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)

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.

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

HYPONATREMIA IN ONCOLOGY

Prevalence and etiology:

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

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

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

Mortality:

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

Notes on treatment:

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

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

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

While a few non controlled studies (27) (28) have reported that urea is effective in normalizing hypoNa, hypercorrection with hypernatremia has also been reported in the same studies. In fact, the urea-induced increase in serum sodium concentration is not easily predicted, as it depends on both hydration status and urine osmolality. Thus, while the European Guidelines (13) recommend urea as the treatment of choice in patients with SIAD when water restriction is ineffective or not feasible, poor palatability, scarce clinical experience and the risk of hypercorrection suggest that advantages and disadvantages of urea should be balanced against the possible use of vasopressin receptor antagonists in this clinical setting.

Therefore, a valuable option in cancer patients with SIAD could be represented by vaptans. In a recent prospective study on small cell lung cancer patients with severe SIAD, tolvaptan led to an effective correction and stabilization of the serum sodium levels, also enabling patients to receive chemotherapy without any delay (29). In addition, the use of vaptans may avoid withdrawal of hypoNa-inducing chemotherapies.

The duration of treatment for hypoNa is largely dependent on the cause. In drug-induced hypoNa, the electrolyte alteration is usually reverted within days after the cessation of the involved drug. Conversely, in ADH secreting tumors, hypoNa usually requires a longer and somewhat unpredictable duration of therapy, which is also dependent on the response to anti-tumoral treatments (30).

In summary, we suggest that hypoNa should be carefully taken into account and timely corrected in oncology patients, preferably avoiding severe fluid restriction or agents that may increases nausea (urea), taking into account that the normalization of sodium levels has been found to have a positive effect on the prognosis and length of in-hospital stay (31).

HYPONATREMIA IN THE ELDERLY

Prevalence and etiology:

The prevalence of hypoNa is increased in elderly patients compared with that in the general population, reaching almost 50% of all acute geriatric admissions (32, 33).

In the elderly, the etiology of hypoNa is multifactorial in 50–75% of cases (34, 35). SIAD is the most common cause, even if a risk of over-diagnosis has been claimed (34). Other frequent causes are congestive heart failure, water and sodium homeostasis alterations, renal and hepatic dysfunction, and especially drug-induced hypoNa, because older people often receive multiple pharmacological treatments (Table 5) (35) .

In elderly patients alterations of electrolyte and water balance are favoured by age-related reduction in total body water, reduced renal function (36), decreased cortical blood flow and glomerular filtration rate, impaired responsiveness to sodium balance changes (37), osmoreceptors hypersensitivity, and higher ADH release (38). Additionally, the ability to excrete free water is reduced (39).

Mortality:

HypoNa is associated with increased all-cause mortality in elderly subjects: a recent study showed that the adjusted hazards ratio (95%CI) in hyponatremic men without chronic kidney disease (CKD), stroke or heart failure was 1.30 (confidence interval 1.02 to 1.66) (40).

Notes on clinical features and diagnosis:

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

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

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

Notes on treatment:

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

HYPONATREMIA IN CONGESTIVE HEART FAILURE

Prevalence and etiology

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

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

Mortality

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

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

Notes on treatment

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

HYPONATREMIA IN DECOMPENSATED LIVER CIRRHOSIS

Prevalence and etiology

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

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

translocation, maintains splanchnic vasodilation (60). In this clinical setting, pathophysiological mechanisms triggered by decreased EABV are essentially the same as in HF. Thus, while total body sodium balance is increased, the development of hypoNa is facilitated by reduced sodium delivery to the distal nephron and high circulating vasopressin levels (60).

Mortality

The negative prognostic role of hypoNa in patients with liver cirrhosis has been clearly documented (59, 60). In a study performed in 6769 patients with liver failure waiting for liver transplantation, of whom 422 had deceased within 90 days since entering the waiting list, the investigators found an increased risk of death associated with hypoNa, even independent of the MELD score (61). Accordingly a recent meta-analysis of the available data documented that hypoNa was associated with more than 3-fold increased risk of mortality in patients with cirrhosis (9).

Notes on treatment

In patients with liver failure, treatment with vaptans has been shown to ameliorate fluid balance in some studies (62-64). Moreover, treatment with satavaptan was associated with greater increase in serum sodium values and decreased ascites formation in cirrhotic patients receiving either diuretics (65) and spironolactone (59). However, one of those studies (65) also found an increase in the risk of death due to complication of cirrhosis in patients treated with both satavaptan and diuretics, which subsequently lead to drug withdrawal from commerce. Lixivaptan, on top of standard treatment with spironolactone, proved to be effective in increasing free water clearance and serum sodium values in patients with decompensated liver cirrhosis (66).

Tolvaptan, so far the only vaptan approved in Europe, so far, and allowed only in patient with hypoNa secondary to SIAD, has been also tested on top of standard treatment with furosemide and spironolactone in patients with decompensated 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 volume and body weight (67), as well as in increasing serum sodium values (68, 69), however both the European guidelines (13) and the US expert consensus document (14) recommend against the use of vaptans in patients with liver disease. Anyway, as hypoNa may complicate the use of high-dose loop diuretics in oliguric patients with refractory ascites and may predispose them to hepatic encephalopathy, a cautious use of tolvaptan in combination with diuretics may represent a treatment strategy that should be explored in future research (60). In any case, liver function should be closely monitored, and the drug should be discontinued if worsening of it is detected.

HYPONATREMIA IN CHRONIC KIDNEY DISEASE

Prevalence and etiology

Prevalence and incidence values of hypoNa in chronic kidney disease (CKD) are respectively 13.5% and 26% (mean follow-up 5.5 years) (70). HypoNa is especially common among patients with stage 5 CKD on dialysis (End-Stage Renal Disease, ESRD): 29.3% prevalence in hemodialysis, 14.5% incidence in peritoneal dialysis (71).

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).

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

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

Mortality:

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

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

Notes on treatment:

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

HYPONATREMIA IN NEUROSURGERY

Prevalence and etiology:

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

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

Mortality

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

reviewed 198 consecutive patients with SAH and indicated sodium fluctuation, rather than hypoNa per se, as a significant factor associated with worse neurologic outcome (91)

Specific notes on clinical features and diagnosis:

Most observational studies have shown that SIAD is the commonest cause of hypotonic hypoNa in neurosurgical patients (86). However, in this setting it is essential to differentiate SIAD and cerebral salt wasting syndrome (CSWS) as a possible cause of hypoNa, especially in pediatric series and in patients with SAH (86, 92, 93). The differential diagnosis between CSWS and SIAD may not be easy in clinical practice, the former having hypovolemia as a crucial point for the proper diagnosis (94).

In the evaluation of the hyponatremic patient after neurosurgery, it is essential to consider the possible occurrence of DI with a triphasic pattern (95) and the possible late occurrence of hypoNA due to SIAD, which can occur after the patient has been discharged (88-90)

In order to improve the outcome in neurosurgical patients, we suggest careful monitoring of serum sodium on admission and during the hospital stay. Whenever hypoNa is observed, a proper work-up has to be instructed to elucidate the underlying cause, bearing in mind that the evaluation of extracellular fluid volume status is mandatory. Also in case of early discharge the patients should receive clear instructions on what to do if hypoNa-compatible symptoms appear.

HYPONATREMIA IN THE PATIENT WITH TRAUMA AND POLYTRAUMA

Prevalence and etiology

Little is known about hypoNa in patients with polytrauma (PT). In several studies, hypoNa has been reported in up to 15% of patients after trauma or PT (96, 97). After PT, the occurrence of hypoNa can be related to the event *per se* (fluid depletion, hemorrhage), to the immediate treatment at the site of trauma or Emergency Department (hypotonic intravenous fluids), or to a pre-existing comorbidity disease, especially in the elderly.

Mortality

HypoNa is associated with poor prognosis and increased mortality in patients with crush syndrome: in a retrospective study conducted in Chinese reference hospitals during the Wenchuan earthquake the presence of hypoNA was common, up to 50% of patients were affected and 15% of them died. However, here the hypoNa was mainly correlated with the development of acute kidney failure (96).

Notes on clinical features and diagnosis

Hip fracture is the commonest cause of traumatic death in Europe: immediate surgery has been associated with higher rates of independent living, lower mortality rates, improved patient outcomes by reducing pain scores, and lowering the risk of decubitus ulcers. The occurrence of hypoNa ($[Na]^+$ <135 mEq/L) in the course of the pre-surgical planning was the main medical pre-operative risk factor for surgery delay after 36 hours from trauma (98).

Rather than considering hypoNa always as a consequence of PT, this electrolyte disorder could be the cause of trauma: even mild hypoNa in fact has been associated with unsteady gait, falls, impaired concentration, and risk of fractures, especially hip and femur fractures (6, 99). In an extensive series of elderly adults, fracture risk incidence was higher in patients with HypoNa, also after adjusting for osteoporosis. Patients with moderate-severe hypoNa ($[Na]^+$ <130 mEq/L)

presented an 11-fold risk of fractures (100), and fragility fractures increased incrementally with a categorical decrease in median serum sodium levels in multivariate logistic regression models (101).

Notes on treatment

Specific consensus about the treatment of hypoNa targeted to PT patients has not been developed, yet. In general, we suggest to follow currently available guidelines and recommendations for the management of hypoNa.

HypoNa is common in PT patients without neurological involvement: however, larger studies are needed to investigate the relationship between trauma and serum sodium levels, and hypotonic intravenous fluids should be supplied carefully to patients with PT.

HypoNa is not always recognized in patients with PT: we suggest to pay attention to sodium balance in such patients. Population studies with a large number of participants have to be performed.

HYPONATREMIA IN THE OUTPATIENT SETTING

Prevalence and etiology:

The prevalence of hypoNa in this setting greatly depends on the age of the population considered (102-105). In a young and ethnically diverse population, the prevalence of hypoNa was 6.3% (105), but with aging the potential risk of developing hypoNa increases (103, 106).

In the outpatient setting, hyponatremic individuals are more likely to be smokers, to have black ethnicity, a history of diabetes mellitus, congestive HF or cirrhosis and to use thiazide diuretics, antiepileptic drugs or SSRI (103, 105).

However, in the Dallas Heart Study, among hyponatremic individuals with no predisposing medical conditions, 20% of them had criteria discriminators of the diagnosis of SIAD (105).

Mortality:

There are limited data in the literature regarding hypoNa in the outpatient setting, but similarly to hospitalized patients, also in the outpatient studies hypoNa has been reported to be an independent mortality risk factor (9, 102, 105, 107, 108). In a recent survey, hypoNa was found to be associated with a nearly two-fold increase in deaths, even after adjusting for major risk factors (105).

Specific notes on clinical features and diagnosis:

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

Actually, in clinical practice, hypoNa very often represents an incidental finding during an outpatient visit for another reason and it is difficult for the physician to formulate promptly a correct etiological diagnosis, which greatly depends on additional laboratory tests that may not be readily available.

Notes on treatment:

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

In the case of hypoNa secondary to SIAD, when vaptans use is indicated, patients should be hospitalized, because of the need of close initial monitoring, and to identify the appropriate dose (9, 109). A day-hospital admission may be suitable if there are no other serious concomitant disorders (110).

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

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

LIFE-THREATENING HYPONATREMIA

Prevalence and etiology:

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

Mortality:

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

Specific notes on clinical features and diagnosis:

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

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

Notes on treatment:

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

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

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

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

HYPONATREMIA OVERCORRECTION: CONDITIONS AT RISK, PREVENTION, TREATMENT

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

In such a circumstance, administration of a hypotonic solution should be started, as intravenous 5% dextrose or free water 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 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 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) (13). It is mandatory that specific measures to blunt overcorrection of hypoNa must be implemented by/or under the direction of experienced medical personnel (13) .

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

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

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

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

CONCLUSIONS

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

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

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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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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 inadeguate urinary dilution (< 100 mOsm/Kg of water)
Elevated plasma AVP levels, despite the presence of hypotonicity and clinical euvolemia

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924 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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