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Current treatment practice and outcomes. Report of the hyponatremia registry

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Current management practices for hyponatremia (HN) are incompletely understood. The HN Registry has recorded diagnostic measures, utilization, efficacy, and outcomes of therapy for eu- or hypervolemic HN. To better understand current practices, we analyzed data from 3087 adjudicated adult patients in the registry with serum sodium concentration of 130 mEq/l or less from 225 sites in the United States and European Union. Common initial monotherapy treatments were fluid restriction (35%), administration of isotonic (15%) or hypertonic saline (2%), and tolvaptan (5%); 17% received no active agent. Median (interquartile range) mEq/l serum sodium increases during the first day were as follows: no treatment, 1.0 (0.0–4.0); fluid restriction, 2.0 (0.0–4.0); isotonic saline, 3.0 (0.0–5.0); hypertonic saline, 5.0 (1.0–9.0); and tolvaptan, 4.0 (2.0–9.0). Adjusting for initial serum sodium concentration with logistic regression, the relative likelihoods for correction by 5 mEq/l or more (referent, fluid restriction) were 1.60 for hypertonic saline and 2.55 for tolvaptan. At discharge, serum sodium concentration was under 135 mEq/l in 78% of patients and 130 mEq/l or less in 49%. Overly rapid correction occurred in 7.9%. Thus, initial HN treatment often uses maneuvers of limited efficacy. Despite an association with poor outcomes and availability of effective therapy, most patients with HN are discharged from hospital still hyponatremic. Studies to assess short- and long-term benefits of correction of HN with effective therapies are needed.

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Hyponatremia (HN), defined as a serum sodium concentration ($[Na^+]$) below the lower limit of normal, is the most common electrolyte disorder in hospitalized patients, with a prevalence as high as 30–42%.[1,2] HN is independently associated with mortality in congestive heart failure (CHF), cirrhosis, and hospitalized patients in general[3–7] and with increased hospital costs and readmission rates.[8,9] Chronic HN has been linked to impaired gait and balance, increased falls and fracture rates, and osteoporosis.[10–13] However, a causal role of HN for these associations is largely unproven.[14]

Correction of severe HN of sudden onset can be genuinely lifesaving,[15,] and treatment of chronic HN associated with neurological symptoms is undeniably beneficial. Despite the widespread clinical impression that correction of less severe chronic HN is also worthwhile, evidence-based data demonstrating clinical benefit are limited.[10,16–18]

Hypovolemic HN responds readily to volume repletion. Until recently, treatment of hypervolemic HN has been limited to fluid restriction (FR) and correction of the underlying disorder. Treatment modalities for euvolemic HN have included FR, hypertonic saline (HS), loop diuretics, demeclocycline, and urea. With the approval of the vasopressin-receptor antagonists conivaptan and tolvaptan, more targeted treatment for euvolemic and hypervolemic HN became available. It remains uncertain how treatment options are employed, and how correction magnitude and incidence of adverse outcomes are affected by the type of therapy. With this background, the multinational HN

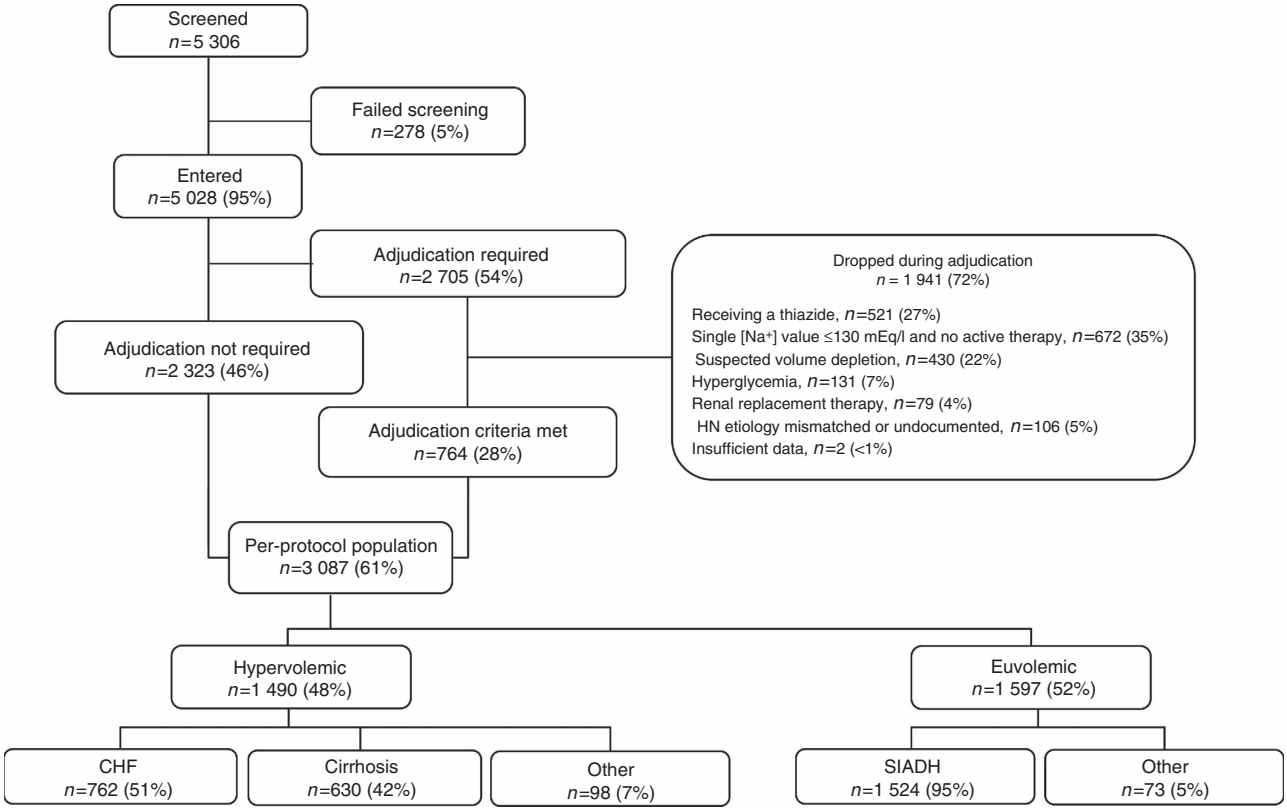

Figure 1 | Consort diagram showing patient flow. The 3087 patients in bottom row constitute the per-protocol group. All analyses are based on this group. Note: patients reporting multiple comorbidities were counted in the "Other" group. See Materials and Methods section and Supplementary Table S4 online for description of the adjudication process. CHF, congestive heart failure; HN, hyponatremia; [Na^+], sodium concentration; SIADH, syndrome of inappropriate antidiuretic hormone secretion.

Registry was initiated to assess the current state of treatment of euvolemic and hypervolemic HN in diverse, real-world hospital settings. Its specific purpose was to determine which diagnostic and treatment modalities are currently employed, how effective they are, and how rapidly and reliably they result in an increase in [Na^+]. An additional goal was to determine which treatments posed the greatest risk of overly rapid correction and osmotic demyelination.[19]

RESULTS

Characteristics of study population

A total of 5028 patients were entered (Figure 1) between September 2010 and February 2013. One or more criteria requiring adjudication were met by 2705 patients (54% of those entered), and 1941 of those (72%) failed adjudication. The 764 patients (28%) retained after adjudication and the 2323 (46% of those entered) not requiring adjudication comprise the 3087 individuals of the per-protocol data set. A sensitivity analysis performed with and without the 951 potentially hypovolemic patients excluded because of thiazide use or evidence of volume depletion showed no significant differences in rates of [Na^+] change or achievement of [Na^+] correction benchmarks. The syndrome of inappropriate antidiuretic hormone (SIADH), CHF, and cirrhosis data sets include patients in whom these diagnoses were made by treating physicians.

Patient demographics and baseline characteristics are shown in Table 1. Patients with cirrhosis were younger and more likely to be male compared with patients with SIADH or CHF. A prior episode of HN was known to have occurred in 909 patients (29%) and was most likely in patients with cirrhosis and least likely in those with SIADH. Most patients (71%) were under the care of a generalist rather than an internal medicine subspecialist.

Diagnosis

In the 1524 patients with SIADH, serum osmolality was measured in 66%, urine osmolality in 68%, and urine [Na^+] in 63%; all three tests were performed in 47%, and none in 11%. Cortisol was measured in 33% of patients and thyroid-stimulating hormone in 64%. All five of these measurements were made in 21% of patients.

Treatment selection

As shown in Table 2, 17% of patients received no active HN therapy. Utilization varied with [Na^+]. Only 3% of patients with severe HN received no therapy compared with 13% with