TABLE 63-2 CAUSES OF ACUTE HYPONATREMIA

Iatrogenic
Postoperative: premenopausal women
Hypotonic fluids with cause of ↑ vasopressin
Glycine irrigation: TURP, uterine surgery
Colonoscopy preparation
Recent institution of thiazides
Polydipsia
MDMA ("ecstasy," "Molly") ingestion
Exercise induced
Multifactorial, e.g., thiazide and polydipsia

Abbreviations: MDMA, 3,4-methylenedioxymethamphetamine; TURP, transurethral resection of the prostate.

marathons and other endurance events, has similarly been linked to both a "nonosmotic" increase in circulating AVP and excessive free water intake. The recreational drugs Molly and ecstasy, which share an active ingredient (MDMA, 3,4-methylenedioxymethamphetamine), cause a rapid and potent induction of both thirst and AVP, leading to severe acute hyponatremia.

Persistent, chronic hyponatremia results in an efflux of organic osmolytes (creatine, betaine, glutamate, myoinositol, and taurine) from brain cells; this response reduces intracellular osmolality and the osmotic gradient favoring water entry. This reduction in intracellular osmolytes is largely complete within 48 h, the time period that clinically defines chronic hyponatremia; this temporal definition has considerable relevance for the treatment of hyponatremia (see below). The cellular response to chronic hyponatremia does not fully protect patients from symptoms, which can include vomiting, nausea, confusion, and seizures, usually at plasma Na^+ concentration <125 m*M*. Even patients who are judged "asymptomatic" can manifest subtle gait and cognitive defects that reverse with correction of hyponatremia; notably, chronic "asymptomatic" hyponatremia increases the risk of falls. Chronic hyponatremia also increases the risk of bony fractures owing to the associated neurologic dysfunction and to a hyponatremia-associated reduction in bone density. Therefore, every attempt should be made to correct safely the plasma Na^+ concentration in patients with chronic hyponatremia, even in the absence of overt symptoms (see the section on treatment of hyponatremia below).

The management of chronic hyponatremia is complicated significantly by the asymmetry of the cellular response to correction of plasma Na^+ concentration. Specifically, the *reaccumulation* of organic osmolytes by brain cells is attenuated and delayed as osmolality increases after correction of hyponatremia, sometimes resulting in degenerative loss of oligodendrocytes and an osmotic demyelination syndrome (ODS). Overly rapid correction of hyponatremia (>8–10 m*M* in 24 h or 18 m*M* in 48 h) is also associated with a disruption in integrity of the blood-brain barrier, allowing the entry of immune mediators that may contribute to demyelination. The lesions of ODS classically affect the pons, a structure wherein the delay in the reaccumulation of osmotic osmolytes is particularly pronounced; clinically, patients with central pontine myelinolysis can present 1 or more days after overcorrection of hyponatremia with paraparesis or quadriparesis, dysphagia, dysarthria, diplopia, a "locked-in syndrome," and/or loss of consciousness. Other regions of the brain can also be involved in ODS, most commonly in association with lesions of the pons but occasionally in isolation; in order of frequency, the lesions of extrapontine myelinolysis can occur in the cerebellum, lateral geniculate body, thalamus, putamen, and cerebral cortex or subcortex. Clinical presentation of ODS can, therefore, vary as a function of the extent and localization of extrapontine myelinolysis, with the reported development of ataxia, mutism, parkinsonism, dystonia, and catatonia. Relowering of plasma Na^+ concentration after overly rapid correction can prevent or attenuate ODS (see the section on treatment of hyponatremia below). However, even appropriately slow correction can be associated with ODS, particularly in patients with additional risk factors; these include alcoholism, malnutrition, hypokalemia, and liver transplantation.

Diagnostic Evaluation of Hyponatremia Clinical assessment of hyponatremic patients should focus on the underlying cause; a detailed drug history is particularly crucial (Table 63-1). A careful clinical assessment of volume status is obligatory for the classical diagnostic approach to hyponatremia (Fig. 63-5). Hyponatremia is frequently multifactorial, particularly when severe; clinical evaluation should consider *all* the possible causes for excessive circulating AVP, including volume status, drugs, and the presence of nausea and/or pain. Radiologic imaging may also be appropriate to assess whether patients have a pulmonary or CNS cause for hyponatremia. A screening chest x-ray may fail to detect a small-cell carcinoma of the lung; computed tomography (CT) scanning of the thorax should be considered in patients at high risk for this tumor (e.g., patients with a smoking history).

Laboratory investigation should include a measurement of serum osmolality to exclude pseudohyponatremia, which is defined as the coexistence of hyponatremia with a normal or increased plasma tonicity. Most clinical laboratories measure plasma Na^+ concentration by testing diluted samples with automated ion-sensitive electrodes, correcting for this dilution by assuming that plasma is 93% water. This correction factor can be inaccurate in patients with pseudohyponatremia due to extreme hyperlipidemia and/or hyperproteinemia, in whom serum lipid or protein makes up a greater percentage of plasma volume. The measured osmolality should also be converted to the effective osmolality (tonicity) by subtracting the measured concentration of urea (divided by 2.8, if in mg/dL); patients with hyponatremia have an effective osmolality of <275 mOsm/kg.

Elevated BUN and creatinine in routine chemistries can also indicate renal dysfunction as a potential cause of hyponatremia, whereas hyperkalemia may suggest adrenal insufficiency or hypoaldosteronism. Serum glucose should also be measured; plasma Na^+ concentration falls by ~1.6–2.4 m*M* for every 100-mg/dL increase in glucose, due to glucose-induced water efflux from cells; this "true" hyponatremia resolves after correction of hyperglycemia. Measurement of serum uric acid should also be performed; whereas patients with SIAD-type physiology will typically be hypouricemic (serum uric acid <4 mg/dL), volume-depleted patients will often be hyperuricemic. In the appropriate clinical setting, thyroid, adrenal, and pituitary function should also be tested; hypothyroidism and secondary adrenal failure due to pituitary insufficiency are important causes of euvolemic hyponatremia, whereas primary adrenal failure causes hypovolemic hyponatremia. A cosyntropin stimulation test is necessary to assess for primary adrenal insufficiency.

Urine electrolytes and osmolality are crucial tests in the initial evaluation of hyponatremia. A urine Na^+ concentration <20–30 m*M* is consistent with hypovolemic hyponatremia, in the clinical absence of a hypervolemic, Na^+-avid syndrome such as CHF (Fig. 63-5). In contrast, patients with SIAD will typically excrete urine with an Na^+ concentration that is >30 m*M*. However, there can be substantial overlap in urine Na^+ concentration values in patients with SIAD and hypovolemic hyponatremia, particularly in the elderly; the ultimate "gold standard" for the diagnosis of hypovolemic hyponatremia is the demonstration that plasma Na^+ concentration corrects after hydration with normal saline. Patients with thiazide-associated hyponatremia may also present with higher than expected urine Na^+ concentration and other findings suggestive of SIAD; one should defer making a diagnosis of SIAD in these patients until 1–2 weeks after discontinuing the thiazide. A urine osmolality <100 mOsm/kg is suggestive of polydipsia; urine osmolality >400 mOsm/kg indicates that AVP excess is playing a more dominant role, whereas intermediate values are more consistent with multifactorial pathophysiology (e.g., AVP excess with a significant component of polydipsia). Patients with hyponatremia due to decreased solute intake (beer potomania) typically have urine Na^+ concentration <20 m*M* and urine osmolality in the range of <100 to the low 200s. Finally, the measurement of urine K^+ concentration is required to calculate the urine-to-plasma electrolyte ratio, which is useful to predict the response to fluid restriction (see the section on treatment of hyponatremia below).