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

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72 INTRODUCTION

73 Hyponatremia (hypoNa, serum sodium levels <135 mEq/L), is the most frequently observed electrolyte disorder in
74 clinical practice, affecting up to 15-30% of hospitalized patients (1). HypoNa is characterized by an excess of water
75 relative to exchangeable total body sodium, that can be normal, increased or decreased. As a consequence, hypoNa can
76 be classified by the fluid volume status of the patient (euvoletic, hypovolemic and hypervolemic hypoNa), or by plasma
77 tonicity, i.e., the effective osmolality, (isotonic, hypertonic and hypotonic hypoNa). Hypotonic hypoNa is the most
78 commonly observed form in daily clinical practice (2). Severe hypoNa, especially if acutely developed (i.e. in less than
79 48 hours), may determine major neurological symptoms due to brain edema, a potentially life-threatening complication
80 if not promptly recognized and treated (3). However, even mild hypoNa (130-134 mEq/L) may also be associated with
81 other strictly related clinical problems, often insidious and scarcely symptomatic, such as bone demineralization or gait
82 instability and attention deficits, which may increase the risk of falls and bone fractures, especially in the elderly (4-8).
83 Accordingly, recent meta-analyses have shown that even milder forms of hypoNa are associated with an increased risk
84 of mortality in different clinical settings (9), along with prolonged hospital stay, increased readmission rates and higher
85 hospital costs (10).

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

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

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

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

103 In the intention of the task-force the present paper should be considered nor as a formal Guideline nor as an all-inclusive
104 in-depth review on the topic. Rather, this paper should be viewed as a pocket guide to support the practical approach to
105 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 increase 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 $\text{Na} < 130 \text{ mEq/L}$ (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 myelinolysis 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 $< 130 \text{ mEq/L}$ (57-59), whereas severe hypoNa (serum $\text{Na} \leq 120 \text{ mEq/L}$) 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):

- 285 • Direct renal sodium loss, such as in salt-losing nephropathies (chronic pyelonephritis, chronic drug-associated
 286 or toxic tubule-interstitial), characterized by reduced renal sodium reabsorption, sodium and potassium
 287 depletion, reduced concentration ability, hypovolemia and ADH stimulation (73). The consequence is hypoNa
 288 with volume depletion.
- 289 • Reduced urinary dilution capacity due to severe impairment of glomerular filtration rate with ensuing lower
 290 availability of preurine at the diluting segments of the distal nephron and reduced ability to generate free water.
 291 In this case hypoNa will be euvolemic or hypervolemic (74) (72).
- 292 • Oligoanuria or anuria along with free water/hypotonic fluid intakes exceeding losses, such as the case of ESRD
 293 on chronic dialysis or in acute kidney injury. These forms of hypoNa are usually hypervolemic (74).

294 Mortality

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

297 Notes on treatment

298 There is paucity of data in the literature concerning the treatment of hypoNa in patients with CKD on conservative therapy.
 299 The oral vasopressin V₂-receptor antagonist tolvaptan has been tested in small studies performed in CKD patients with or
 300 without congestive heart failure (78). On the whole, a significant increase in urine volume was observed, together with
 301 an increase in serum sodium concentration. Moreover, treatment with tolvaptan was not associated with deterioration of
 302 kidney function in these patients.

303 The problems of the treatment of hypoNa during renal replacement therapy (RRT), and the inherent risks of overcorrection
 304 and osmotic demyelization syndrome, have been addressed mainly in the critically ill patients. Specifically, reducing
 305 serum sodium concentration in the substitution fluids has been advocated as the best approach to avoid the risk of
 306 overcorrection during continuous veno-venous hemofiltration or continuous veno-venous hemodialysis (79). When
 307 standard intermittent hemodialysis is chosen, sodium concentration in the dialysate should be reduced to a minimum of
 308 130 mEq/L, and blood flow rate as low as 50 mL/min together with short duration (e.g., 3 hours) of dialysis session should
 309 be prescribed (80).

310

311 **HYPONATREMIA IN NEUROLOGY**

312 Prevalence and etiology:

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

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

316 In subjects with stroke, many factors including dietary sodium restriction for hypertension control, use of thiazide
 317 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 ($[\text{Na}]^+ < 135 \text{ mEq/L}$) 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 ($[\text{Na}]^+ < 130 \text{ mEq/L}$)

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 transurethral 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 be 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 individualized. 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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523 REFERENCES

- 524 1. Upadhyay A, Jaber BL, Madias NE. Incidence and prevalence of hyponatremia. *Am J*
525 *Med.* 2006;119(7 Suppl 1):S30-5.
- 526 2. Adroge HJ, Madias NE. Hyponatremia. *N Engl J Med.* 2000;342(21):1581-9.
- 527 3. Gill G, Huda B, Boyd A, Skagen K, Wile D, Watson I, et al. Characteristics and mortality
528 of severe hyponatraemia--a hospital-based study. *Clin Endocrinol (Oxf).* 2006;65(2):246-9.
- 529 4. Renneboog B, Musch W, Vandemergel X, Manto MU, Decaux G. Mild chronic
530 hyponatremia is associated with falls, unsteadiness, and attention deficits. *Am J Med.*
531 2006;119(1):71 e1-8.
- 532 5. Gankam Kengne F, Andres C, Sattar L, Melot C, Decaux G. Mild hyponatremia and risk of
533 fracture in the ambulatory elderly. *QJM.* 2008;101(7):583-8.
- 534 6. Kinsella S, Moran S, Sullivan MO, Molloy MG, Eustace JA. Hyponatremia independent of
535 osteoporosis is associated with fracture occurrence. *Clin J Am Soc Nephrol.* 2010;5(2):275-80.
- 536 7. Verbalis JG, Barsony J, Sugimura Y, Tian Y, Adams DJ, Carter EA, et al. Hyponatremia -
537 induced osteoporosis. *J Bone Miner Res.* 2010;25(3):554-63.
- 538 8. Barsony J, Sugimura Y, Verbalis JG. Osteoclast response to low extracellular sodium and
539 the mechanism of hyponatremia-induced bone loss. *J Biol Chem.* 2011;286(12):10864-75.
- 540 9. Corona G, Giuliani C, Parenti G, Norello D, Verbalis JG, Forti G, et al. Moderate
541 hyponatremia is associated with increased risk of mortality: evidence from a meta-analysis.
542 *PLoS One.* 2013;8(12):e80451.
- 543 10. Corona G, Giuliani C, Parenti G, Colombo GL, Sforza A, Maggi M, et al. The Economic
544 Burden of Hyponatremia: Systematic Review and Meta-Analysis. *Am J Med.* 2016;129(8):823-
545 35 e4.
- 546 11. Chambrey R, Trepiccione F. Relative roles of principal and intercalated cells in the
547 regulation of sodium balance and blood pressure. *Curr Hypertens Rep.* 2015;17(4):538.
- 548 12. Cuesta M, Garrahy A, Thompson CJ. SIAD: practical recommendations for diagnosis and
549 management. *J Endocrinol Invest.* 2016;39(9):991-1001.
- 550 13. Spasovski G, Vanholder R, Allolio B, Annane D, Ball S, Bichet D, et al. Clinical practice
551 guideline on diagnosis and treatment of hyponatraemia. *Intensive Care Med.* 2014;40(3):320-
552 31.
- 553 14. Verbalis JG, Goldsmith SR, Greenberg A, Korzelius C, Schrier RW, Sterns RH, et al.
554 Diagnosis, evaluation, and treatment of hyponatremia: expert panel recommendations. *Am J*
555 *Med.* 2013;126(10 Suppl 1):S1-42.
- 556 15. Hoorn EJ, Lindemans J, Zietse R. Development of severe hyponatraemia in hospitalized
557 patients: treatment-related risk factors and inadequate management. *Nephrol Dial*
558 *Transplant.* 2006;21(1):70-6.
- 559 16. Rondon-Berrios H, Berl T. Vasopressin receptor antagonists: Characteristics and
560 clinical role. *Best Pract Res Clin Endocrinol Metab.* 2016;30(2):289-303.
- 561 17. Spasovski G, Vanholder R, Allolio B, Annane D, Ball S, Bichet D, et al. Clinical practice
562 guideline on diagnosis and treatment of hyponatraemia. *Nephrol Dial Transplant.* 2014;29
563 *Suppl 2:i1-i39.*
- 564 18. Regolisti G, Cabassi A, Antonucci E, Brusasco I, Cademartiri C, Pistolesi V, et al.
565 [Hyponatremia in clinical practice]. *G Ital Nefrol.* 2015;32(1).
- 566 19. Aylwin S, Burst V, Peri A, Runkle I, Thatcher N. 'Dos and don'ts' in the management of
567 hyponatremia. *Curr Med Res Opin.* 2015;31(9):1755-61.
- 568 20. Glover DJ, Glick JH. Metabolic oncologic emergencies. *CA Cancer J Clin.* 1987;37(5):302-
569 20.
- 570 21. Silverman P, Distelhorst CW. Metabolic emergencies in clinical oncology. *Semin Oncol.*
571 1989;16(6):504-15.

- 572 22. Berghmans T, Paesmans M, Body JJ. A prospective study on hyponatraemia in medical
573 cancer patients: epidemiology, aetiology and differential diagnosis. *Support Care Cancer*.
574 2000;8(3):192-7.
- 575 23. Liamis G, Milionis H, Elisaf M. A review of drug-induced hyponatremia. *Am J Kidney Dis*.
576 2008;52(1):144-53.
- 577 24. Doshi SM, Shah P, Lei X, Lahoti A, Salahudeen AK. Hyponatremia in hospitalized cancer
578 patients and its impact on clinical outcomes. *Am J Kidney Dis*. 2012;59(2):222-8.
- 579 25. Sterns RH, Silver SM, Hix JK. Urea for hyponatremia? *Kidney Int*. 2015;87(2):268-70.
- 580 26. Decaux G, Unger J, Brimiouille S, Mockel J. Hyponatremia in the syndrome of
581 inappropriate secretion of antidiuretic hormone. Rapid correction with urea, sodium chloride,
582 and water restriction therapy. *JAMA*. 1982;247(4):471-4.
- 583 27. Decaux G, Andres C, Gankam Kengne F, Soupart A. Treatment of euvolemic
584 hyponatremia in the intensive care unit by urea. *Crit Care*. 2010;14(5):R184.
- 585 28. Soupart A, Coffernils M, Couturier B, Gankam-Kengne F, Decaux G. Efficacy and
586 tolerance of urea compared with vaptans for long-term treatment of patients with SIADH. *Clin*
587 *J Am Soc Nephrol*. 2012;7(5):742-7.
- 588 29. Peterleit C, Zaba O, Teber I, Luders H, Grohe C. A rapid and efficient way to manage
589 hyponatremia in patients with SIADH and small cell lung cancer: treatment with tolvaptan.
590 *BMC Pulm Med*. 2013;13:55.
- 591 30. Verbalis JG. Managing hyponatremia in patients with syndrome of inappropriate
592 antidiuretic hormone secretion. *Endocrinol Nutr*. 2010;57 Suppl 2:30-40.
- 593 31. Berardi R, Caramanti M, Castagnani M, Guglielmi S, Marcucci F, Savini A, et al.
594 Hyponatremia is a predictor of hospital length and cost of stay and outcome in cancer
595 patients. *Support Care Cancer*. 2015;23(10):3095-101.
- 596 32. Berl T. An elderly patient with chronic hyponatremia. *Clin J Am Soc Nephrol*.
597 2013;8(3):469-75.
- 598 33. Mannesse CK, Vondeling AM, van Marum RJ, van Solinge WW, Egberts TC, Jansen PA.
599 Prevalence of hyponatremia on geriatric wards compared to other settings over four decades:
600 a systematic review. *Ageing Res Rev*. 2013;12(1):165-73.
- 601 34. Soiza RL, Cumming K, Clarke JM, Wood KM, Myint PK. Hyponatremia: Special
602 Considerations in Older Patients. *J Clin Med*. 2014;3(3):944-58.
- 603 35. Shapiro DS, Sonnenblick M, Galperin I, Melkonyan L, Munter G. Severe hyponatraemia
604 in elderly hospitalized patients: prevalence, aetiology and outcome. *Intern Med J*.
605 2010;40(8):574-80.
- 606 36. Beck LH. Changes in renal function with aging. *Clin Geriatr Med*. 1998;14(2):199-209.
- 607 37. Lindeman RD, Tobin J, Shock NW. Longitudinal studies on the rate of decline in renal
608 function with age. *J Am Geriatr Soc*. 1985;33(4):278-85.
- 609 38. Moran D, Fronk C, Mandel E. Managing hyponatremia in adults. *JAAPA*. 2014;27(4):23-
610 9; quiz 30.
- 611 39. Kugler JP, Hustead T. Hyponatremia and hypernatremia in the elderly. *Am Fam*
612 *Physician*. 2000;61(12):3623-30.
- 613 40. Wannamethee SG, Shaper AG, Lennon L, Papacosta O, Whincup P. Mild hyponatremia,
614 hypernatremia and incident cardiovascular disease and mortality in older men: A population-
615 based cohort study. *Nutr Metab Cardiovasc Dis*. 2016;26(1):12-9.
- 616 41. Hoyle GE, Chua M, Soiza RL. Volaemic assessment of the elderly hyponatraemic patient:
617 reliability of clinical assessment and validation of bioelectrical impedance analysis. *QJM*.
618 2011;104(1):35-9.
- 619 42. De Luca L, Klein L, Udelson JE, Orlandi C, Sardella G, Fedele F, et al. Hyponatremia in
620 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.

- 720 78. Tanaka A, Katsuno T, Ozaki T, Sakata F, Kato N, Suzuki Y, et al. The efficacy of tolvaptan
721 as a diuretic for chronic kidney disease patients. *Acta Cardiol.* 2015;70(2):217-23.
- 722 79. Dangoisse C, Dickie H, Tovey L, Ostermann M. Correction of hyper- and hyponatraemia
723 during continuous renal replacement therapy. *Nephron Clin Pract.* 2014;128(3-4):394-8.
- 724 80. Wendland EM, Kaplan AA. A proposed approach to the dialysis prescription in severely
725 hyponatremic patients with end-stage renal disease. *Semin Dial.* 2012;25(1):82-5.
- 726 81. Ball SG, Iqbal Z. Diagnosis and treatment of hyponatraemia. *Best Pract Res Clin*
727 *Endocrinol Metab.* 2016;30(2):161-73.
- 728 82. Gisby M, Lundberg J, Landin M, O'Reilly K, Robinson P, Sobocki P, et al. The burden of
729 illness in patients with hyponatraemia in Sweden: a population-based registry study. *Int J Clin*
730 *Pract.* 2016;70(4):319-29.
- 731 83. Rodrigues B, Staff I, Fortunato G, McCullough LD. Hyponatremia in the prognosis of
732 acute ischemic stroke. *J Stroke Cerebrovasc Dis.* 2014;23(5):850-4.
- 733 84. Hiew FL, Winer JB, Rajabally YA. Hyponatraemia in Guillain-Barre syndrome revisited.
734 *Acta Neurol Scand.* 2016;133(4):295-301.
- 735 85. Holland-Bill L, Christiansen CF, Heide-Jorgensen U, Ulrichsen SP, Ring T, Jorgensen JO,
736 et al. Hyponatremia and mortality risk: a Danish cohort study of 279 508 acutely hospitalized
737 patients. *Eur J Endocrinol.* 2015;173(1):71-81.
- 738 86. Sherlock M, O'Sullivan E, Agha A, Behan LA, Owens D, Finucane F, et al. Incidence and
739 pathophysiology of severe hyponatraemia in neurosurgical patients. *Postgrad Med J.*
740 *2009;85(1002):171-5.*
- 741 87. Mapa B, Taylor BE, Appelboom G, Bruce EM, Claassen J, Connolly ES, Jr. Impact of
742 Hyponatremia on Morbidity, Mortality, and Complications After Aneurysmal Subarachnoid
743 Hemorrhage: A Systematic Review. *World Neurosurg.* 2016;85:305-14.
- 744 88. Kelly DF, Laws ER, Jr., Fossett D. Delayed hyponatremia after transsphenoidal surgery
745 for pituitary adenoma. Report of nine cases. *J Neurosurg.* 1995;83(2):363-7.
- 746 89. Kristof RA, Rother M, Neuloh G, Klingmuller D. Incidence, clinical manifestations, and
747 course of water and electrolyte metabolism disturbances following transsphenoidal pituitary
748 adenoma surgery: a prospective observational study. *J Neurosurg.* 2009;111(3):555-62.
- 749 90. Olson BR, Rubino D, Gumowski J, Oldfield EH. Isolated hyponatremia after
750 transsphenoidal pituitary surgery. *J Clin Endocrinol Metab.* 1995;80(1):85-91.
- 751 91. Bales J, Cho S, Tran TK, Korab GA, Khandelwal N, Spiekerman CF, et al. The Effect of
752 Hyponatremia and Sodium Variability on Outcomes in Adults with Aneurysmal Subarachnoid
753 Hemorrhage. *World Neurosurg.* 2016;96:340-9.
- 754 92. Williams C, Simon TD, Riva-Cambrin J, Bratton SL. Hyponatremia with intracranial
755 malignant tumor resection in children. *J Neurosurg Pediatr.* 2012;9(5):524-9.
- 756 93. Kao L, Al-Lawati Z, Vavao J, Steinberg GK, Katznelson L. Prevalence and clinical
757 demographics of cerebral salt wasting in patients with aneurysmal subarachnoid hemorrhage.
758 *Pituitary.* 2009;12(4):347-51.
- 759 94. Palmer BF. Hyponatremia in patients with central nervous system disease: SIADH
760 versus CSW. *Trends Endocrinol Metab.* 2003;14(4):182-7.
- 761 95. Loh JA, Verbalis JG. Diabetes insipidus as a complication after pituitary surgery. *Nat*
762 *Clin Pract Endocrinol Metab.* 2007;3(6):489-94.
- 763 96. Zhang L, Fu P, Wang L, Cai G, Zhang L, Chen D, et al. Hyponatraemia in patients with
764 crush syndrome during the Wenchuan earthquake. *Emerg Med J.* 2013;30(9):745-8.
- 765 97. Roquilly A, Mahe PJ, Seguin P, Guitton C, Floch H, Tellier AC, et al. Hydrocortisone
766 therapy for patients with multiple trauma: the randomized controlled HYPOLYTE study.
767 *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 baroreceptor activation by volume expansion by crystalloid
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 serotonergic 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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Table 2 Diagnosis of SIAD [modified from (120)]

Essential features

Decreased effective osmolality (< 275 mOsm/Kg of water)

Urine osmolality > 100 mOsm/Kg of water

Clinical euvolemia

- No clinical signs of volume depletion of extracellular fluid (orthostasis, tachycardia, decreased skin turgor, or dry mucous membranes)
- No clinical signs of excessive volume of extracellular fluid (edema or ascites)

Urinary sodium > 40 mmol/liter with normal dietary salt intake

Normal thyroid and adrenal function

No recent use of diuretic agents

Supplemental features

Plasma acid uric < 4 mg/dL

Blood urea nitrogen < 10 ml/dL

Fractional sodium excretion $> 1\%$; fractional urea excretion $> 55\%$

Failure to correct hyponatremia after 0.9% saline infusion

Correction of hyponatremia through fluid restriction

Abnormal results on test of water load ($< 80\%$ excretion of 20 ml of water per kilogram of body weight over a period of 4 hours), or inadequate urinary dilution (< 100 mOsm/Kg of water)

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	REFERE NCES
<ul style="list-style-type: none"> • Vinca alkaloids vincristine, vinblastine • Platinum compounds cisplatin, carboplatin • Alkylating agents ev cyclophosphamide, melphalan, ifosfamide • Anthracyclines • TK and monoclonal antibody inhibitor Afatinib Brivanib Cetuximab Gefinib Limifanib Pazopanib Sorafenib Vorinostat • Others Methotrexate IFN α-γ Pentostatina IL2 	Chemotherapy	<p>Increase AVP secretion Increase AVP secretion and renal wairst syndrome Increase AVP secretion and increase renal sensitivity Ipervolemic hyponatremia</p> <p>Direct natriuretic effect and interference in Na pathway and increase AVP secretion Possible role for iatrogenic hypotiroidism</p> <p>Increase AVP secretion and possible fluid redistribution</p>	<p>(23), (121),(122) (123)</p> <p>(122, 123)</p> <p>(121, 122) (124)</p> <p>(122, 125)</p> <p>(23, 121- 123)</p>
<ul style="list-style-type: none"> • 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)
<ul style="list-style-type: none"> • Tricyclic antidepressant Amitriptyline Protryptiline 	Antidepressant	Increase AVP secretion	(23, 122, 123)

<ul style="list-style-type: none"> Desipramine SSRI MAO inhibitors Others Duloxetine, Venlafaxine, Mitrazapina		Reset osmostat	(23)
<ul style="list-style-type: none"> Carbamazepine, Oxcarbazepine Sodium valproate Lamotrigine 	Antiepileptic	Increase AVP secretion and potentiation AVP effect Reset osmostat	(23, 123, 126)
<ul style="list-style-type: none"> Phenothiazine 	Antiemetic	Drug induced polydipsia	(122)
<ul style="list-style-type: none"> Corticosteroid 	Anti-edema, nausea	Hyperglycemia – pseudo hyponatremia	(122, 123)
<ul style="list-style-type: none"> First antidiabetic generation Clorpropamide, Tolbutamide	Diabetes	Potentiation AVP effect	(123)
<ul style="list-style-type: none"> Antibiotics Ciprofloxacin Trimethoprim/sulphamethoxazole Linezolid Cefoperazone sulbactam	Infections	Increase AVP secretion Hypovolemic hyponatremia	(23) (127) (128)
<ul style="list-style-type: none"> Proton pump inhibitor Omeprazole, esomeprazole	Prevention gastric ulceration stress or or drug related	Increase AVP secretion	(23)
<ul style="list-style-type: none"> Hypotensive drug Diuretic loop furosemide ACE-I thiazide	Hypertension therapy	Hypovolemic hyponatremia Increase osmotic renal losses Increase AVP secretion Increase of thirst	(23)
<ul style="list-style-type: none"> Mannitol 	Anti –edema	Pseudo hyponatremia	(122, 123)
<ul style="list-style-type: none"> Hypotonic solution Isotonic solution 	Hydration	Dilutional	(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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