic osmotic demyelination syndrome (ODS); therefore, a 4 to 6 mEq/L daily increase in serum Na concentration should be the goal in most patients. With the possible exception of hyponatremia caused by heart failure or hepatic cirrhosis, a rapid initial increase in serum Na for severe symptoms and avoidance of overcorrection are best achieved with 3% saline given in either a peripheral or central vein. Inadvertent overcorrection can be avoided in high-risk patients with chronic hyponatremia by administration of desmopressin to prevent excessive urinary water losses. In patients with hyponatremia with oliguric kidney failure, controlled correction can be achieved with modified hemodialysis or continuous renal replacement therapies. ODS is potentially reversible, even in severely affected patients who are quadriplegic, unresponsive, and ventilator dependent. Supportive care should be offered several weeks before concluding that the condition is hopeless.

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Abbreviations: Na = sodium; ODS = osmotic demyelination syndrome; SIADH = syndrome of inappropriate antidiuretic hormone secretion

Hyponatremia is common in critical care units, and it can be deadly.¹⁻³ To avoid iatrogenic injury, the intensivist must have a clear understanding of this complex electrolyte disturbance: why the serum sodium (Na) level falls and why it rises, how the brain responds to a changing serum Na concentration, what the goals of therapy should be, and how to achieve them.

WHY THE SERUM NA LEVEL RISES AND FALLS

Except for nonhypotonic hyponatremia (eg, hyperglycemia, mannitol-induced hyponatremia, postprostatectomy syndrome, pseudohyponatremia), which we will not discuss, the serum Na concentration is a function of the content of three of the body's constituents: exchangeable Na and potassium (as opposed to "nonexchangeable," osmotically inactive electrolytes bound to bone), and water. The relationship, which has been validated empirically as well as theoretically, is expressed in the following simplified formula (where N_{ae} is exchangeable Na and K_e is potassium)^{4,5}:

$$\text{Serum Na concentration} = \frac{\text{Total body}(N_{ae} + K_e)}{\text{Total body Water}}$$

(Equation 1)

The serum Na concentration will fall if the ratio of these variables changes because of the loss of Na and potassium without a proportional amount of water (decreasing the numerator), if water is retained without a proportional amount of salt (increasing the denominator), or both. Conversely, the serum Na concentration will rise with the administration of concentrated Na or potassium or with the loss of dilute urine or electrolyte-free water in GI secretions.

Extrarenal Na and potassium losses do not cause the serum Na concentration to fall, because these losses occur with a proportional amount of water. In fact, in the case of vomitus, osmotic diarrhea, or bacterial or viral enteritis, a net loss of free water may occur. Urinary Na and potassium losses can contribute to the genesis of hyponatremia, but only if the urine is more concentrated than plasma, which requires the presence of the antidiuretic hormone, vasopressin. Therefore, hyponatremia means a disturbance of water balance.

Water excretion by the kidney is guided by the hypothalamic antidiuretic hormone, arginine vasopressin. The hormone is normally released from the posterior pituitary in response to dehydration (hyponatremia) and pathologically released when the serum

Na concentration is normal or low in response to a variety of stimuli, including an inadequate circulation, stress, hypoxia, cortisol deficiency, and neurologic disease. In addition, vasopressin can be produced and secreted ectopically, for example, in patients with small cell carcinoma of the lung. Without vasopressin, the urine is more dilute than plasma, owing to reabsorption of Na in water-impermeable segments of the nephron. When vasopressin is acting, water channels are inserted into the renal collecting duct, allowing equilibration with the surrounding hypertonic renal medulla, concentrating the urine. With normal kidney function and high levels of vasopressin, the urine can be four times as concentrated as normal plasma. Without vasopressin, the urine osmolality can fall as low as 50 mOsm/kg.

Urinary Na excretion is determined by hemodynamic stimuli that activate the sympathetic nervous system and alter the secretion of aldosterone and natriuretic hormones. Mediated by these neurohumoral signals, an adequately filled arterial circulation promotes Na excretion to match Na intake, whereas an underfilled or inadequate circulation promotes Na retention. Urine Na excretion is essentially unaffected by the serum Na concentration. To understand how the interplay of these neurohormonal signals affect serum Na concentration, consider three scenarios commonly seen in critical care units.

Urinary Na Losses in Cerebral Disease

A variety of neurologic insults promote vasopressin release and the excretion of urine more concentrated than plasma. To maintain cerebral perfusion, large volumes of isotonic fluid are commonly prescribed for acute neurologic conditions, particularly subarachnoid hemorrhage. Volume expansion suppresses aldosterone secretion and enhances release of natriuretic hormones that increase urine Na excretion. Excretion of hypertonic urine having a Na plus potassium concentration higher than plasma causes the serum Na concentration to fall (Fig 1).

Urine Na loss in patients with hyponatremia with brain pathology is often called “cerebral salt wasting.”⁷⁶ This description is based on the premise that Na losses are the primary disturbance and that they occur

<u>Input</u>		<u>Output</u>	<u>Net</u>
154 mEq	154 mEq	308 mEq	0 mEq
2 liters		1 liter	+1 liter

FIGURE 1. Desalination phenomenon. When vasopressin levels are high, infusion of isotonic saline can paradoxically cause a fall in serum sodium, a phenomenon known as “desalination.” The sodium delivered by 2 L isotonic saline (0.9% sodium chloride), each containing 154 mEq of sodium, are excreted in 1 L of hypertonic urine, having a sodium concentration of 308 mEq/L. The net effect is desalination of one of the liters of isotonic saline and, therefore, retention of 1 L of electrolyte-free water by the body.

despite hypovolemia. Unfortunately, adequacy of the circulation is a concept that cannot be reliably measured, and, thus, the incidence of cerebral salt wasting is not clear. Although it may be difficult to distinguish between syndrome of inappropriate antidiuretic hormone secretion (SIADH) and salt wasting with associated hypovolemia, there is no practical reason to do so; all patients with hyponatremia with cerebral pathology can be treated with hypertonic saline, an intervention that will raise the serum Na concentration in both SIADH and cerebral salt wasting, while correcting hypovolemia if it is present.

Generation of electrolyte-free water from isotonic saline, a phenomenon called “desalination,” is not unique to acute neurologic insults; it occurs in any patient with the SIADH who is volume expanded.⁷ For example, surgery is virtually always accompanied by stress-induced SIADH; while hyponatremia is inevitable if hypotonic fluids are given postoperatively, it can also follow administration of isotonic fluids.

Correction of Hypovolemic Hyponatremia

True hypovolemia is a potent stimulus for vasopressin secretion that can override osmotic signals to suppress the hormone. Thus, patients who are hypovolemic excrete low volumes of concentrated, relatively salt-free urine. Hyponatremia develops if water intake exceeds urinary and insensible water losses. After treatment with isotonic or hypertonic saline, the hypovolemic stimulus resolves, vasopressin levels fall, and the urine becomes maximally dilute; the resulting loss of water may cause the serum Na concentration to rise by > 2 mEq/L/h.^{8,9}

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Kidney Failure

Acute kidney injury or advanced chronic kidney disease results in a urine osmolality that remains at a level nearly equal to plasma, even if vasopressin levels are low; electrolyte-free water intake in oliguric kidney failure inevitably leads to hyponatremia. Recovery from kidney failure increases water losses, driven by excretion of urea; loss of electrolyte-free “urea water” causes the serum Na concentration to rise even if vasopressin levels are high.

BRAIN RESPONSES TO A CHANGING SERUM Na CONCENTRATION

Because Na does not readily cross the blood-brain barrier, water flows into or out of the brain in response to osmotic forces.^{10,11} If the serum Na concentration falls rapidly, the resulting increase in brain water increases intracranial pressure, sometimes with a fatal outcome.

If the brain were unable to adapt, even mild hyponatremia would cause fatal brain swelling. Fortunately, brain cells can achieve osmotic equality with the plasma by extruding solute, as well as by taking on water. Brain cells contain high concentrations of organic solutes called organic osmolytes that are extruded in response to cell swelling. Loss of organic solutes reduces brain swelling so that with a slow onset of hyponatremia (over ≥ 48 h), it may be difficult to detect cerebral edema even at serum Na concentrations < 100 mEq/L.¹²

Possibly because of the delay in brain organic-osmolyte repletion, rapid correction of chronic (> 48 h duration) hyponatremia triggers a cascade of adverse events culminating in the programmed death of myelin-producing oligodendrocytes.^{13,14} The injury presents clinically with progressive neurologic findings starting 2 to 6 days after correction (the osmotic demyelination syndrome [ODS]).^{15,16} Classically associated with demyelination of the central pons (central pontine myelinolysis), lesions of ODS are equally common outside the pons (extrapontine myelinolysis). Experimental models have shown that ODS is caused by rapid correction and not hyponatremia itself; it can be prevented by relowering the plasma Na concentration after excessive correction.¹⁷⁻¹⁹ Several factors place the patient at particularly high risk of developing ODS: serum Na concentration ≤ 105 mEq/L, hypokalemia, alcoholism, malnutrition, and liver disease. On the other hand, the risk of ODS is low in patients without these risk factors whose serum Na concentration is > 120 mEq/L and in patients with a very short duration of hyponatremia, particularly patients with psychosis and marathon runners with acute, self-induced water intoxication.

Patients with pontine demyelination aspirate and often require ventilator support. Once thought to carry a dismal prognosis, ODS is potentially reversible, even in severely affected patients who are quadriplegic, unresponsive, and ventilator dependent.^{20,21} Most patients survive, and about one-third may enjoy a full neurologic recovery. Supportive care should be continued for several weeks before concluding that the condition is hopeless.

GOALS OF THERAPY

The serum Na concentration should be increased enough to prevent complications of untreated hyponatremia while steering clear of correction rates that risk iatrogenic brain injury. Evidence for the optimal approach to management of acute or chronic hyponatremia comes from clinical observational studies and from experimental models; no randomized trials have been performed comparing treatments.

Increasing the Plasma Na Concentration Enough

Acute Hyponatremia: Brain death from cerebral edema is the most feared complication of acute (< 24 h) hyponatremia. These catastrophes have occurred primarily in women and children given hypotonic IV fluids after surgery and in patients with self-induced water intoxication associated with psychosis, marathon running, or use of the recreational drug “ecstasy,” and in patients with intracranial pathology.^{2,19,22} Nonspecific symptoms (eg, headache, nausea and vomiting, drowsiness, or mild confusion) can rapidly progress to seizures, respiratory arrest, and permanent or fatal brain injury.²³ Hypoxia from noncardiogenic pulmonary edema exacerbates brain swelling caused by hyponatremia, resulting in a vicious cycle.²⁴

Seizures can complicate both acute and chronic hyponatremia, but are most common when the serum Na concentration falls abruptly due to self-induced water intoxication.²⁵ Seizures are uncommon in chronic hyponatremia, even at extremely low serum Na concentrations, and they usually reflect an underlying seizure disorder.²⁶⁻²⁸ Response to antiepileptic medications can be poor unless the serum Na concentration is increased.

While there is a general consensus that serious neurologic symptoms warrant aggressive therapy, few published papers include data on how much the serum Na concentration increased after treatment of hyponatremic seizures and coma with hypertonic saline. A review of the available literature concluded that a 4 to 6 mEq/L increase is sufficient in these circumstances.⁹

Most of what we know about the treatment of cerebral edema with hypertonic saline is derived from

experience in normonatremic patients with neurosurgical emergencies. Like acute hyponatremia, a 4 to 6 mEq/L increase in serum Na concentration is probably “enough.” A 4-year, single-center study of 63 patients treated for transtentorial herniation caused by a variety of neurosurgical conditions found that a 30 to 60 mL bolus of 23.4% saline (equivalent to 234 to 468 mL of 3% saline), which increased the plasma Na concentration by 5 mEq/L, promptly reversed clinical signs of herniation and reduced intracranial pressure by nearly 50% within 1 h.²⁹ A placebo-controlled trial found that infusion of 2 mL/kg of 7.2% saline increasing the plasma Na concentration by 4 to 7 mEq/L at 30 min and by 1 to 5 mEq/L after 210 min was enough to decrease intracranial pressure and to increase cerebral perfusion pressure in patients with subarachnoid hemorrhage.³⁰

Severe Chronic Hyponatremia: Although patients with chronic hyponatremia rarely, if ever, succumb to cerebral edema, many clinicians fear an adverse outcome unless the serum Na concentration is raised to a level thought to be “safe” (variably set at > 120 mEq/L or even > 130 mEq/L). There is little evidence to support this belief, but unfortunately, it continues to influence clinical practice.

Patients who are admitted to the hospital from home with profoundly low serum Na concentrations have a surprisingly good prognosis, and there is no evidence that large increases in serum Na concentration are needed to ensure their survival. Most patients with serum Na concentration < 110 mEq/L were admitted because of an electrolyte disturbance caused by medications and/or mild GI or respiratory conditions that are not, themselves, life threatening.^{27,31} Patients in the hospital with milder hyponatremia are more likely to have a severe underlying illness—the reason for their hospitalization and the cause of their electrolyte disturbance. Epidemiologic studies have shown that as the serum Na concentration falls progressively, hospital mortality rates progressively rise; paradoxically, however, as the serum Na concentration falls below 120 mEq/L, mortality rates begin to fall, such that below 110 mEq/L, mortality is not much different from that of normonatremic patients.³¹ Survival cannot be attributed to aggressive efforts to achieve a “safe” Na concentration level; on the contrary, excessive therapy of profound hyponatremia appears to increase morbidity.^{26,27} Therefore, rather than increasing the serum Na concentration to a preconceived level of safety, the goal of therapy is to promptly increase the serum Na concentration enough to reduce hyponatremic symptoms and to slowly restore hyponatremia over several days.

Although death from chronic hyponatremia is uncommon and the risk of seizures is relatively low,

hyponatremia causes distressing symptoms that deserve treatment.³² Even mild, chronic hyponatremia that seems to be “asymptomatic” causes gait disturbances and disturbed cognition, and it markedly increases the risk of falls and fractures.^{33–35} Hyponatremia may also have adverse effects on a variety of other organ systems.³⁶ Therefore, normonatremia should be restored eventually, if possible, in all patients. Correction by 4 to 6 mEq/L/d is sufficient. Larger increases are unnecessary and increase the risk of inadvertent overcorrection and iatrogenic injury.

Avoid Iatrogenic Injury From Excessive Correction

Osmotic Demyelination Syndrome: Owing to an adaptive loss of brain-cell solutes (organic osmolytes), brain swelling is usually undetectable and neurologic symptoms are seldom severe among patients whose serum Na concentrations fall gradually.^{26,27,37} Once adapted to hyponatremia, a process that takes about 2 days, the brain is vulnerable to injury if the serum Na concentration is normalized too rapidly, because it may take a week to replace lost osmolytes when hyponatremia is corrected.^{10,11}

Several observational studies have shown that correction of severe (< 120 mEq/L), chronic (> 48 h) hyponatremia by > 10 to 12 mEq/L in a single day or by > 18 mEq/L in 2 days is commonly complicated by ODS.^{16,26,27,38,39} These should be regarded as limits not to be exceeded rather than as therapeutic goals, particularly in high-risk patients. As discussed later in this article, inadvertent overcorrection of hyponatremia is common, and there have been isolated case reports after correction of hyponatremia by < 10 mEq/L/d. Therefore, it is wise to set targeted correction rates considerably below rates known to be associated with iatrogenic injury.

A Universal Therapeutic Goal: Rule of Sixes

If an increase of 4 to 6 mEq/L in serum Na concentration is “enough” to improve the most severe symptoms of acute hyponatremia, it is reasonable to set a therapeutic goal of 4 to 6 mEq/L/d for all patients with severe, chronic hyponatremia, including patients with extremely low serum Na concentrations.^{12,22} Setting the target at 4 to 6 mEq/L/d allows enough room for error should correction inadvertently exceed the rate that was intended.

This recommendation translates to an easy to remember “rule of sixes”: “Six a day makes sense for safety; so give six in six hours for severe sx’s[symptoms] and stop.” In other words, for all patients, the therapeutic goal is correction by ≤ 6 mEq/L/d.^{22,40} For patients with severe symptoms, or other indications for urgent

intervention, the day's correction is frontloaded in the first 6 h and correction is then postponed until the next day, when it is resumed at a rate of 4 to 6 mEq/L/d.

ACHIEVING THERAPEUTIC GOALS

General Measures

Unless the urine is maximally dilute, patients with hyponatremia should be fluid restricted. In the ICU setting, this means careful attention to unintended sources of electrolyte-free water such as tube feedings and IV medications that are administered in 5% dextrose in water (D5W). As some of these are unavoidable, it may be necessary to administer 300 mL 3% saline (150 mEq of Na) to compensate for every liter of free water.

Hypertonic Saline

In the past, pharmacy literature has advocated that a central vein be used for infusion of 3% saline. However, there is no evidence to support this recommendation and the most recent edition of a standard pharmacy reference work no longer mandates infusion in a central vein.⁴⁰

Avoiding Hyponatremia in Patients With Intracranial Disease

Patients with intracranial disease are at a high risk for herniation if nondiseased brain is allowed to swell because of hyponatremia. Fluid restriction alone will be ineffective if urine electrolyte concentrations are high. Fluid restriction may also impair cerebral perfusion and it has been associated with worse neurologic outcomes. Therefore, the most reliable way to prevent the serum Na concentration from falling is to administer Na solutions that are higher in concentration than the urine. A sliding scale has been proposed, using intermittent infusions of 3% saline and administration of salt tablets to maintain normonatremia (Table 1).⁴¹

Table 1—Sliding Scale Protocol to Avoid Hyponatremia in Neurosurgical Patients With Serum Sodium < 140 mEq/L

Serum Sodium	ΔInfusion Rate
< 130 mEq/L	Increase by 20 mL/h to maximum of 80 mL/h
130-135 mEq/L	Increase by 10 mL/h to maximum of 80 mL/h
136-140 mEq/L	No change in infusion rate
> 140 mEq/L	Hold infusion and resume when in therapeutic range

3 g NaCl orally or by nasogastric tube is given continuously q6h, while 3% IV NaCl is given at variable rates, initially at 20 mL/h, adjusting infusion rate q6h based on serum sodium. Δ = change in; NaCl = sodium chloride.

Urgent Interventions

Acute (< 24 h), symptomatic hyponatremia, severe neurologic symptoms (seizures and coma) regardless of the duration of hyponatremia, and symptomatic hyponatremia with coexistent intracranial pathology should be treated urgently with hypertonic saline. The most effective strategy is to administer a 100-mL bolus of 3% saline, with two additional doses administered every 15 min if the patient's condition has not yet improved.^{9,22,42,43}

Avoiding Overcorrection of Chronic Hyponatremia

In many patients, the ability to excrete dilute urine is only temporarily or reversibly impaired. Once the cause of water retention ends, excretion of dilute urine can increase the serum Na concentration by much more than the clinician intends or expects.^{44,45} Examples include volume resuscitation in patients with excess vasopressin due to hypovolemia or low solute intakes (eg, beer potomania); discontinuation of thiazide diuretics; hormone replacement for adrenal insufficiency; spontaneous resolution of a reversible cause of SIADH, such as nausea, hypoxia, or recent surgery; and discontinuation of medications that cause SIADH.^{9,22,46} Once the urine becomes maximally dilute, the resulting water diuresis can increase the serum Na level by ≥ 2 mEq/L/h.

If the serum Na concentration is increasing too rapidly, urinary water losses can be matched with D5W in water, or alternatively, 2 to 4 μ g desmopressin can be given parenterally to halt water diuresis.⁴⁶ In our experience, the latter strategy is less labor intensive and is more predictable. If the serum Na level has already increased by > 10 to 12 mEq/L over 24 h in a patient with chronic hyponatremia with a serum Na concentration < 120 mEq/L, or by > 8 mEq/L over 24 h in a high-risk patient (eg, serum Na concentration ≤ 105 mEq/L, hypokalemia, malnutrition, hepatic cirrhosis, alcoholism), relowering the serum Na concentration to a level approximately 8 mEq/L higher than the previous day's level should be considered. This can be accomplished by giving desmopressin and repeated infusions of 3 mL/kg D5W given over 1 h, determining the serum Na concentration after each infusion until the goal is met. The blood glucose should be carefully monitored to avoid water losses from glucosuria that will increase the serum Na concentration.

In contrast to dosing strategies in diabetes insipidus, when desmopressin is used to manage overcorrection of hyponatremia, escape from antidiuresis is undesirable; therefore, desmopressin is given at intervals of 6 to 8 h.¹² Once the rate of correction has been slowed or stopped by regular doses of desmopressin, correction of hyponatremia can resume,

Table 2—Desmopressin/3% NaCl for Controlled Correction of Severe Hyponatremia

Consider for Patients With Severe (< 120 mEq/L) Chronic Hyponatremia
Monitoring
Urine output q8h
“Stat” or crisis serum Na and K every 4-6 h
Desmopressin 2-4 µg q8h. Continue until serum Na is > 128 mEq/L
3% Saline
Start or change infusion rates within 1 h of obtaining serum Na values so that subsequent levels will accurately reflect therapy
Severe symptoms
50-100 mL bolus and/or
1 mL/kg/h until serum Na has increased by 4-6 mEq/L
Mild to moderate symptoms or following treatment of severe symptoms
Initial infusion rate at 0.2-0.4 mL/kg/h
Adjust infusion rate to achieve correction at 0.2 mEq/L/h
Reduce infusion to adjust for K replacement
100 mM KCl: no adjustment
KCl elixir or 400 mM (mEq/L) KCl: 1 mEq KCl = 2 mL 3% NaCl
Stop infusion daily after 4-6 mEq/L increase in serum Na
Resume infusion daily until serum Na > 128 mEq/L
Pitfalls
Unexpected free water intake in tube feedings and IV medications
Inability to restrict oral water intake (avoid in psychotic polydipsia)
Large urine water losses despite desmopressin
Glycosuria
Urea (high protein intake, steroids, recovery from azotemia)
Dosing of desmopressin and 3% NaCl in extreme obesity
Timing of blood draws not coordinated with changes in Na infusion

K = potassium; KCl = potassium chloride; Na = sodium. See Table 1 legend for expansion of other abbreviations.

slowly increasing the plasma Na concentration with the concurrent administration of 3% saline.⁴⁷

We have used a more proactive strategy to manage most of the patients we see with chronic hyponatremia whose serum Na concentrations are < 120 mEq/L. As there have been no randomized trials comparing treatment regimens for symptomatic hyponatremia, our approach is based on observational studies and clinical experience. Rather than giving desmopressin to stop water diuresis after it has already begun, we start desmopressin at the start of therapy along with 3% saline (which can be infused in a peripheral vein) to achieve a more controlled rate of correction. The administered desmopressin creates a state of iatrogenic SIADH and eliminates water losses as a variable that increases the serum Na concentration. Hypertonic saline is titrated to achieve the desired rate of correction, with an initial bolus if clinically indicated. Combination therapy is continued until the serum Na concentration has been increased to > 128 mEq/L. We avoid desmopressin in patients who are unable or unwilling to curtail their water intake and do not use it when there is little likelihood of a reversible

cause for water retention (eg, SIADH due to small cell lung cancer or brain tumor). In hypotensive patients with severe hyponatremia who require large amounts of isotonic fluid for volume resuscitation, we would still give desmopressin to prevent an unwanted water diuresis, but initial therapy with hypertonic saline may be unnecessary since each liter of 0.9% saline will increase the serum Na concentration by approximately 1 mEq/L.

Potassium Repletion

The dose of hypertonic saline must be reduced in patients with hyponatremia who are potassium depleted. Because the plasma Na concentration is a function of potassium as well as Na (Equation 1), potassium replacement increases the serum Na concentration if hypertonic solutions of potassium, either orally or IV, are used.⁴⁸ A recent report described a case of ODS following overcorrection primarily attributable to replacement of a large potassium deficit.⁴⁹ We have infused 400 mM (400 mEq/L) potassium chloride with desmopressin to achieve a controlled rate of correction in patients with profound hyponatremia and severe hypokalemia.

Hyponatremia in Edematous Conditions

Hyponatremia is associated with poor outcomes in patients with heart failure and liver disease, but it is not known if correction of hyponatremia improves outcomes. Hypertonic saline is usually avoided in patients with edema, but 3% saline combined with high doses of loop diuretics has been reported to improve outcomes when compared with treatment with high-dose diuretics alone.⁵⁰

Vasopressin receptor antagonists (vaptans) are an attractive therapy for hyponatremia in patients with edema who have intact kidney function and they are effective in both heart failure and cirrhosis.^{51,52} Vaptans have been called “aquaretics” because they increase the excretion of water (decreasing the denominator of Equation 1) without affecting the excretion of electrolytes. The most compelling case for vaptan therapy is in patients with hyponatremia who are awaiting liver transplantation. Normalizing the serum Na concentration before surgery may help avoid iatrogenic injury caused by a sudden perioperative increase in serum Na levels. Vaptans may also be useful as part of a diuretic regimen in patients with hyponatremia who have heart failure.

Vaptans have been used in ICU settings for other causes of hyponatremia, but there is no proven advantage of this costly therapy over hypertonic saline in nonedematous patients. Vaptans cannot be recommended for hyponatremic emergencies because a

substantial percentage of patients do not respond to them.⁵³ There is very little published experience with their use in the treatment of severe hyponatremia; in one postmarketing series, every patient with a serum Na concentration < 120 mEq/L treated with conivaptan was corrected excessively.⁵⁴ It is unknown whether administration of desmopressin to a patient undergoing a vaptan-induced water diuresis is effective; therefore, if vaptans are used to treat severe hyponatremia, the clinician must be prepared to match water losses with D5W to prevent overcorrection.

Renal Replacement Therapy

Hyponatremia is common in patients with oliguric kidney failure and treatment with conventional hemodialysis will increase the serum Na concentration very rapidly. Fortunately, ODS after dialysis is rare and uremia has been shown to be protective against ODS in experimental models. However, large increases in the serum Na concentration during dialysis should be avoided if possible.⁵⁵ A regimen has been proposed using the lowest commercially available setting for dialysate Na, low blood-flow rates, and shortened dialysis times.⁵⁶ Continuous renal replacement therapy can also be used to achieve steady, but slow correction by diluting the replacement fluid or dialysate to a Na concentration slightly higher than the patient's serum Na concentration.⁵⁷

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