Approach to hyponatremia according to the clinical setting: Consensus statement from the Italian Society of Endocrinology (SIE), Italian Society of Nephrology (SIN), and Italian Association of Medical Oncology (AIOM)

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25 April 2024

APPROACH TO HYPONATREMIA ACCORDING TO THE CLINICAL SETTING. CONSENSUS STATEMENT FROM THE ITALIAN SOCIETY OF ENDOCRINOLOGY (SIE), ITALIAN SOCIETY OF NEPHROLOGY (SIN) AND ITALIAN ASSOCIATION OF MEDICAL ONCOLOGY (AIOM)

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INTRODUCTION

Hyponatremia (hypoNa, serum sodium levels <135 mEq/L), is the most frequently observed electrolyte disorder in clinical practice, affecting up to 15-30% of hospitalized patients (1). HypoNa is characterized by an excess of water relative to exchangeable total body sodium, that can be normal, increased or decreased. As a consequence, hypoNa can be classified by the fluid volume status of the patient (euvolemic, hypovolemic and hypervolemic hypoNa), or by plasma tonicity, i.e., the effective osmolality, (isotonic, hypertonic and hypotonic hypoNa). Hypotonic hypoNa is the most commonly observed form in daily clinical practice (2). Severe hypoNa, especially if acutely developed (i.e in less than 48 hours), may determine major neurological symptoms due to brain edema, a potentially life-threatening complication if not promptly recognized and treated (3). However, even mild hypoNa (130-134 mEq/L) may also be associated with other strictly related clinical problems, often insidious and scarcely symptomatic, such as bone demineralization or gait instability and attention deficits, which may increase the risk of falls and bone fractures, especially in the elderly (4-8). Accordingly, recent meta-analyses have shown that even milder forms of hypoNa are associated with an increased risk of mortality in different clinical settings (9), along with prolonged hospital stay, increased readmission rates and higher hospital costs (10).

Although the main mechanisms of renal sodium and water handling, especially for what concerns the fine regulation by the distal nephron, have been fully elucidated (11), several clinical issues make the approach to hypoNa a complex task. In fact, on one hand it should be timely diagnosed and appropriately managed according to the severity of the neurological status, but on the other hand an overly rapid correction may cause neurological damage possibly leading to the Osmotic Demyelination Syndrome (ODS) (12-14). Conditions that may be associated with a risk of hypercorrection of hypoNa and their related mechanisms are showed in Table 1.

Nevertheless, despite its high prevalence, especially among hospitalized patients, and its clinical impact, hypoNa is often neglected, or under- or mistreated (15). This is mainly due to both an empirical approach (i.e. not pathophysiology-driven) and to the high degree of heterogeneity of the clinical settings where hypoNa is encountered.

In recent years a new class of drugs, namely the vasopressin receptor antagonists or vaptans, has become available for the treatment of hypoNa secondary to the Syndrome of Inappropriate Antidiuresis (SIAD), one of the most frequent causes of hypoNa (16). Tolvaptan is the only licensed vaptan in Europe, so far (12). However, there is no agreement between the European Guidelines (17) and the recommendations of an US Expert Group (14) concerning the use of vaptans in clinical practice (18).

On this basis, a task force generated by the Fluid and Electrolytes Disorder Club of the Italian Society of Endocrinology, the Italian Society of Nephrology and the Italian Association of Medical Oncology has joined together, in order to prepare a practical guide to recognize and manage hypoNa in different clinical settings.

In the intention of the task-force the present paper should be considered nor as a formal Guideline nor as an all-inclusive in-depth review on the topic. Rather, this paper should be viewed as a pocket guide to support the practical approach to hyponatremic patients by different specialists.

106   We propose a simplified diagnostic algorithm for hypoNa (Figure 1, Table 2) and a treatment algorithm for hypoNa
107   secondary to SIAD (Figure 2). The treatment strategies for hypovolemic (rehydration) or hypervolemic hypoNa (fluid
108   restriction, hypertonic saline solution, furosemide) are very well established and for a detailed description we redirect
109   the reader to the already mentioned recommendations/guidelines (14, 17). Here, we would like to remind that fluid
110   restriction is not very effective and in several clinical situations this approach aiming to correct hypoNa is going to fail
111   (19).

112

113   **HYPONATREMIA IN ONCOLOGY**

114   *Prevalence and etiology:*

115   HypoNa in patients with cancer is a common finding because three major pathogenetic factors may concur to its
116   development: the tumor, through the ectopic secretion of the antidiuretic hormone (ADH), also named vasopressin, the
117   anti-neoplastic treatments, and again the tumor itself, through non-hormonal mechanisms.

118   About 14% of all cases of hypoNa occurs in oncological patients (3). SIAD is one of the leading causes of hypoNa in
119   inpatients with cancer, affecting 1 to 2% of the entire cancer population (20, 21). The likelihood that SIAD is the cause
120   of hypoNa in cancer patients is >30% (22).

121   SIAD is commonly reported in small-cell lung cancer. However, hypoNa has been also reported in other tumors, such as
122   gastrointestinal, genitourinary, breast, prostate or hematological malignancies. SIAD in these patients may also be caused
123   by pharmacological treatments, e.g. by a number of chemotherapeutic agents, opioid analgesics, antidepressants,
124   including tricyclics and selective serotonin reuptake inhibitors (SSRI), as well as phenothiazines used as antiemetic agents
125   (Table 3) (23). Of notice, hypoNa in oncology patients may be secondary to other conditions besides SIAD (Table 4)
126   (22), and for this reason a careful differential diagnosis is needed. Finally, hypoNa can be precipitated by fluid and salt
127   losses due to emesis or diarrhea, with severely symptomatic acute hypoNa that can be superimposed to a relatively stable
128   chronic electrolyte imbalance.

129   *Mortality:*

130   HypoNa significantly contributes to both morbidity and mortality in cancer patients, and it is an independent prognostic
131   marker: in a large study, the hazard ratio risk of 90-day mortality for mild, moderate, and severe hypoNa was 2.04, 4.74
132   and 3.46, respectively (24).

133   *Notes on treatment:*

134   In general, the treatment strategy of hypoNa in oncologic patients is not different from that suggested by the available
135   recommendations (12-14).

136   However, specific situations may occur. For instance, in patients with mild hypoNa secondary to SIAD, fluid restriction
137   may be problematic, because of the need of parenteral hydration used during chemotherapy.

138   The use of urea for the treatment of hypoNa, especially in cases of SIAD, has also been proposed since the '80s (25, 26).
139   The rationale of this approach is based on the capability of urea to increase the free water clearance by the kidney. The
140   urea dosages usually used in patients with SIAD to correct serum sodium range between 15–30 g/day taken orally after
141   a meal in one or two doses (25).

142   While a few non controlled studies (27) (28) have reported that urea is effective in normalizing hypoNa, hypercorrection

143   with hypernatremia has also been reported in the same studies. In fact, the urea-induced increase in serum sodium

144   concentration is not easily predicted, as it depends on both hydration status and urine osmolality. Thus, while the European

145   Guidelines (13) recommend urea as the treatment of choice in patients with SIAD when water restriction is ineffective or

146   not feasible, poor palatability, scarce clinical experience and the risk of hypercorrection suggest that advantages and

147   disadvantages of urea should be balanced against the possible use of vasopressin receptor antagonists in this clinical

148   setting.

149   Therefore, a valuable option in cancer patients with SIAD could be represented by vaptans. In a recent prospective study

150   on small cell lung cancer patients with severe SIAD, tolvaptan led to an effective correction and stabilization of the serum

151   sodium levels, also enabling patients to receive chemotherapy without any delay (29). In addition, the use of vaptans may

152   avoid withdrawal of hypoNa-inducing chemotherapies.

153   The duration of treatment for hypoNa is largely dependent on the cause. In drug-induced hypoNa, the electrolyte

154   alteration is usually reverted within days after the cessation of the involved drug. Conversely, in ADH secreting tumors,

155   hypoNa usually requires a longer and somewhat unpredictable duration of therapy, which is also dependent on the

156   response to anti-tumoral treatments (30).

157   In summary, we suggest that hypoNa should be carefully taken into account and timely corrected in oncology patients,

158   preferably avoiding severe fluid restriction or agents that may increases nausea (urea), taking into account that the

159   normalization of sodium levels has been found to have a positive effect on the prognosis and length of in-hospital stay

160   (31).

161

162   **HYPONATREMIA IN THE ELDERLY**

163   *Prevalence and etiology:*

164   The prevalence of hypoNa is increased in elderly patients compared with that in the general population, reaching almost

165   50% of all acute geriatric admissions (32, 33).

166   In the elderly, the etiology of hypoNa is multifactorial in 50–75% of cases (34, 35). SIAD is the most common cause,

167   even if a risk of over-diagnosis has been claimed (34). Other frequent causes are congestive heart failure, water and

168   sodium homeostasis alterations, renal and hepatic dysfunction, and especially drug-induced hypoNa, because older people

169   often receive multiple pharmacological treatments (Table 5) (35) .

170   In elderly patients alterations of electrolyte and water balance are favoured by age-related reduction in total body water,

171   reduced renal function (36), decreased cortical blood flow and glomerular filtration rate, impaired responsiveness to

172   sodium balance changes (37), osmoreceptors hypersensitivity, and higher ADH release (38). Additionally, the ability to

173   excrete free water is reduced (39).

174   *Mortality:*

175   HypoNa is associated with increased all-cause mortality in elderly subjects: a recent study showed that the adjusted

176   hazards ratio (95%CI) in hyponatremic men without chronic kidney disease (CKD), stroke or heart failure was 1.30

177   (confidence interval 1.02 to 1.66) (40).

178   *Notes on clinical features and diagnosis:*

179 HypoNa in the elderly is mostly mild, chronic and apparently asymptomatic, but it often associated with bone
180 demineralization and cognitive impairment, increased risk of falls and fractures (7, 34).

181 Conversely, acute hypoNa in the elderly is characterized by confusion, irritability, lethargy, anorexia and nausea, but pre-
182 existing cognitive and sensory impairment might interfere with timely identification of symptoms (34, 38).

183 The diagnosis in older people may be challenging, due to polypharmacy, difficult assessment of fluid volume status by
184 clinical examination, presence of several confounding co-morbidities, and difficulties in obtaining a reliable clinical
185 history (34, 41).

186 *Notes on treatment:*

187 Treatment of both acute and chronic hypoNa in the elderly does not differ from that of younger patients (14, 34). Vaptans
188 could represent an option in hypoNa secondary to SIAD also in the elderly. The use of low doses - at least initially - may
189 reduce the risk of overtreatment. Appropriate hydration should be strictly monitored. In the case of hypovolemic hypoNa,
190 rehydration should be provided with special caution, especially when cardiac function is reduced and/or chronic kidney
191 disease coexist (36).

192

193 **HYPONATREMIA IN CONGESTIVE HEART FAILURE**

194 *Prevalence and etiology*

195 The prevalence of hypoNa among patients with heart failure (HF) is about 20-25% (42) (43) (44) (45) (46), however, it
196 may be higher in patients admitted for acutely decompensated HF (ADHF): 38% at hospital admission and 28% as new-
197 onset hyponatremia during hospital stay (47).

198 In this clinical setting, effective arterial blood volume (EABV) is decreased, due to low cardiac output and systemic
199 venous congestion. The decreased EABV releases the tonic baroreceptor-dependent inhibition on efferent sympathetic
200 tone and vasopressin release. The ensuing hyperactivation of the sympathetic nervous system, together with renal
201 hypoperfusion, is associated with decreased glomerular filtration rate, increased proximal sodium reabsorption and
202 reduced sodium delivery to distal nephron segments. These latter mechanisms and the high circulating vasopressin levels
203 – always disproportionate to the reduced plasma tonicity - are mainly responsible for decreased free water clearance and
204 development of HypoNa. On the other hand, secondary hyperaldosteronism due to increased renin release and elevated
205 circulating angiotensin II favors increased sodium reabsorption at the distal nephron, increased total body sodium balance,
206 edema formation and hypervolemic hypoNa (48).

207 *Mortality*

208 A correlation between hypoNa and overall mortality was first documented 30 years ago in HF. Moreover, in patients with
209 ADHF hypoNa is associated with an increased mortality and risk of re-hospitalization (47) (49). In particular, a recent
210 meta-analysis of the available data documented that hypoNa doubled the risk of mortality in patients with HF (9). In
211 addition, patients admitted for ADHF and normal serum sodium values at admission, it has also been shown that the
212 development and worsening of hypoNa during hospital stay are strongly correlated with an increase in overall and
213 cardiovascular mortality (50).

214 Finally, a recent retrospective study in patients admitted for ADHF with hypoNa at admission reported that even persistent
215 hypoNa at the time of hospital discharge is associated with a significant increase re-hospitalization or mortality at 30 days
216 (51).

217 *Notes on treatment*

218 Clearly, sodium and fluid restriction, diuretics, blockers of the renin-angiotensin-aldosterone system, and betablockers,
219 are the mainstay of treatment in patients with HF. While hypoNa bears a clear negative prognostic impact, few data are
220 currently available in the literature to clearly ascertain whether correction of hypoNa per se may ameliorate outcomes in
221 patients with HF (13). As a matter of fact, long-term treatment with tolvaptan in patients with HF was not associated with
222 decreased mortality or risk of re-hospitalization compared with placebo, notwithstanding greater weight loss, better
223 dyspnea relief, and a significant increase in serum sodium values at discharge (52). However, a post-hoc analysis of the
224 Acute and Chronic Therapeutic Impact of a Vasopressin antagonist (ACTIV) study (53) suggested a possible correlation
225 between increased serum sodium levels and increased survival. Furthermore, a post-hoc analysis of the Efficacy of
226 Vasopressin Antagonism in Heart Failure Outcome Study With Tolvaptan (EVEREST) trial showed decreased incidence
227 of the combined endpoint of cardiovascular mortality and cardiovascular morbidity in tolvaptan-treated patients with
228 serum sodium values Na <130 mEq/L (54). Thus, expert consensus by US investigators (14) suggested that vaptans
229 (tolvaptan, and possibly conivaptan, not licensed in Europe, so far) may represent a useful therapeutic tool in patients
230 with CHF and mild-to-moderate hyponatremia. On the other hand, based on the results of an extended meta-analysis
231 indicating a non-significant trend towards increased mortality in hyponatremic patients with expanded extracellular fluid
232 volume, European guidelines (13) are against the use of vaptans in conditions where hyponatremia is associated with
233 expanded extracellular fluid volume. A faster decongestion with dyspnea relief represents a desirable goal in the treatment
234 of patients with ADHF, and no cases of osmotic myelinolisis have been reported either in the ACTIV and EVEREST
235 trials or in the subgroup of patients with CHF enrolled in the Study of Ascending Levels of Tolvaptan in Hyponatremia
236 1 and 2 (SALT-1 and SALT-2) trials (55). For these reasons, the use of tolvaptan may be envisaged as a potentially useful
237 add-on treatment strategy in patients with CHF and mild-to moderate hypoNa. However, very recently, the Targeting
238 Acute Congestion with Tolvaptan in Congestive Heart Failure (TACTICS-HF) trial (56) reported no significant
239 differences in dyspnea relief and in-hospital or post-discharge clinical outcomes in patients with ADHF treated with
240 tolvaptan 30 mg given at 0, 24 and 48 hours on top of fixed-dose furosemide compared with patients receiving placebo,
241 despite greater weight loss and net fluid loss in tolvaptan-treated patients. Thus, at the present time no firm
242 recommendation about the use of vaptans in CHF can be supported by the available literature data.

243

244 **HYPONATREMIA IN DECOMPENSATED LIVER CIRRHOSIS**

245 *Prevalence and etiology*

246 The prevalence of hypoNa in patients admitted for decompensated liver cirrhosis reaches 57% (57). Between 21% and
247 28% of patients have serum sodium values <130 mEq/L (57-59), whereas severe hypoNa (serum Na ≤120 mEq/L) is
248 relatively infrequent (<1.2%) in this setting (57).

249 Post-sinusoidal capillary hypertension, hypoalbuminemia and splanchnic vasodilation play a pivotal role in ascites
250 accumulation; specifically, overproduction of nitric oxide, mainly due to circulating endotoxin associated with bacterial

251   translocation, maintains splanchnic vasodilation (60). In this clinical setting, pathophysiological mechanisms triggered

252   by decreased EABV are essentially the same as in HF. Thus, while total body sodium balance is increased, the

253   development of hypoNa is facilitated by reduced sodium delivery to the distal nephron and high circulating vasopressin

254   levels (60).

255   *Mortality*

256   The negative prognostic role of hypoNa in patients with liver cirrhosis has been clearly documented (59, 60). In a study

257   performed in 6769 patients with liver failure waiting for liver transplantation, of whom 422 had deceased within 90 days

258   since entering the waiting list, the investigators found an increased risk of death associated with hypoNa, even independent

259   of the MELD score (61). Accordingly a recent meta-analysis of the available data documented that hypoNa was associated

260   with more than 3-fold increased risk of mortality in patients with cirrhosis (9).

261   *Notes on treatment*

262   In patients with liver failure, treatment with vaptans has been shown to ameliorate fluid balance in some studies (62-64).

263   Moreover, treatment with satavaptan was associated with greater increase in serum sodium values and decreased ascites

264   formation in cirrhotic patients receiving either diuretics (65) and spironolactone (59). However, one of those studies (65)

265   also found an increase in the risk of death due to complication of cirrhosis in patients treated with both satavaptan and

266   diuretics, which subsequently lead to drug withdrawal from commerce. Lixivaptan, on top of standard treatment with

267   spironolactone, proved to be effective in increasing free water clearance and serum sodium values in patients with

268   decompensated liver cirrhosis (66).

269   Tolvaptan, so far the only vaptan approved in Europe, so far, and allowed only in patient with hypoNa secondary to SIAD,

270   has been also tested on top of standard treatment with furosemide and spironolactone in patients with decompensated

271   liver cirrhosis. Although the drug proved to be effective, also at low doses (e.g., 3.5 and 7.5 mg/day), in reducing ascites

272   volume and body weight (67), as well as in increasing serum sodium values (68, 69), however both the European

273   guidelines (13) and the US expert consensus document (14) recommend against the use of vaptans in patients with liver

274   disease. Anyway, as hypoNa may complicate the use of high-dose loop diuretics in oliguric patients with refractory ascites

275   and may predispose them to hepatic encephalopathy, a cautious use of tolvaptan in combination with diuretics may

276   represent a treatment strategy that should be explored in future research (60). In any case, liver function should be closely

277   monitored, and the drug should be discontinued if worsening of it is detected.

278

279   **HYPONATREMIA IN CHRONIC KIDNEY DISEASE**

280   *Prevalence and etiology*

281   Prevalence and incidence values of hypoNa in chronic kidney disease (CKD) are respectively 13.5% and 26% (mean

282   follow-up 5.5 years) (70). HypoNa is especially common among patients with stage 5 CKD on dialysis (End-Stage Renal

283   Disease, ESRD): 29.3% prevalence in hemodialysis, 14.5% incidence in peritoneal dialysis (71).

284   Three main pathogenetic mechanisms may lead to hypoNa in renal patients (72):

- Direct renal sodium loss, such as in salt-losing nephropathies (chronic pyelonephritis, chronic drug-associated or toxic tubule-interstitial), characterized by reduced renal sodium reabsorption, sodium and potassium depletion, reduced concentration ability, hypovolemia and ADH stimulation (73). The consequence is hypoNa with volume depletion.

- Reduced urinary dilution capacity due to severe impairment of glomerular filtration rate with ensuing lower availability of preurine at the diluting segments of the distal nephron and reduced ability to generate free water. In this case hypoNa will be euvolemic or hypervolemic (74) (72).

- Oligoanuria or anuria along with free water/hypotonic fluid intakes exceeding losses, such as the case of ESRD on chronic dialysis or in acute kidney injury. These forms of hypoNa are usually hypervolemic (74).

Mortality

Low sodium levels are associated with increased mortality risk, both in CKD patients on conservative treatment (70) and in ESRD patients on dialysis (75) (76, 77).

Notes on treatment

There is paucity of data in the literature concerning the treatment of hypoNa in patients with CKD on conservative therapy. The oral vasopressin V_2-receptor antagonist tolvaptan has been tested in small studies performed in CKD patients with or without congestive heart failure (78). On the whole, a significant increase in urine volume was observed, together with an increase in serum sodium concentration. Moreover, treatment with tolvaptan was not associated with deterioration of kidney function in these patients.

The problems of the treatment of hypoNa during renal replacement therapy (RRT), and the inherent risks of overcorrection and osmotic demyelization syndrome, have been addressed mainly in the critically ill patients. Specifically, reducing serum sodium concentration in the substitution fluids has been advocated as the best approach to avoid the risk of overcorrection during continuous veno-venous hemofiltration or continuous veno-venous hemodialysis (79). When standard intermittent hemodialysis is chosen, sodium concentration in the dialysate should be reduced to a minimum of 130 mEq/L, and blood flow rate as low as 50 mL/min together with short duration (e.g., 3 hours) of dialysis session should be prescribed (80).

HYPONATREMIA IN NEUROLOGY

Prevalence and etiology:

HypoNa is a frequent complication of traumatic brain injury and meningitis (81).

Limited information is available for other neurological disorders. A large Swedish registry study documented that epilepsy and stroke accounted for about 10% of all cases of hypoNa (82).

In subjects with stroke, many factors including dietary sodium restriction for hypertension control, use of thiazide diuretics and infections might precipitate hypoNa (83).

318 Several antiepileptic drugs (AEDs) and in particular carbamazepine, oxcarbazepine, eslicarbazepine and levetiracetam
319 may cause asymptomatic or mildly symptomatic hypoNa secondary to SIAD, which in turn may exacerbate seizures
320 (Table 3) (81).

321 HypoNa can occur in Guillain–Barré syndrome (GBS) as a consequence of SIAD caused by the intravenous
322 immunoglobulin therapy, or of renal salt wasting syndrome as part of GBS-related dysautonomia (84).

323 *Mortality:*

324 HypoNa is associated with an increased risk of mortality in patients with neurological diseases: in a Danish cohort study,
325 the adjusted 30-day relative risk of death among hyponatremic patients compared to patients with normonatremia was 1.5
326 (0.9 –2.5) (85).

327 Serum sodium evaluation should be mandatory in the presence of neurological symptoms. Routine sodium monitoring
328 for patients receiving AEDs is not usually necessary, except in elderly subjects or in those receiving AED polytherapy or
329 sodium depleting drugs (81).

330 *Notes on treatment:*

331 HypoNa in neurological patients should be managed according to the general recommendations. Treatment mainly
332 depends on etiology; it has been shown for instance that in traumatic brain injury treatment usually lasts 0.5-2 years (30).
333 In SIAD caused by AEDs, the possibility to reduce the dose, switch to a different drug or stop treatment should be
334 evaluated together with the neurologist.

335

336 **HYPONATREMIA IN NEUROSURGERY**

337 *Prevalence and etiology:*

338 Hypotonic hypoNa is a frequent finding in the neurosurgical patients, with the highest rate (20-50%) in some series among
339 patients with subarachnoid hemorrhage (SAH) (86, 87). Observational studies have shown that brain tumors, during their
340 course, may be associated with hypoNa in about 15-20% of cases (86). The occurrence of hypoNa as a result of
341 transphenoidal surgery varies a lot in the different series, depending on the selection criteria. Symptomatic hypoNa was
342 much less frequent (4-7%) than asymptomatic hypoNa, which in some series occurred in up to 20-35% of patients,
343 according to serum sodium measured every day for at least 12 days after surgery (88-90).

344 Some neurosurgical disorders, such as acute and chronic SAH, subdural hematoma, hemorrhagic stroke, tumors, cysts,
345 metastases, and inflammatory diseases of the brain, pituitary, or hypothalamus, become harder to manage when hypoNa
346 develops (86, 87, 90-92). Such a complication may occur both before and after surgery. HypoNa may also be observed at
347 presentation in patients with pituitary apoplexy yet much less frequently than hypernatremia due to diabetes insipidus
348 (DI).

349 *Mortality*

350 Besides hypoNa, several other factors may contribute to increase the mortality risk in the neurosurgery setting. A recent
351 systematic review, aimed at characterizing the effect of hypoNa on morbidity and mortality after SAH, included thirteen
352 studies with a total number of 2387 patients and showed that hypoNa was associated with increased morbidity (especially
353 due to vasospasm), but it did not influence mortality (87). Interestingly, a recent retrospective observational study

354 reviewed 198 consecutive patients with SAH and indicated sodium fluctuation, rather than hypoNa per se, as a significant

355 factor associated with worse neurologic outcome (91)

356 *Specific notes on clinical features and diagnosis:*

357 Most observational studies have shown that SIAD is the commonest cause of hypotonic hypoNa in neurosurgical patients

358 (86). However, in this setting it is essential to differentiate SIAD and cerebral salt wasting syndrome (CSWS) as a possible

359 cause of hypoNa, especially in pediatric series and in patients with SAH (86, 92, 93). The differential diagnosis between

360 CSWS and SIAD may not be easy in clinical practice, the former having hypovolemia as a crucial point for the proper

361 diagnosis (94).

362 In the evaluation of the hyponatremic patient after neurosurgery, it is essential to consider the possible occurrence of DI

363 with a triphasic pattern (95) and the possible late occurrence of hypoNA due to SIAD, which can occur after the patient

364 has been discharged (88-90)

365 In order to improve the outcome in neurosurgical patients, we suggest careful monitoring of serum sodium on admission

366 and during the hospital stay. Whenever hypoNa is observed, a proper work-up has to be instructed to elucidate the

367 underlying cause, bearing in mind that the evaluation of extracellular fluid volume status is mandatory. Also in case of

368 early discharge the patients should receive clear instructions on what to do if hypoNa-compatible symptoms appear.

369

370 **HYPONATREMIA IN THE PATIENT WITH TRAUMA AND POLYTRAUMA**

371 *Prevalence and etiology*

372 Little is known about hypoNa in patients with polytrauma (PT). In several studies, hypoNa has been reported in up to

373 15% of patients after trauma or PT (96, 97). After PT, the occurrence of hypoNa can be related to the event *per se* (fluid

374 depletion, hemorrhage), to the immediate treatment at the site of trauma or Emergency Department (hypotonic intravenous

375 fluids), or to a pre-existing comorbidity disease, especially in the elderly.

376 *Mortality*

377 HypoNa is associated with poor prognosis and increased mortality in patients with crush syndrome: in a retrospective

378 study conducted in Chinese reference hospitals during the Wenchuan earthquake the presence of hypoNA was common,

379 up to 50% of patients were affected and 15% of them died. However, here the hypoNa was mainly correlated with the

380 development of acute kidney failure (96).

381 *Notes on clinical features and diagnosis*

382 Hip fracture is the commonest cause of traumatic death in Europe: immediate surgery has been associated with higher

383 rates of independent living, lower mortality rates, improved patient outcomes by reducing pain scores, and lowering the

384 risk of decubitus ulcers. The occurrence of hypoNa ($[Na]^+$ <135 mEq/L) in the course of the pre-surgical planning was

385 the main medical pre-operative risk factor for surgery delay after 36 hours from trauma (98).

386 Rather than considering hypoNa always as a consequence of PT, this electrolyte disorder could be the cause of trauma:

387 even mild hypoNa in fact has been associated with unsteady gait, falls, impaired concentration, and risk of fractures,

388 especially hip and femur fractures (6, 99). In an extensive series of elderly adults, fracture risk incidence was higher in

389 patients with HypoNa, also after adjusting for osteoporosis. Patients with moderate-severe hypoNa ($[Na]^+$ <130 mEq/L)

390 presented an 11-fold risk of fractures (100), and fragility fractures increased incrementally with a categorical decrease in

391 median serum sodium levels in multivariate logistic regression models (101).

392 *Notes on treatment*

393 Specific consensus about the treatment of hypoNa targeted to PT patients has not been developed, yet. In general, we

394 suggest to follow currently available guidelines and recommendations for the management of hypoNa.

395 HypoNa is common in PT patients without neurological involvement: however, larger studies are needed to investigate

396 the relationship between trauma and serum sodium levels, and hypotonic intravenous fluids should be supplied carefully

397 to patients with PT.

398 HypoNa is not always recognized in patients with PT: we suggest to pay attention to sodium balance in such patients.

399 Population studies with a large number of participants have to be performed.

400

401 **HYPONATREMIA IN THE OUTPATIENT SETTING**

402 *Prevalence and etiology:*

403 The prevalence of hypoNa in this setting greatly depends on the age of the population considered (102-105). In a young

404 and ethnically diverse population, the prevalence of hypoNa was 6.3% (105), but with aging the potential risk of

405 developing hypoNa increases (103, 106).

406 In the outpatient setting, hyponatremic individuals are more likely to be smokers, to have black ethnicity, a history of

407 diabetes mellitus, congestive HF or cirrhosis and to use thiazide diuretics, antiepileptic drugs or SSRI (103, 105).

408 However, in the Dallas Heart Study, among hyponatremic individuals with no predisposing medical conditions, 20% of

409 them had criteria discriminators of the diagnosis of SIAD (105).

410 *Mortality:*

411 There are limited data in the literature regarding hypoNa in the outpatient setting, but similarly to hospitalized patients,

412 also in the outpatient studies hypoNa has been reported to be an independent mortality risk factor (9, 102, 105, 107, 108).

413 In a recent survey, hypoNa was found to be associated with a nearly two-fold increase in deaths, even after adjusting for

414 major risk factors (105).

415 *Specific notes on clinical features and diagnosis:*

416 HypoNa in the outpatient is more likely to be mild, chronic and asymptomatic (103, 105, 107).

417 Actually, in clinical practice, hypoNa very often represents an incidental finding during an outpatient visit for another

418 reason and it is difficult for the physician to formulate promptly a correct etiological diagnosis, which greatly depends on

419 additional laboratory tests that may not be readily available.

420 *Notes on treatment:*

421 In the case of moderately or severely symptomatic hypoNa, hospitalization should be considered.

422 In the case of hypoNa secondary to SIAD, when vaptans use is indicated, patients should be hospitalized, because of the

423 need of close initial monitoring, and to identify the appropriate dose (9, 109). A day-hospital admission may be suitable

424 if there are no other serious concomitant disorders (110).

425 A regular outpatient follow-up is recommended, to evaluate the effectiveness of the therapy as well as the possibility of
426 discontinuing it.

427   We suggest that hypoNa in this setting should be taken into consideration even if mild to moderate hypoNa to timely
428 correct it, particularly in the elderly and in patients assuming drugs, thus likely limiting the consequences of persistent
429 low sodium levels.

430

431 **LIFE-THREATENING HYPONATREMIA**

432 *Prevalence and etiology:*

433 Acute and severely symptomatic hypoNa is rare. However, if not rapidly recognized and correctly treated, it may carry a
434 high morbidity and mortality rate, even in previously healthy subjects, such as for example marathon runners, in which
435 an incidence of 13% has been documented (111). Other causes can be represented by the rapid ingestion of large amounts
436 of water, for example in psychiatric patients, or of other hypotonic liquids, such as in beer potomania or tea and toast diet.
437 Other conditions associated with acute and potentially life-threatening hypoNa are the postoperative period, in particular
438 after prostate transuretral resection or post uterine endoscopic surgery due to the use of hypotonic irrigant solutions,
439 colonoscopy preparation, the use of some drugs such as oxytocin or cyclophosphamide, or a recent prescription of
440 thiazides or desmopressin, and use of recreational drugs such as ecstasy (MDMA) (13, 112). The severity of the picture
441 correlates both with the magnitude and the rate of sodium decrease.

442

443 *Mortality:*

444   Mortality in this setting has been noted to be as high as 55% (113). However, the estimate from a broad-based literature
445 survey gives much lower values (114).

446 *Specific notes on clinical features and diagnosis:*

447 HypoNa may be itself the direct cause of death because of brain stem herniation due to cerebral edema for serum hypo-
448 tonicity. Risk factors for brain edema are both the rate and the depth of sodium fall.

449 The risk of death as a consequence of brain edema is increased in the presence of an intracranial disease, in the case of
450 post-operative hypoNa or acute water intoxication.

451 *Notes on treatment:*

452 Prompt infusion of hypertonic saline, independent of volume status, may save lives in life-threatening hypoNa.

453 In this emergency setting hypertonic 3% NaCl saline solution is administered as a 100/150 mL bolus (or 2 ml/Kg of body
454 weight) given over 10-20 min, strictly monitoring sodium levels (every 20 min), and repeating the bolus administration,
455 as needed, up to a maximum of 3 times. According to the European guidelines, this protocol is recommended until a
456 serum sodium increase of 5 mEq/L is achieved (13).

457 In the case of symptoms improvement and/or after a 5-6 mEq/L increase in serum sodium (symptoms relief can take
458 longer), 3% NaCl should be stopped, but the i.v. access kept. Meanwhile a diagnosis-specific process should be initiated,
459 and appropriate management performed (13, 14).

460 In the absence of symptoms improvement after the first few hours, i.v. hypertonic 3% NaCl saline should be continued
461 aiming for an additional 1 mEq/L/h increase in serum sodium, limiting the overall 24 hours increase to 8-10 mEq/L and
462 stopping anyway the infusion upon reaching a serum sodium level of 130 mEq/L (13, 14). Therapy should be guided by
463 frequent monitoring of serum sodium concentration (possibly every 2 hours, but at least every 4 hours).

464

465 **HYPONATREMIA OVERCORRECTION: CONDITIONS AT RISK, PREVENTION, TREATMENT**

466 Excessive correction of hypoNa (i.e. too much and/or too rapid increase of serum sodium levels) is associated with an
467 increased risk of negative neurologic outcomes (i.e. the ODS), especially in the chronic forms of hypoNa. On this regard,
468 specific attention is to be paid to the fact that during sodium correction an adequate renal response to hypotonicity (i.e.
469 an hypotonic polyuria) is often spontaneously (and rapidly) restored, even since the first 8-12 hours from treatment start.
470 This usually happens when pathogenetic factors responsible for the electrolyte derangement are promptly taken away,
471 such as for example by volume expansion with 0.9% saline in hypovolemic hypoNa, or by ceasing the trigger mechanism
472 for inappropriate secretion/response to ADH (i.e. drugs or inflammation). Thus, since the most frequent cause of hypoNa
473 overcorrection is actually the reactivation of the normal renal physiological response (increased free water clearance),
474 special attention should be paid to hypoNa settings characterized by rapidly reversible causes (Table 1) (18). A hypotonic
475 polyuria with maximally diluted urine output may in fact further increase the programmed/estimated rate of correction.

476 In such a circumstance, administration of a hypotonic solution should be started, as intravenous 5% dextrose or free water
477 by a nasogastric tube, initially at 10 ml/Kg/h over 1 h (13) or in repeated 3ml/kg infusions (14) and then matched to
478 urinary output in terms of rate and tonicity; desmopressin (i.v. or s.c.) at 2-4 μg every 8 hours can be associated, in order
479 to bring back the rate of correction to below 12 mEq/L/24 hours (or better to a target of 6-8 mEq/L in the first 24 hours)
480 (13). It is mandatory that specific measures to blunt overcorrection of hypoNa must be implemented by/or under the
481 direction of experienced medical personnel (13) .

482 Another possible (and underrated) cause of overcorrection of hypoNa is represented by the administration of potassium
483 salts along with NaCl, aiming at correcting coexisting hypokalemia/potassium depletion. Based on the original Edelman
484 equation, potassium and sodium salts are equivalent in terms of tonicity effects (115). In fact, in case of cellular potassium
485 depletion, the administered potassium enters the cells, with ensuing Na exit in order to maintain the electrical equilibrium.
486 Thus, serum sodium values increase (116).

487 The risk of overcorrection is not significantly reduced by the use of specific formulas aimed at estimating the rate and the
488 temporal trajectory of serum sodium during correction (117). Formulas may be useful to set the start of therapy, but they
489 do not completely avoid the risk of overcorrection due to their inherent limitations: they do not take into account the
490 possibility of a rapidly restored diluting capacity by the kidney, ongoing losses and other electrolyte supplements are
491 difficult to be integrated in the calculation, as it is the case of potassium administration in potassium depletion (117).
492 More conservatively, in these cases it is better to frequently check (at least every 4 hours in the first 24 hours) the actual
493 serum sodium levels.

494 Finally, it should kept in mind that some conditions are associated with a higher risk of ODS due to overly rapid correction
495 of hypoNa: serum sodium levels less than 105 mEq/L, alcoholism, malnutrition, advanced liver disease (14) Table 1.

496   These conditions must be recognized even before the start of treatment and a great caution should be used in these
497   situations.

498

499   **CONCLUSIONS**

500   Despite being the most common electrolyte disorder encountered in clinical practice, hypoNa is frequently
501   underdiagnosed and/or not appropriately treated. This may be due to a lack of awareness of the implications of this
502   condition on patient outcomes, particularly when hospital-acquired and mildly or moderately symptomatic. Appropriate
503   workup and treatment in the various clinical settings associated with hypoNa require a multidisciplinary approach. In
504   such a need, this task force has provided the above-outlined suggestions and warnings. Ineffective management of hypoNa
505   can negatively affect patient prognosis. New therapeutic options for the correction of hypoNa, particularly vaptans, the
506   vasopressin receptor antagonists, represent an effective tool to safely treat this disorder and improve outcomes among a
507   wide range of patients with hypoNa secondary to SIAD. However, the different clinical scenarios in which hypoNa may
508   occur suggest that a thoughtful and personalized management should be individuated. This scenario is even more complex
509   when we consider that not all the hospitals are properly equipped to perform an accurate differential diagnosis of hypoNa.
510   As an example, the infrequent availability of osmometers in the medium/small hospital facilities is a limiting factor for
511   the diagnosis of SIAD. Thus, we propose that clinicians may refer to calculated serum and/or urinary osmolality according
512   to recently reviewed formulae (118).

513   A rapid recognition and optimal treatment of hypoNa can reduce the risk of death (119), also reducing the length of
514   hospitalization and associated costs, and improving the quality of life.

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REFERENCES

1.   Upadhyay A, Jaber BL, Madias NE. Incidence and prevalence of hyponatremia. Am J Med. 2006;119(7 Suppl 1):S30-5.

2.   Adrogue HJ, Madias NE. Hyponatremia. N Engl J Med. 2000;342(21):1581-9.

3.   Gill G, Huda B, Boyd A, Skagen K, Wile D, Watson I, et al. Characteristics and mortality of severe hyponatraemia--a hospital-based study. Clin Endocrinol (Oxf). 2006;65(2):246-9.

4.   Renneboog B, Musch W, Vandemergel X, Manto MU, Decaux G. Mild chronic hyponatremia is associated with falls, unsteadiness, and attention deficits. Am J Med. 2006;119(1):71 e1-8.

5.   Gankam Kengne F, Andres C, Sattar L, Melot C, Decaux G. Mild hyponatremia and risk of fracture in the ambulatory elderly. QJM. 2008;101(7):583-8.

6.   Kinsella S, Moran S, Sullivan MO, Molloy MG, Eustace JA. Hyponatremia independent of osteoporosis is associated with fracture occurrence. Clin J Am Soc Nephrol. 2010;5(2):275-80.

7.   Verbalis JG, Barsony J, Sugimura Y, Tian Y, Adams DJ, Carter EA, et al. Hyponatremia-induced osteoporosis. J Bone Miner Res. 2010;25(3):554-63.

8.   Barsony J, Sugimura Y, Verbalis JG. Osteoclast response to low extracellular sodium and the mechanism of hyponatremia-induced bone loss. J Biol Chem. 2011;286(12):10864-75.

9.   Corona G, Giuliani C, Parenti G, Norello D, Verbalis JG, Forti G, et al. Moderate hyponatremia is associated with increased risk of mortality: evidence from a meta-analysis. PLoS One. 2013;8(12):e80451.

10.   Corona G, Giuliani C, Parenti G, Colombo GL, Sforza A, Maggi M, et al. The Economic Burden of Hyponatremia: Systematic Review and Meta-Analysis. Am J Med. 2016;129(8):823-35 e4.

11.   Chambrey R, Trepiccione F. Relative roles of principal and intercalated cells in the regulation of sodium balance and blood pressure. Curr Hypertens Rep. 2015;17(4):538.

12.   Cuesta M, Garrahy A, Thompson CJ. SIAD: practical recommendations for diagnosis and management. J Endocrinol Invest. 2016;39(9):991-1001.

13.   Spasovski G, Vanholder R, Allolio B, Annane D, Ball S, Bichet D, et al. Clinical practice guideline on diagnosis and treatment of hyponatraemia. Intensive Care Med. 2014;40(3):320-31.

14.   Verbalis JG, Goldsmith SR, Greenberg A, Korzelius C, Schrier RW, Sterns RH, et al. Diagnosis, evaluation, and treatment of hyponatremia: expert panel recommendations. Am J Med. 2013;126(10 Suppl 1):S1-42.

15.   Hoorn EJ, Lindemans J, Zietse R. Development of severe hyponatraemia in hospitalized patients: treatment-related risk factors and inadequate management. Nephrol Dial Transplant. 2006;21(1):70-6.

16.   Rondon-Berrios H, Berl T. Vasopressin receptor antagonists: Characteristics and clinical role. Best Pract Res Clin Endocrinol Metab. 2016;30(2):289-303.

17.   Spasovski G, Vanholder R, Allolio B, Annane D, Ball S, Bichet D, et al. Clinical practice guideline on diagnosis and treatment of hyponatraemia. Nephrol Dial Transplant. 2014;29 Suppl 2:i1-i39.

18.   Regolisti G, Cabassi A, Antonucci E, Brusasco I, Cademartiri C, Pistolesi V, et al. [Hyponatremia in clinical practice]. G Ital Nefrol. 2015;32(1).

19.   Aylwin S, Burst V, Peri A, Runkle I, Thatcher N. 'Dos and don'ts' in the management of hyponatremia. Curr Med Res Opin. 2015;31(9):1755-61.

20.   Glover DJ, Glick JH. Metabolic oncologic emergencies. CA Cancer J Clin. 1987;37(5):302-20.

21.   Silverman P, Distelhorst CW. Metabolic emergencies in clinical oncology. Semin Oncol. 1989;16(6):504-15.

22.   Berghmans T, Paesmans M, Body JJ. A prospective study on hyponatraemia in medical cancer patients: epidemiology, aetiology and differential diagnosis. Support Care Cancer. 2000;8(3):192-7.

23.   Liamis G, Milionis H, Elisaf M. A review of drug-induced hyponatremia. Am J Kidney Dis. 2008;52(1):144-53.

24.   Doshi SM, Shah P, Lei X, Lahoti A, Salahudeen AK. Hyponatremia in hospitalized cancer patients and its impact on clinical outcomes. Am J Kidney Dis. 2012;59(2):222-8.

25.   Sterns RH, Silver SM, Hix JK. Urea for hyponatremia? Kidney Int. 2015;87(2):268-70.

26.   Decaux G, Unger J, Brimioulle S, Mockel J. Hyponatremia in the syndrome of inappropriate secretion of antidiuretic hormone. Rapid correction with urea, sodium chloride, and water restriction therapy. JAMA. 1982;247(4):471-4.

27.   Decaux G, Andres C, Gankam Kengne F, Soupart A. Treatment of euvolemic hyponatremia in the intensive care unit by urea. Crit Care. 2010;14(5):R184.

28.   Soupart A, Coffernils M, Couturier B, Gankam-Kengne F, Decaux G. Efficacy and tolerance of urea compared with vaptans for long-term treatment of patients with SIADH. Clin J Am Soc Nephrol. 2012;7(5):742-7.

29.   Petereit C, Zaba O, Teber I, Luders H, Grohe C. A rapid and efficient way to manage hyponatremia in patients with SIADH and small cell lung cancer: treatment with tolvaptan. BMC Pulm Med. 2013;13:55.

30.   Verbalis JG. Managing hyponatremia in patients with syndrome of inappropriate antidiuretic hormone secretion. Endocrinol Nutr. 2010;57 Suppl 2:30-40.

31.   Berardi R, Caramanti M, Castagnani M, Guglielmi S, Marcucci F, Savini A, et al. Hyponatremia is a predictor of hospital length and cost of stay and outcome in cancer patients. Support Care Cancer. 2015;23(10):3095-101.

32.   Berl T. An elderly patient with chronic hyponatremia. Clin J Am Soc Nephrol. 2013;8(3):469-75.

33.   Mannesse CK, Vondeling AM, van Marum RJ, van Solinge WW, Egberts TC, Jansen PA. Prevalence of hyponatremia on geriatric wards compared to other settings over four decades: a systematic review. Ageing Res Rev. 2013;12(1):165-73.

34.   Soiza RL, Cumming K, Clarke JM, Wood KM, Myint PK. Hyponatremia: Special Considerations in Older Patients. J Clin Med. 2014;3(3):944-58.

35.   Shapiro DS, Sonnenblick M, Galperin I, Melkonyan L, Munter G. Severe hyponatraemia in elderly hospitalized patients: prevalence, aetiology and outcome. Intern Med J. 2010;40(8):574-80.

36.   Beck LH. Changes in renal function with aging. Clin Geriatr Med. 1998;14(2):199-209.

37.   Lindeman RD, Tobin J, Shock NW. Longitudinal studies on the rate of decline in renal function with age. J Am Geriatr Soc. 1985;33(4):278-85.

38.   Moran D, Fronk C, Mandel E. Managing hyponatremia in adults. JAAPA. 2014;27(4):23-9; quiz 30.

39.   Kugler JP, Hustead T. Hyponatremia and hypernatremia in the elderly. Am Fam Physician. 2000;61(12):3623-30.

40.   Wannamethee SG, Shaper AG, Lennon L, Papacosta O, Whincup P. Mild hyponatremia, hypernatremia and incident cardiovascular disease and mortality in older men: A population-based cohort study. Nutr Metab Cardiovasc Dis. 2016;26(1):12-9.

41.   Hoyle GE, Chua M, Soiza RL. Volaemic assessment of the elderly hyponatraemic patient: reliability of clinical assessment and validation of bioelectrical impedance analysis. QJM. 2011;104(1):35-9.

42.   De Luca L, Klein L, Udelson JE, Orlandi C, Sardella G, Fedele F, et al. Hyponatremia in patients with heart failure. Am J Cardiol. 2005;96(12A):19L-23L.

621 43.   Gheorghiade M, Abraham WT, Albert NM, Gattis Stough W, Greenberg BH, O'Connor
622 CM, et al. Relationship between admission serum sodium concentration and clinical outcomes
623 in patients hospitalized for heart failure: an analysis from the OPTIMIZE-HF registry. Eur
624 Heart J. 2007;28(8):980-8.
625 44.   Friedewald VE, Emmett M, Gheorghiade M, Roberts WC. The editor's roundtable:
626 pathophysiology and management of hyponatremia and the role of vasopressin antagonists.
627 Am J Cardiol. 2011;107(9):1357-64.
628 45.   Farmakis D, Filippatos G, Parissis J, Kremastinos DT, Gheorghiade M. Hyponatremia in
629 heart failure. Heart Fail Rev. 2009;14(2):59-63.
630 46.   Gheorghiade M, Rossi JS, Cotts W, Shin DD, Hellkamp AS, Pina IL, et al. Characterization
631 and prognostic value of persistent hyponatremia in patients with severe heart failure in the
632 ESCAPE Trial. Arch Intern Med. 2007;167(18):1998-2005.
633 47.   Wald R, Jaber BL, Price LL, Upadhyay A, Madias NE. Impact of hospital-associated
634 hyponatremia on selected outcomes. Arch Intern Med. 2010;170(3):294-302.
635 48.   Urso C, Brucculeri S, Caimi G. Acid-base and electrolyte abnormalities in heart failure:
636 pathophysiology and implications. Heart Fail Rev. 2015;20(4):493-503.
637 49.   Bettari L, Fiuzat M, Shaw LK, Wojdyla DM, Metra M, Felker GM, et al. Hyponatremia and
638 long-term outcomes in chronic heart failure--an observational study from the Duke Databank
639 for Cardiovascular Diseases. J Card Fail. 2012;18(1):74-81.
640 50.   Konishi M, Haraguchi G, Ohigashi H, Sasaoka T, Yoshikawa S, Inagaki H, et al.
641 Progression of hyponatremia is associated with increased cardiac mortality in patients
642 hospitalized for acute decompensated heart failure. J Card Fail. 2012;18(8):620-5.
643 51.   De Vecchis R, Di Maio M, Di Biase G, Ariano C. Effects of Hyponatremia Normalization
644 on the Short-Term Mortality and Rehospitalizations in Patients with Recent Acute
645 Decompensated Heart Failure: A Retrospective Study. J Clin Med. 2016;5(10).
646 52.   Konstam MA, Gheorghiade M, Burnett JC, Jr., Grinfeld L, Maggioni AP, Swedberg K, et al.
647 Effects of oral tolvaptan in patients hospitalized for worsening heart failure: the EVEREST
648 Outcome Trial. JAMA. 2007;297(12):1319-31.
649 53.   Rossi J, Bayram M, Udelson JE, Lloyd-Jones D, Adams KF, Oconnor CM, et al.
650 Improvement in hyponatremia during hospitalization for worsening heart failure is
651 associated with improved outcomes: insights from the Acute and Chronic Therapeutic Impact
652 of a Vasopressin Antagonist in Chronic Heart Failure (ACTIV in CHF) trial. Acute Card Care.
653 2007;9(2):82-6.
654 54.   Hauptman PJ, Burnett J, Gheorghiade M, Grinfeld L, Konstam MA, Kostic D, et al. Clinical
655 course of patients with hyponatremia and decompensated systolic heart failure and the effect
656 of vasopressin receptor antagonism with tolvaptan. J Card Fail. 2013;19(6):390-7.
657 55.   Schrier RW, Gross P, Gheorghiade M, Berl T, Verbalis JG, Czerwiec FS, et al. Tolvaptan, a
658 selective oral vasopressin V2-receptor antagonist, for hyponatremia. N Engl J Med.
659 2006;355(20):2099-112.
660 56.   Felker GM, Mentz RJ, Adams KF, Cole RT, Egnaczyk GF, Patel CB, et al. Tolvaptan in
661 Patients Hospitalized With Acute Heart Failure: Rationale and Design of the TACTICS and the
662 SECRET of CHF Trials. Circ Heart Fail. 2015;8(5):997-1005.
663 57.   Angeli P, Wong F, Watson H, Gines P, Investigators C. Hyponatremia in cirrhosis:
664 Results of a patient population survey. Hepatology. 2006;44(6):1535-42.
665 58.   Gines P, Berl T, Bernardi M, Bichet DG, Hamon G, Jimenez W, et al. Hyponatremia in
666 cirrhosis: from pathogenesis to treatment. Hepatology. 1998;28(3):851-64.
667 59.   Gines P, Guevara M. Hyponatremia in cirrhosis: pathogenesis, clinical significance, and
668 management. Hepatology. 2008;48(3):1002-10.
669 60.   Fukui H. Do vasopressin V2 receptor antagonists benefit cirrhotics with refractory
670 ascites? World J Gastroenterol. 2015;21(41):11584-96.

671 61.   Kim WR, Biggins SW, Kremers WK, Wiesner RH, Kamath PS, Benson JT, et al.
672 Hyponatremia and mortality among patients on the liver-transplant waiting list. N Engl J Med.
673 2008;359(10):1018-26.
674 62.   Guyader D, Patat A, Ellis-Grosse EJ, Orczyk GP. Pharmacodynamic effects of a
675 nonpeptide antidiuretic hormone V2 antagonist in cirrhotic patients with ascites. Hepatology.
676 2002;36(5):1197-205.
677 63.   Gines P, Wong F, Watson H, Terg R, Bruha R, Zarski JP, et al. Clinical trial: short-term
678 effects of combination of satavaptan, a selective vasopressin V2 receptor antagonist, and
679 diuretics on ascites in patients with cirrhosis without hyponatraemia--a randomized, double-
680 blind, placebo-controlled study. Aliment Pharmacol Ther. 2010;31(8):834-45.
681 64.   Wong F, Gines P, Watson H, Horsmans Y, Angeli P, Gow P, et al. Effects of a selective
682 vasopressin V2 receptor antagonist, satavaptan, on ascites recurrence after paracentesis in
683 patients with cirrhosis. J Hepatol. 2010;53(2):283-90.
684 65.   Wong F, Watson H, Gerbes A, Vilstrup H, Badalamenti S, Bernardi M, et al. Satavaptan
685 for the management of ascites in cirrhosis: efficacy and safety across the spectrum of ascites
686 severity. Gut. 2012;61(1):108-16.
687 66.   Gerbes AL, Gulberg V, Gines P, Decaux G, Gross P, Gandjini H, et al. Therapy of
688 hyponatremia in cirrhosis with a vasopressin receptor antagonist: a randomized double-blind
689 multicenter trial. Gastroenterology. 2003;124(4):933-9.
690 67.   Okita K, Kawazoe S, Hasebe C, Kajimura K, Kaneko A, Okada M, et al. Dose-finding trial
691 of tolvaptan in liver cirrhosis patients with hepatic edema: A randomized, double-blind,
692 placebo-controlled trial. Hepatol Res. 2014;44(1):83-91.
693 68.   Sakaida I, Kawazoe S, Kajimura K, Saito T, Okuse C, Takaguchi K, et al. Tolvaptan for
694 improvement of hepatic edema: A phase 3, multicenter, randomized, double-blind, placebo-
695 controlled trial. Hepatol Res. 2014;44(1):73-82.
696 69.   Watkins PB, Lewis JH, Kaplowitz N, Alpers DH, Blais JD, Smotzer DM, et al. Clinical
697 Pattern of Tolvaptan-Associated Liver Injury in Subjects with Autosomal Dominant Polycystic
698 Kidney Disease: Analysis of Clinical Trials Database. Drug Saf. 2015;38(11):1103-13.
699 70.   Kovesdy CP, Lott EH, Lu JL, Malakauskas SM, Ma JZ, Molnar MZ, et al. Hyponatremia,
700 hypernatremia, and mortality in patients with chronic kidney disease with and without
701 congestive heart failure. Circulation. 2012;125(5):677-84.
702 71.   Dimitriadis C, Sekercioglu N, Pipili C, Oreopoulos D, Bargman JM. Hyponatremia in
703 peritoneal dialysis: epidemiology in a single center and correlation with clinical and
704 biochemical parameters. Perit Dial Int. 2014;34(3):260-70.
705 72.   Khan S, Floris M, Pani A, Rosner MH. Sodium and Volume Disorders in Advanced
706 Chronic Kidney Disease. Adv Chronic Kidney Dis. 2016;23(4):240-6.
707 73.   Negro A, Regolisti G, Perazzoli F, Davoli S, Sani C, Rossi E. Ifosfamide-induced renal
708 Fanconi syndrome with associated nephrogenic diabetes insipidus in an adult patient.
709 Nephrol Dial Transplant. 1998;13(6):1547-9.
710 74.   Combs S, Berl T. Dysnatremias in patients with kidney disease. Am J Kidney Dis.
711 2014;63(2):294-303.
712 75.   Waikar SS, Curhan GC, Brunelli SM. Mortality associated with low serum sodium
713 concentration in maintenance hemodialysis. Am J Med. 2011;124(1):77-84.
714 76.   Nigwekar SU, Wenger J, Thadhani R, Bhan I. Hyponatremia, mineral metabolism, and
715 mortality in incident maintenance hemodialysis patients: a cohort study. Am J Kidney Dis.
716 2013;62(4):755-62.
717 77.   Hecking M, Karaboyas A, Saran R, Sen A, Inaba M, Rayner H, et al. Dialysate sodium
718 concentration and the association with interdialytic weight gain, hospitalization, and
719 mortality. Clin J Am Soc Nephrol. 2012;7(1):92-100.

78. Tanaka A, Katsuno T, Ozaki T, Sakata F, Kato N, Suzuki Y, et al. The efficacy of tolvaptan as a diuretic for chronic kidney disease patients. Acta Cardiol. 2015;70(2):217-23.

79. Dangoisse C, Dickie H, Tovey L, Ostermann M. Correction of hyper- and hyponatraemia during continuous renal replacement therapy. Nephron Clin Pract. 2014;128(3-4):394-8.

80. Wendland EM, Kaplan AA. A proposed approach to the dialysis prescription in severely hyponatremic patients with end-stage renal disease. Semin Dial. 2012;25(1):82-5.

81. Ball SG, Iqbal Z. Diagnosis and treatment of hyponatraemia. Best Pract Res Clin Endocrinol Metab. 2016;30(2):161-73.

82. Gisby M, Lundberg J, Landin M, O'Reilly K, Robinson P, Sobocki P, et al. The burden of illness in patients with hyponatraemia in Sweden: a population-based registry study. Int J Clin Pract. 2016;70(4):319-29.

83. Rodrigues B, Staff I, Fortunato G, McCullough LD. Hyponatremia in the prognosis of acute ischemic stroke. J Stroke Cerebrovasc Dis. 2014;23(5):850-4.

84. Hiew FL, Winer JB, Rajabally YA. Hyponatraemia in Guillain-Barre syndrome revisited. Acta Neurol Scand. 2016;133(4):295-301.

85. Holland-Bill L, Christiansen CF, Heide-Jorgensen U, Ulrichsen SP, Ring T, Jorgensen JO, et al. Hyponatremia and mortality risk: a Danish cohort study of 279 508 acutely hospitalized patients. Eur J Endocrinol. 2015;173(1):71-81.

86. Sherlock M, O'Sullivan E, Agha A, Behan LA, Owens D, Finucane F, et al. Incidence and pathophysiology of severe hyponatraemia in neurosurgical patients. Postgrad Med J. 2009;85(1002):171-5.

87. Mapa B, Taylor BE, Appelboom G, Bruce EM, Claassen J, Connolly ES, Jr. Impact of Hyponatremia on Morbidity, Mortality, and Complications After Aneurysmal Subarachnoid Hemorrhage: A Systematic Review. World Neurosurg. 2016;85:305-14.

88. Kelly DF, Laws ER, Jr., Fossett D. Delayed hyponatremia after transsphenoidal surgery for pituitary adenoma. Report of nine cases. J Neurosurg. 1995;83(2):363-7.

89. Kristof RA, Rother M, Neuloh G, Klingmuller D. Incidence, clinical manifestations, and course of water and electrolyte metabolism disturbances following transsphenoidal pituitary adenoma surgery: a prospective observational study. J Neurosurg. 2009;111(3):555-62.

90. Olson BR, Rubino D, Gumowski J, Oldfield EH. Isolated hyponatremia after transsphenoidal pituitary surgery. J Clin Endocrinol Metab. 1995;80(1):85-91.

91. Bales J, Cho S, Tran TK, Korab GA, Khandelwal N, Spiekerman CF, et al. The Effect of Hyponatremia and Sodium Variability on Outcomes in Adults with Aneurysmal Subarachnoid Hemorrhage. World Neurosurg. 2016;96:340-9.

92. Williams C, Simon TD, Riva-Cambrin J, Bratton SL. Hyponatremia with intracranial malignant tumor resection in children. J Neurosurg Pediatr. 2012;9(5):524-9.

93. Kao L, Al-Lawati Z, Vavao J, Steinberg GK, Katznelson L. Prevalence and clinical demographics of cerebral salt wasting in patients with aneurysmal subarachnoid hemorrhage. Pituitary. 2009;12(4):347-51.

94. Palmer BF. Hyponatremia in patients with central nervous system disease: SIADH versus CSW. Trends Endocrinol Metab. 2003;14(4):182-7.

95. Loh JA, Verbalis JG. Diabetes insipidus as a complication after pituitary surgery. Nat Clin Pract Endocrinol Metab. 2007;3(6):489-94.

96. Zhang L, Fu P, Wang L, Cai G, Zhang L, Chen D, et al. Hyponatraemia in patients with crush syndrome during the Wenchuan earthquake. Emerg Med J. 2013;30(9):745-8.

97. Roquilly A, Mahe PJ, Seguin P, Guitton C, Floch H, Tellier AC, et al. Hydrocortisone therapy for patients with multiple trauma: the randomized controlled HYPOLYTE study. JAMA. 2011;305(12):1201-9.

768   98.   Aqil A, Hossain F, Sheikh H, Aderinto J, Whitwell G, Kapoor H. Achieving hip fracture
769   surgery within 36 hours: an investigation of risk factors to surgical delay and
770   recommendations for practice. J Orthop Traumatol. 2016;17(3):207-13.
771   99.   Sharif S, Dominguez M, Imbriano L, Mattana J, Maesaka JK. Recognition of
772   Hyponatremia As a Risk Factor for Hip Fractures in Older Persons. J Am Geriatr Soc.
773   2015;63(9):1962-4.
774   100.   Murthy K, Koshkina O, Marcantonio AJ, Pala N, Breeze JL, Paulus J, et al. Hyponatremia
775   and Fracture Risk: A Hospital-Based Case--Control Study. J Am Geriatr Soc. 2015;63(8):1699-
776   701.
777   101.   Usala RL, Fernandez SJ, Mete M, Cowen L, Shara NM, Barsony J, et al. Hyponatremia Is
778   Associated With Increased Osteoporosis and Bone Fractures in a Large US Health System
779   Population. J Clin Endocrinol Metab. 2015;100(8):3021-31.
780   102.   Hawkins RC. Age and gender as risk factors for hyponatremia and hypernatremia. Clin
781   Chim Acta. 2003;337(1-2):169-72.
782   103.   Tasdemir V, Oguz AK, Sayin I, Ergun I. Hyponatremia in the outpatient setting: clinical
783   characteristics, risk factors, and outcome. Int Urol Nephrol. 2015;47(12):1977-83.
784   104.   Liamis G, Rodenburg EM, Hofman A, Zietse R, Stricker BH, Hoorn EJ. Electrolyte
785   disorders in community subjects: prevalence and risk factors. Am J Med. 2013;126(3):256-63.
786   105.   Gankam-Kengne F, Ayers C, Khera A, de Lemos J, Maalouf NM. Mild hyponatremia is
787   associated with an increased risk of death in an ambulatory setting. Kidney Int.
788   2013;83(4):700-6.
789   106.   Liamis G, Filippatos TD, Elisaf MS. Thiazide-associated hyponatremia in the elderly:
790   what the clinician needs to know. J Geriatr Cardiol. 2016;13(2):175-82.
791   107.   Sajadieh A, Binici Z, Mouridsen MR, Nielsen OW, Hansen JF, Haugaard SB. Mild
792   hyponatremia carries a poor prognosis in community subjects. Am J Med. 2009;122(7):679-
793   86.
794   108.   Hoorn EJ, Rivadeneira F, van Meurs JB, Ziere G, Stricker BH, Hofman A, et al. Mild
795   hyponatremia as a risk factor for fractures: the Rotterdam Study. J Bone Miner Res.
796   2011;26(8):1822-8.
797   109.   Verbalis JG, Adler S, Schrier RW, Berl T, Zhao Q, Czerwiec FS, et al. Efficacy and safety of
798   oral tolvaptan therapy in patients with the syndrome of inappropriate antidiuretic hormone
799   secretion. Eur J Endocrinol. 2011;164(5):725-32.
800   110.   De las Penas R, Ponce S, Henao F, Camps Herrero C, Carcereny E, Escobar Alvarez Y, et
801   al. SIADH-related hyponatremia in hospital day care units: clinical experience and
802   management with tolvaptan. Support Care Cancer. 2016;24(1):499-507.
803   111.   Almond CS, Shin AY, Fortescue EB, Mannix RC, Wypij D, Binstadt BA, et al.
804   Hyponatremia among runners in the Boston Marathon. N Engl J Med. 2005;352(15):1550-6.
805   112.   Ben-Abraham R, Szold O, Rudick V, Weinbroum AA. 'Ecstasy' intoxication: life-
806   threatening manifestations and resuscitative measures in the intensive care setting. Eur J
807   Emerg Med. 2003;10(4):309-13.
808   113.   Arieff AI. Central nervous system manifestations of disordered sodium metabolism.
809   Clin Endocrinol Metab. 1984;13(2):269-94.
810   114.   Berl T. Treating hyponatremia: what is all the controversy about? Ann Intern Med.
811   1990;113(6):417-9.
812   115.   Edelman IS, Leibman J, O'Meara MP, Birkenfeld LW. Interrelations between serum
813   sodium concentration, serum osmolarity and total exchangeable sodium, total exchangeable
814   potassium and total body water. J Clin Invest. 1958;37(9):1236-56.
815   116.   Sterns RH, Hix JK, Silver S. Treating profound hyponatremia: a strategy for controlled
816   correction. Am J Kidney Dis. 2010;56(4):774-9.

817   117.   Hanna RM, Yang WT, Lopez EA, Riad JN, Wilson J. The utility and accuracy of four
818   equations in predicting sodium levels in dysnatremic patients. Clin Kidney J. 2016;9(4):530-9.
819   118.   Trepiccione F, Capasso G, Lippi G. [Serum and urine osmolality: clinical and laboratory
820   features]. G Ital Nefrol. 2014;31(5).
821   119.   Corona G, Giuliani C, Verbalis JG, Forti G, Maggi M, Peri A. Hyponatremia improvement
822   is associated with a reduced risk of mortality: evidence from a meta-analysis. PLoS One.
823   2015;10(4):e0124105.
824   120.   Ellison DH, Berl T. Clinical practice. The syndrome of inappropriate antidiuresis. N Engl
825   J Med. 2007;356(20):2064-72.
826   121.   Grohe C, Berardi R, Burst V. Hyponatraemia--SIADH in lung cancer diagnostic and
827   treatment algorithms. Crit Rev Oncol Hematol. 2015;96(1):1-8.
828   122.   Onitilo AA, Kio E, Doi SA. Tumor-related hyponatremia. Clin Med Res. 2007;5(4):228-
829   37.
830   123.   Berardi R, Rinaldi S, Caramanti M, Grohe C, Santoni M, Morgese F, et al. Hyponatremia
831   in cancer patients: Time for a new approach. Crit Rev Oncol Hematol. 2016;102:15-25.
832   124.   Berardi R, Santoni M, Rinaldi S, Nunzi E, Smerilli A, Caramanti M, et al. Risk of
833   Hyponatraemia in Cancer Patients Treated with Targeted Therapies: A Systematic Review and
834   Meta-Analysis of Clinical Trials. PLoS One. 2016;11(5):e0152079.
835   125.   Illouz F, Braun D, Briet C, Schweizer U, Rodien P. Endocrine side-effects of anti-cancer
836   drugs: thyroid effects of tyrosine kinase inhibitors. Eur J Endocrinol. 2014;171(3):R91-9.
837   126.   Lu X, Wang X. Hyponatremia induced by antiepileptic drugs in patients with epilepsy.
838   Expert Opin Drug Saf. 2017;16(1):77-87.
839   127.   Tsapepas D, Chiles M, Babayev R, Rao MK, Jaitly M, Salerno D, et al. Incidence of
840   Hyponatremia with High-Dose Trimethoprim-Sulfamethoxazole Exposure. Am J Med.
841   2016;129(12):1322-8.
842   128.   Tanaka R, Suzuki Y, Takumi Y, Iwao M, Sato Y, Hashinaga K, et al. A Retrospective
843   Analysis of Risk Factors for Linezolid-Associated Hyponatremia in Japanese Patients. Biol
844   Pharm Bull. 2016;39(12):1968-73.
845   129.   Spital A. Diuretic-induced hyponatremia. Am J Nephrol. 1999;19(4):447-52.
846   130.   Gandhi S, Shariff SZ, Al-Jaishi A, Reiss JP, Mamdani MM, Hackam DG, et al. Second-
847   Generation Antidepressants and Hyponatremia Risk: A Population-Based Cohort Study of
848   Older Adults. Am J Kidney Dis. 2017;69(1):87-96.
849   131.   Buon M, Gaillard C, Martin J, Fedrizzi S, Mosquet B, Coquerel A, et al. Risk of proton
850   pump inhibitor-induced mild hyponatremia in older adults. J Am Geriatr Soc.
851   2013;61(11):2052-4.
852   132.   Izzedine H, Fardet L, Launay-Vacher V, Dorent R, Petitclerc T, Deray G. Angiotensin-
853   converting enzyme inhibitor-induced syndrome of inappropriate secretion of antidiuretic
854   hormone: case report and review of the literature. Clin Pharmacol Ther. 2002;71(6):503-7.
855   133.   Yamada H, Asano T, Aoki A, Ikoma A, Yoshida M, Kusaka I, et al. Combination therapy of
856   angiotensin II receptor blocker and thiazide produces severe hyponatremia in elderly
857   hypertensive subjects. Intern Med. 2014;53(7):749-52.
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863   Table 1: Conditions at risk for hypoNa overcorrection

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CONDITION	MECHANISM OF HYPERCORRECTION
Hypovolemia	Elimination of the stimulus for ADH secretion due to baroceptor activation by volume expansion by cristalloid
Low solute diet (Beer potomay, tea and toast diet etc.)	Diet correction increases dietary solute load → increased renal free water clearance
Thiazide diuretic therapy	Discontinuation of the drug directly restores renal diluting capacity
SSRI antidepressive drug therapy	Discontinuation of the drug reduces the serotoninergic stimulus on ADH secretion
Hypopituitarism	Restoration of physiologic suppression of ADH secretion by cortisol replacement therapy
Hypoxemia	Elimination of non osmotic stimulus on ADH by normalization of blood gases
Stress, pain, nausea	Elimination of transient stimuli on ADH secretion
Hypokalemia, potassium depletion	With K administration, sodium leaves the cell in exchange with potassium entrance, in order to maintain electroneutrality

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883   Table 2 Diagnosis of SIAD [modified from (120)]
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886   **Essential features**
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888   Decreased effective osmolality (< 275 mOsm/Kg of water)
889   Urine osmolality > 100 mOsm/Kg of water
890   Clinical euvolemia
891   -   No clinical signs of volume depletion of extracellular fluid (orthostasis, tachycardia, decreased skin turgor, or
892   dry mucous membranes)
893   -   No clinical signs of excessive volume of extracellular fluid (edema or ascites)
894   Urinary sodium > 40 mmol/liter with normal dietary salt intake
895   Normal thyroid and adrenal function
896   No recent use of diuretic agents
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898   **Supplemental features**
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900   Plasma acid uric < 4 mg/dL
901   Blood urea nitrogen < 10 ml/dL
902   Fractional sodium excretion > 1%; fractional urea excretion > 55%
903   Failure to correct hyponatremia after 0.9% saline infusion
904   Correction of hyponatremia through fluid restriction
905   Abnormal results on test of water load (< 80% excretion of 20 ml of water per kilogram of body weight over a period of
906   4 hours), or inadeguate urinary dilution (< 100 mOsm/Kg of water)
907   Elevated plasma AVP levels, despite the presence of hypotonicity and clinical euvolemia
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Table 3 Drugs possibly used in oncological patients that may induce hyponatremia

DRUGS	INDICATION for use	MECHANISM INVOLVED	REFERENCES

• Vinca alkaloids vincristine, vinblastine
• Platinum compounds cisplatin, carboplatin
• Alkylating agents ev cyclophosphamide, melphalan, ifosfamide
• Antracyclines
• TK and monoclonal antibody inhibitor
  Afatinib
  Brivanib
  Cetuximab
  Gefinib
  Limifanib
  Pazopanib
  Sorafenib
  Vorinostat
• Others
  Metothexate
  IFN α-γ
  Pentostatina
  IL2
	Chemotherapy	Increase AVP secretion
		Increase AVP secretion and renal waist syndrome
		Increase AVP secretion and increase renal sensitivity
		Ipervolemic hyponatremia
		
		Direct natriuretic effect and interference in Na pathway and increase AVP secretion
		Possible role for iatrogenic hypotiroidism
		
		Increase AVP secretion and possible fluid redistribution
			(23), (121),(122) (123)
			
			(122, 123)
			
			(121, 122) (124)
			
			(122, 125)
			
			(23, 121-123)

• Opioid • Acetaminophen • Non-steroidal anti-inflammatory drugs	Pain control	Increased renal sensitivity, indirect increase in ACP secretion secondary to nausea or hypotension	(23, 122, 123)

• Triciclyc antidepressant
  Amitryptiline
  Protryptiline
	Antidepressant	Increase AVP secretion	(23, 122, 123)

Desipramine • SSRI • MAO inhibitors • Others Duloxetine, Venlafaxine, Mitrazapina		Reset osmostat	(23)
• Carbamazepine,Oxcarbazepine • Sodium valproato • Lamotrigine	Antiepilectic	Increase AVP secretion and potentiation AVP effect Reset osmostat	(23, 123, 126)
• Phenotiazine	Antiemetic	Drug induced polydipsia	(122)
• Corticosteroid	Anti-edema, nausea	Hyperglycemia – pseudohyponatremia	(122, 123)
• First antidiabetic generation Clorpropamide, Tolbutamide	Diabete	Potentiation AVP effect	(123)
• Antibiotics Ciprofloxacina Trimethoprim/sulphametoxazole Linezolid Cefoperazone sulbactam	Infections	Increase AVP secretion Hypovolemic hyponatremia	(23) (127) (128)
• Proton pump inhibitor Omeprazole, esomeprazolo	Prevention gastric ulceration stress or or drug related	Increase AVP secretion	(23)
• Hypotensive drug Diuretic loop furosemide ACE-I thiazide	Hypertension therapy	Hypovolemic hyponatremia Increase osmotic renal losses Increase AVP secretion Increase of thirst	(23)
• Mannitol	Anti –edema	Pseudohyponatremia	(122, 123)
• Hypotonic solution • Isotonic solution	Hydratation	Diluitional	(122, 123)

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927 Table 4: Causes of HypoNa in cancer patients [modified from Ref. (22)].

CAUSES	%
SIAD	30.4
Dehydration	28.7
Diuretic use	14.0
Hypervolemia	7.8
Kidney failure	3.5
Hypotonic solutions	1.7
Miscellaneous	5.2
Not defined	1.7
False positive	7.0
Mixed causes	9.6
Total	100

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942   Table 5: Drugs commonly used in elderly patients that may cause or worsen hypoNa -(129) (130) (131) (132) (133)

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DRUG CLASSES	Principal drugs involved in the class
➢ **Diuretic drugs**	loop diuretics thiazides
➢ **Second-generation antidepressants**	citalopram, escitalopram, paroxetine, fluoxetine, fluvoxamine, venlafaxine, duloxetine, mirtazapine, or sertraline
➢ **Proton pump inhibitors**	omeprazole, esomeprazole
➢ **Hypotensive drugs**	Angiotensin-converting enzyme inhibitor

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