

Hyponatremia and its relationship with Hematologic Diseases

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ABSTRACT

Hyponatremia is the most frequent electrolyte problem which is directly linked with higher risk of morbidity and mortality. It is common in hematologic patients who have either benign or malignant diseases. Several underlying processes appear to be implicated in the development of hyponatremia, including hypovolemia, infections, toxins, renal, endocrine, cardiac and hepatic problems, as well as the use of certain medicines. In this article prevalence, clinical sign and symptoms, causes, risk factors and pathophysiology of hyponatremia, as well as the contributing variables and processes that found in patients with hematologic diseases are also described. The role of the syndrome of inappropriate antidiuretic hormone (SIADH) secretion and renal salt wasting syndrome (RSWS) in the development of hyponatremia in the individuals, along with the differential diagnosis and treatment options for these conditions are also discussed here. The difference between real hyponatremia and pseudohyponatremia is further clarified. Finally, in this review we include a realistic approach for evaluating hyponatremia in hematologic patients, as well as hyponatremia therapy concepts.

❖ **Keywords** - Hyponatremia, Hematology, Sodium, Drugs, SIADH, RSWS

I. INTRODUCTION

Hyponatremia is defined as low blood sodium concentration (<135 mEq/L). It affects both hospitalised patients as well as in general population. The key factors influencing the symptoms of this electrolyte disease are the rapidity and degree of the reduction in blood serum sodium concentration. According to an experimental research, low extracellular sodium concentration may promote the carcinogenesis in vitro by upregulating molecular pathways implicated in oxidative stress, proliferation and invasion [1]. The importance of recognising,

evaluating and treating hyponatremia in hematologic patients depends on the fact that it is an independent predictor of poor outcomes in both neoplastic and benign disorders, including lymphomas, sickle cell anaemia, hemolytic uremic syndrome, and allogeneic hematopoietic stem cell transplantation (AlloSCT) [2]. Furthermore, hyponatremia symptoms such as fatigue, disorientation, and even falls might be wrongly ascribed to other conditions such as neutropenic sepsis or central nervous system (CNS) involvement in the setting of the underlying haematological illness. The clinical features of hyponatremia in a variety of haematological illnesses, and its treatments are discussed below.

❖ Prevalence of Hyponatremia

The prevalence of hyponatremia varies extensively in different studies, depending on patient populations and how many hyponatremia instances occur. Mostly it is seen in females, elderly, and hospitalised patients. Thus, the general population has a prevalence of 7.2 %, but hospitalised patients have a prevalence of up to 42.6% [3]. In a study it is found that, up to 30% of elderly patients in nursing homes have been reported to have hyponatremia, and 30% of those using selective serotonin reuptake inhibitors. [4] Patients with hyponatremia who need to be hospitalised tend to remain longer (with related greater expenditures) and are more likely to need re admission. The incidence of hyponatremia (serum sodium levels < 130 mmol/L) on at least 2 out of 3 consecutive days was 11.9 % according to a study of hospitalised children with acute lymphoblastic leukaemia [5]. Furthermore, both neurologic complication and the presence of central nervous system leukaemia are linked with hyponatremia [5]. Hyponatremia was seen in 40% of patients following hematopoietic stem cell transplantation (HSCT) in another single-center study of 140 pediatric patients [6]. The incidence rate of euvolemic and hypervolemic hyponatremia was 395 per 1000 person-years in patients with

lymphoma, according to a large retrospective cohort investigation of patients diagnosed with specific cancer types [7].

❖ **Signs and symptoms of Hyponatremia**

Patients' symptoms might range from non-specific nausea, vomiting, and headache to life-threatening stupor, coma, seizures, respiratory depression, and death in the case of acute (<48-hour) or severe (serum sodium levels < 120 mEq/L) hyponatremia. Chronic moderate hyponatremia (serum sodium levels 120–129 mEq/L) and mild hyponatremia (serum sodium levels 130–134 mEq/L) are frequently asymptomatic and do not show up on a standard clinical examination. Individuals with high salt levels may have modest symptoms such as fatigue, cognitive impairment, disorientation and gait disturbances, as well as falls, osteoporosis and fractures [8, 9]. Very low plasma sodium concentrations (usually < 115 mmol/L) are sometimes associated with neurological complaints. [10] When plasma sodium levels drop drastically, brain cells enlarge as a result of water entering them and starts swelling, this condition is called cerebral edema. Afterthat, pressure inside the skull rises and causes hyponatremic encephalopathy. As pressure increases in the skull, brain herniation occurs. Because of that, brain may

squeeze over the internal components of the skull. Headache, nausea, vomiting, disorientation, seizures, compression of the brain stem, respiratory arrest, and non-cardiogenic fluid buildup in the lungs can result from this. [11] If it is not treated immediately, this can cause death. The intensity of the symptoms is influenced by how quickly and drastically the blood salt level drops. Because of neural adaptation, a slow reduction in concentration, even to extremely low levels, may be easily tolerated if it happens over a few days or weeks. The intensity of neurologic symptoms is also influenced by the existence of underlying neurological illness, such as a seizure condition or non-neurological metabolic problems.

❖ **Causes of Hyponatremia**

There are three main categories for the particular causes of hyponatremia: with low tonicity (lower than normal solute concentration), without low tonicity and falsely low sodium levels. [12] Following that, individuals with poor tonicity are divided into three groups based on their fluid volume: Hypervolemic or high volume, Euvolemic or normal volume and Hypovolemic or low volume. [12] Very little amount of sodium in the diet alone is rarely the cause of hyponatremia. Table 1 shows the causes of hyponatremia. [12]

Hypervolemic	Euvolemic	Hypovolemic
<ul style="list-style-type: none"> • Cirrhosis of the liver • Congestive heart failure • Nephrotic syndrome in the kidneys • Excessive drinking of fluids 	<ul style="list-style-type: none"> • Glucocorticoid deficiency • Not enough ACTH • Hypothyroidism • Syndrome of inappropriate antidiuretic hormone secretion (SIADH) resulting from <ul style="list-style-type: none"> • Mass lesions • Inflammatory diseases • Normal physiologic change of pregnancy • Degenerative demyelinating disorder • Carcinoma lung, prostate, larynx, pancreas • Leukemia • Atypical pneumonia • Chronic obstructive pulmonary disease • AIDS related complex • Drug induced like use of 3,4-Methylenedioxy methamphetamine (MDMA), all 	<ul style="list-style-type: none"> • Diuretic therapy • Mineralocorticoid deficiency • Bowel obstruction • Muscle trauma • Burns • Pancreatitis • Vomiting and diarrhea • Prolonged exercise, perspiration, sweat losses

	classes of psychotropic drugs, including antidepressants, antipsychotics, mood stabilisers, and sedative/hypnotics	
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Table 1: Causes of Hyponatremia

❖ **Pathophysiology**

Hyponatremia has two basic pathophysiological mechanisms which include either loss of effective solutes (sodium and potassium) in excess of water or (more commonly) water retention. Because the capacity of water excretion is sufficient in normal circumstances, water retention resulting in a reduction in serum sodium concentration that happens only when renal excretion of water is impeded. Primary polydipsia is an exception to this rule, in which excessive water intake overwhelms normal excretory capacity (acute water intoxication). [13, 14] Because the inhibition of ADH production is essential for the renal excretion of any water load, high blood levels of arginine vasopressin (also known as antidiuretic hormone (ADH)) should be regarded a requirement for the development and maintenance of hyponatremia. Almost all causes of hyponatremia (except for low dietary solute intake, renal failure, primary polydipsia, or beer potomania syndrome) are accompanied by increased ADH, primarily due to the syndrome of inappropriate ADH secretion (SIADH) or effective circulating volume depletion, regardless of the presence of hypotonicity. In fact, a 15% reduction in effective arterial blood volume due to true hypovolemia (e.g., vomiting, diarrhoea, osmotic diuresis) or edematous states (e.g., congestive heart failure, nephrotic syndrome, hepatic cirrhosis with ascites) causes a reduction in stretch at the carotid and renal baroreceptors, resulting in an increase in ADH excretion and overriding the inhibitory effect of hypotonicity. This highlights the importance of process which is involved in the maintenance of adequate circulating volume at the expense of osmotic dysregulation and hyponatremia [15]. Hyponatremia is influenced by the amount of water consumed and the amount of solutes consumed on a daily basis. Even when the diluting capacity of the kidneys is intact, the kidneys' ability to eliminate significant volumes of water is restricted. The following equation is used to compute the daily urine volume (UV): $UV = USL/U_{osm}$, where USL represents the urine solute load (in mOsm/day) and U_{osm} represents the urine osmolarity. Normal diet supplies 600–900 mOsm

of solute per day, mostly from urea (metabolic product of protein) and electrolytes (sodium, potassium, and associated anions), resulting in an equal USL. If solute intake is 900 mOsm/d, 18 L of urine will be expelled at the lowest possible U_{osm} (50 mOsm). On the other hand, if solute intake is lowered to as low as 100 mOsm/d, which is not frequently observed in malnourished individuals, only 2 L of urine can be expelled. Hyponatremia will follow if these individuals ingest more than 2 L of fluids [16, 17].

❖ **Risk Factors of Hyponatremia**

- Strenuous exercises like running marathons and triathlons, [18]
- Excessive consumption of water without consuming any protein (decrease urea excretion which promotes decrease water excretion),
- Particularly thiazide diuretics (older age, female gender, low body weight, the tendency of water intake, decreased diluting ability of kidney, and hypokalemia increase the risk for thiazide associated hyponatremia), [19]
- Patients with Chronic diseases like liver cirrhosis, congestive heart failure, hypertension, diabetes and severe kidney disease, [20]
- Hospitalised patients with pneumonia and patients who are taking hypotonic fluid. [21]
- Patients who are elderly or who have already experienced hyponatremia [22]
- Trans Sphenoidal Surgery (TSS) for pituitary adenomas may stretch the pituitary stalk and impair neurohypophyseal function (the risk of hyponatremia increased with increased Diaphragma sellae (DS) sinking depth, a larger pituitary stalk deviation angle difference, and a longer postoperative “measurable pituitary stalk” by MRI. [23]
- Cases of acute hyponatremia following conditions fast have been recorded. Reproductive-age women are uniquely susceptible to hyponatremia. Fasting individuals, particularly lactating women, due to reduced milk supply after fasting may

consume water alone, which can lead to dangerous hyponatremia. [24]

- Recently, it was shown that patients with COVID 19 had a higher chance of having hyponatremia. Nearly one- third of coronavirus disease patients were found to develop hyponatremia.[25]

❖ **Causes of Hyponatremia in Patients with Hematologic Diseases**

- Pseudohyponatremia**

When examining hyponatremia, the first step is to rule out the potential of pseudohyponatremia, which can occur as a result of severe hyperlipidemia or hyperproteinemia, both of which diminish the water content of a given volume of blood. As a result, sodium concentration in the serum is artificially reduced (pseudohyponatremia), although sodium concentration in the water phase and serum osmolality remain unaffected. Associated conditions which are related to hyperlipidemia or hyperproteinemia in patients with hematologic diseases are shown in Table 2.

Type of Hyponatremia	Causes	Associated Conditions
Pseudohyponatremia (isotonic hyponatremia: serum osmolality 280–295 mOsm/kg)	Hyperglobulinemia	MM, other paraproteinemias, POEMS syndrome, Castleman’s disease, post-transplant monoclonal gammopathies, NHL, CLL, cryoglobulinemia, cold agglutinin disease, Gaucher disease, HCV or HIV infection, cirrhosis drugs: IVIG, interferon
	Hypertriglyceridemia	HLH, uncontrolled diabetes mellitus drugs: L-asparaginase, ATRA. Interferon
	Hypercholesterolemia	Allogeneic stem cell transplantation, MM, NHL
	Mixed dyslipidemia	Nephrotic syndrome (secondary causes include: HL, monoclonal gammopathy, cryoglobulinemia, POEMS syndrome, leukemia, glycogen storage diseases, sickle cell disease, MDS, GVHD, infections)
Hypertonic hyponatremia: (serum osmolality >295 mOsm/kg)	Hyperglycemia	Diabetes mellitus: preexisting or related to hemochromatosis, thalassemia, and HSCT. Infections. Drugs: glucocorticoids, interferon, tacrolimus, immune checkpoint inhibitors
	Hypervolemic (edematous hyponatremia)	Cirrhosis. Nephrotic syndrome. Renal insufficiency: chemotherapy, contrast media, NSAIDs, infections, post-HSCT, PNH, sickle cell disease and other hemoglobinopathies, MM, lymphomas, paraproteinemia, TTP, HUS, TLS Heart failure: cardiomyopathy due to hemochromatosis, hemoglobinopathies, amyloidosis, or paraproteinemias. Drug-induced heart failure (e.g., anthracyclines, alkylating agents, fluopyrimidines, TKIs), CAR T- cell therapy, thoracic radiation therapy, immune checkpoint inhibitors-induced myocarditis. POEMS syndrome. (Extravascular volume overload is among the

		minor criteria of the syndrome)
	Euvolemic hyponatremia	SIADH: lymphomas, paraproteinemias, HLH, post-HSCT, sickle cell disease, porphyria. Pain and nausea. Pulmonary and CNS infections. Drugs: vinca alkaloids, cyclophosphamide, platinum compound drugs, melphalan, busulfan, interferon, bortezomib, TKIs, methotrexate, tacrolimus, cyclosporine A, CAR T-cells therapy, carbamazepine, SSRIs.
	Hypovolemic hyponatremia	Adrenal insufficiency: adrenal metastases or CNS invasion by lymphomas, AML, ALL, hemoglobinopathies. Infections: CNS infections (e.g., tuberculosis), systemic fungal infections. Bilateral cranial radiation therapy. Drugs: steroids, immune checkpoint inhibitors. Extra-renal salt loss: infection mediated. Renal salt loss: myeloproliferative diseases, LAHS, sickle cell disease. Post-HSCT with CNS complications. Drugs: methotrexate, hydroxyurea, platinum compounds, etc. Adrenal hemorrhage: e.g., coagulopathy.

Table 2: superimposed factors of hyponatremia in hematological patients

(ALL: acute lymphoblastic leukemia, ATRA: all trans retinoic acid, AML: acute myeloid leukemia, CAR: chimeric antigen receptor, CML: chronic myeloid leukemia, CLL: chronic lymphocytic leukemia, CNS: central nervous system, GVHD: graft versus host disease, HCV: hepatitis C virus, HIV: human immunodeficiency virus, HL: Hodgkin's lymphoma, HLH: hemophagocytic lymphohistiocytosis, HSCT: hematopoietic stem cell transplantation, HUS: hemolytic uremic syndrome, IVIG: intravenous immunoglobulin, LAHS: lymphoma-associated hemophagocytic syndrome, MDS: myelodysplastic syndrome, MM: multiple myeloma, NHL: non Hodgkin, POEMS: polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes, SSRIs: selective serotonin reuptake inhibitors.)

Direct or indirect ion-selective electrodes (ISE) can be used to test electrolytes. Because it involves a dilution phase, only indirect ISE is linked to false hyponatremia [26]. As a result, with direct ISE, the problem of pseudo-hyponatremia can

be avoided. Patients with cancer, particularly hematologic malignancies mostly suffer from hypocholesterolemia or some times hyperlipidemia. [27] A patient with multiple myeloma (MM) has been reported to have type III hyperlipoproteinemia with xanthomas. [28] Furthermore, a patient with obstructive jaundice as the first presentation of non-lymphoma Hodgkin's (NHL) was reported to have significant secondary hypercholesterolemia due to cholestasis [29]. L-asparaginase, an important component of acute lymphoblastic leukemia (ALL) treatment, causes hypertriglyceridemia, which can be exacerbated by the use of steroids [30, 31]. Furthermore, all trans retinoic acid (ATRA) used to treat acute promyelocytic leukaemia appears to promote hypertriglyceridemia in a dose-dependent manner [32]. Hypercholesterolemia may result from alloSCT, either as a result of reduced hepatic triglyceride lipase activity or as a result of cholestasis caused by chronic graft versus host disease (GvHD) [33, 34]. Furthermore, hypertriglyceridemia is associated with hemophagocytic lymphohistiocytosis (HLH) which

is one of the diagnostic criteria for the disease [35, 36]. Importantly, some hematologic disorders are associated with nephrotic syndrome and are therefore likely causes of false hyponatremia in the context of hyperlipidemia. Increased hepatic biosynthesis, as well as the impaired clearance of cholesterol and major lipoproteins are the fundamental underlying processes of nephrotic syndrome-related hyperlipidemia, which are induced by a drop in oncotic pressure owing to protein loss in urine [37, 38, 39]. Due to repeated transfusions, hepatitis B and C viruses (HBV and HCV) are prevalent infections in individuals with hemoglobinopathies, such as thalassemias [40, 41]. These infections have been linked to hyperlipidemia caused by nephrotic syndrome or cholestasis, as well as hypergammaglobulinemia caused by chronic liver disease, resulting in pseudohyponatremia [42, 43]. Pseudohyponatremia has also been linked to monoclonal gammopathy and intravenous immunoglobulin (IVIg) treatment [44, 45]. Because a 1 g/dL rise in blood protein concentration reduces serum sodium concentration by roughly 0.7 mEq/L, pseudohyponatremia can occur in the presence of severe hyperproteinemia (>10 g/dL) [46]. Normal serum sodium levels in the context of hyperproteinemia or hyperlipidemia should raise the possibility of hyponatremia (pseudonormonatremia). Moreover, in hypoalbuminemic states (e.g., nephrotic syndrome), indirect ISE may overestimate serum sodium concentration up to 10 mEq/L in comparison with direct ISE [47]. As a result, blood sodium levels should be assessed using the direct ISE technique in the presence of hyperlipidemias, hyper and hypoalbuminemia, whereas serum osmolality should be measured with an osmometer in such circumstances. When the observed serum osmolality is within normal ranges (280–295 mOsm/kg), pseudohyponatremia is present [26].

- **SIADH**

SIADH is one of the most prevalent causes of hyponatremia, and it can be caused by a variety of factors. Although abnormal ADH release is a reason for this syndrome and increased liquid consumption is also necessary for the development of low blood sodium concentrations [48]. When SIADH develops in malignant hematologic diseases (e.g., lymphomas, leukaemia, MM, Waldenström's macroglobulinemia (WM)), it is mostly attributed to ectopic ADH secretion or enhanced interleukin-6 (IL-6) production by malignant cells, as well as CNS infiltration [49,50].

IL-6 causes SIADH by increasing ADH synthesis in the hypothalamus (non-osmotically) [51]. Hemophagocytic syndrome also linked with IL-6-mediated SIADH [52]. High serum levels are also indicated as an etiologic cause of SIADH in a 5-year-old kid with sickle cell disease, where dimercaprol and calcium ethylenediaminetetraacetic acid (EDTA) chelation therapy cured both hyponatremia and increased levels of ADH [53]. However, it looks more likely that elevated levels of IL-6 and stroke caused by abrupt vaso-occlusion are the most relevant factors in SIADH in sickle cell disease. [54] Acute intermittent porphyria and post-AlloSCT both are linked with SIADH. [55, 56] Early manifestation of hyponatremia caused by SIADH after AlloSCT is insidious and can develop rapidly with fatal outcome. [55] SIADH after AlloSCT or even autoSCT is a rather uncommon and underappreciated condition. Nausea, vomiting, and exhaustion are common hyponatremia symptoms that may be easily traced to the conditioning programme before to transplant. Several risk factors have been linked to the development of SCT-related SIADH, including cord blood as the graft source, HLA-mismatched unrelated donor or recipient, age under 4 years [6], cyclophosphamide [57] or busulphan as conditioning regimen components [58], and GvHD prophylaxis with methylprednisolone [6] or tacrolimus [59]. Furthermore, as compared to peripheral blood or bone marrow, cord blood as the source of the transplant has been linked to more severe symptoms, such as seizures, somnolence, and the earlier onset of hyponatremia [60]. The pathogenesis of SCT-related SIADH has been linked to IL-6 and TNF- α . Following SCT from an HLA-mismatched or unrelated donor, these cytokines have been found to be increased [61]. However, there is no link between acute GvHD and SCT-related SIADH as one would expect [6, 60]. The reactivation of varicella zoster virus (VZV), one of the most prevalent post-transplant sequelae with atypical symptoms [62], is another interesting cause of SCT-related SIADH. Severe abdominal pain, inappropriate ADH secretion and diffuse VZV infection preceding skin lesions, according to Rau et al., should encourage doctors to test for VZV DNA in blood for early identification and treatment [63]. Other infections of the respiratory or central nervous systems, as well as a variety of medications, are common underlying causes of SIADH in hematologic disorders. Furthermore, non-osmotic triggers for ADH release include pain,

nausea, and tension; all are common in hematologic patients [48].

- **Hypovolemia**

In clinical practise, extracellular volume depletion is one of the most prevalent causes of hyponatremia. Hematologic patients may develop hypovolemic hyponatremia as a result of renal or extrarenal fluid losses caused by infections, medicines (e.g., chemotherapy-induced vomiting or diarrhoea), or the underlying hematologic diseases. The cerebral salt wasting syndrome (CSWS), initially reported by Peters JP et al. in 1950 [64], is a very unusual cause of volume depletion. The release of brain natriuretic peptide, which causes natriuresis and hypovolemia, is thought to be the primary pathophysiologic mechanism of CSWS [65, 66]. Myeloproliferative diseases have been linked to CSWS, and it is thought that hyperviscosity and microcirculation anomalies induce ischemic lesions in the brain [67]. After AlloSCT, CSWS-induced hyponatremia has been documented, along with CNS consequences (e.g., cerebral haemorrhage, encephalitis) [68] and sickle cell disease [69]. Renal salt wasting syndrome (RSWS) is another name for CSWS, which does not need the presence of cerebral illness [70]. In a patient with natural killer-cell neoplasm and hemophagocytic syndrome, hyponatremia due to renal salt loss attributed to oncolysis-induced cytokine release was reported. [71] Leukemia-induced tubular dysfunction has also been linked to salt-losing nephropathy [72]. Polyuria can also occur in central diabetes insipidus (as a result of leukaemia or lymphoma) [73, 74] or nephrogenic diabetes insipidus (as a result of sickle cell disease or trait, as well as renal amyloidosis) [75, 76].

- **Hyponatremia related to infections in Hematology**

Infections, which often worsen the clinical course of haematological patients, can produce hyponatremia through a variety of pathways [77]. Diarrhea, vomiting, or profuse sweating may occur during an infection, resulting in hypovolemic hyponatremia. Certain infections may be caused by hematopoietic therapies (e.g., chemotherapy) in conjunction with a reduction in underlying humoral or cell-mediated immunity in hematologic patients. For example, diarrhoea caused by severe CMV colitis contributed to hyponatremia in a patient receiving chemotherapy for follicular lymphoma (FL) [78]. Patients with thalassemia who are vulnerable to this virus (endemic in Southeast Asia)

have also been documented to have symptomatic hypovolemic hyponatremia attributed to dengue hemorrhagic fever [79]. SIADH, which is caused by an increase in hypothalamic ADH production, commonly worsens the course of viral, bacterial, fungal, and tuberculous infections that primarily affect the lungs and CNS [77]. As previously stated, infections (mainly viral) can provoke acquired hemophagocytic syndrome, which can lead to IL-6-mediated SIADH [52]. In coronavirus disease 2019 (COVID-19), coronavirus that appears to damage the haematological system (e.g., lymphopenia, coagulopathy), has also been linked to IL-6-related hyponatremia [78, 79]. Other causes of hyponatremia in the context of an infection include primary or secondary adrenal insufficiency (e.g., systemic fungal infections, acquired immunodeficiency syndrome), severe renal injury (e.g., leptospirosis), nephrotic syndrome (e.g., HBV and HCV), CSWS (e.g., cerebral toxoplasmosis or human herpesvirus 6 encephalitis), and congestive heart failure (infection-induced myocarditis) [77]. Infections may also cause hyperglycemia and, as a result, hyponatremia by increasing the release of catecholamines, glucagon, and cortisol. Some antibiotics can cause hyponatremia. For example trimethoprim, which is structurally similar to the potassium-sparing diuretic amiloride, can produce hypovolemic hyponatremia at large dosages [77]. Other antibiotics and antifungal drugs (such as ciprofloxacin, pentamidine, and voriconazole) are infrequently linked to hyponatremia [77]. Several illnesses (e.g., infective endocarditis, leishmaniasis, HIV infection, HCV infection) can cause hypergammaglobulinemia and, as a result, pseudohyponatremia through polyclonal activation of B-lymphocytes [77]. Most of the aforementioned hyponatremia-causing pathophysiological pathways can be seen in HIV infection [77]. Hyponatremia was found to be a mortality predictor in patients under the age of 18 years who had Shiga toxin-producing *Escherichia coli* hemolytic uremic syndrome in an observational, retrospective, cross-sectional study. [80]

- **Hyponatremia due to Disorders of Endocrine System and Metabolism in Hematology**

Diabetes mellitus (DM), a chronic metabolic disease, commonly seen among adult peoples, but day by day its prevalence is steadily increasing. A meta-analysis of observational studies found that DM may raise the incidence of

non-Hodgkin lymphoma, leukaemia, and myeloma [81]. Pathophysiologically, DM is associated with some hematologic illnesses (e.g., hemochromatosis, major thalassemia). It has been proposed that DM is caused by iron excess, with the latter being deposited in the pancreas and producing oxidative stress in β -cells, resulting in pancreatic dysfunction [82,83]. DM is frequently diagnosed within the first decade of life as a consequence of significant thalassemia [83,84]. Infections or some drugs might cause hyperglycemia in haematological individuals [85,86,87]. Corticosteroids, for example, are commonly used to treat both malignant and benign illnesses (such as immune thrombocytopenia and autoimmune hemolytic anaemia). Additionally, immunosuppressive medications such as tacrolimus have been linked to post-transplant DM [87]. Long-term HSCT survivors are more likely to develop metabolic syndrome and diabetes; this is likely due to the long-term effects of rigorous chemotherapy, as well as the immunological and inflammatory effects of GvHD and its treatment [88]. Immune checkpoint inhibitors used to treat Hodgkin's lymphoma (HL), such as pembrolizumab and nivolumab, have been linked to autoimmune diabetes and diabetic ketoacidosis [89]. Finally, interferon treatment has been linked to hyperglycemia and diabetes mellitus (DM) [90]. Because glucose is an osmotically active molecule, osmotic transfers of water from the intracellular to the extracellular space cause dilutional hyponatremia in the setting of hyperglycemia. Serum sodium concentration should be adjusted in hyperglycemic situations; the most frequent calculation is corrected sodium = measured sodium + $(1.6 (\text{glucose} - 100)/100)$. A correction factor of 2.4 should be applied when the glucose levels is more than 400 mg/dL. Poorly managed diabetes can lead to hypovolemic hyponatremia by osmotic diuresis, whereas the excretion of beta-hydroxybutyrate and acetoacetate exacerbates urine sodium losses in diabetic ketoacidosis [91]. In the absence of hyperglycemia, DM may cause hyponatremia, potentially through insulin-induced activation of aquaporin-2 (AQP2) [92]. The apical cell membranes of the main cells of the kidney's collecting duct, as well as intracellular vesicles present throughout these cells, contain AQP2. It is involved in water reabsorption and is controlled by vasopressin. As a result of elevated AQP2 expression, excessive water reabsorption and hyponatremia occur. [93] Hyponatremia can also be caused by other endocrine conditions, such as

primary adrenal insufficiency (Addison's disease), secondary adrenal insufficiency, and hypothyroidism [11]. In hematologic patients, the link between infections and adrenal insufficiency has been studied. Both SIADH and hypopituitarism have been linked to hyponatremia in individuals with intravascular large B-cell lymphoma [94, 95]. Diffuse large B cell lymphoma (DLBCL), also can cause hyponatremia by invading the contralateral adrenal or hypothalamus [96, 97]. Indeed, a recent meta-analysis found that malignancies, such as lymphomas, may lead to adrenal insufficiency as a result of bilateral adrenal infiltration [98]. A case of bilateral adrenal haemorrhage in a patient with acute myeloid leukaemia (AML) also found. [99] Furthermore, in ALL cases, adrenal insufficiency may be caused by solitary adrenocorticotropic hormone (ACTH) deficiency [100]. Hemoglobinopathies, such as thalassemias and sickle cell disease, can cause a variety of endocrine problems, including hypogonadotropic hypogonadism, diabetes mellitus, hypothyroidism, hypoparathyroidism, and adrenal insufficiency, which are all caused by iron excess [101,102]. A patient with WM, adrenal insufficiency was observed due to plasma cell infiltration with light-chain (AL) amyloid deposition in the pituitary and adrenal gland [50]. Adrenal insufficiency can arise when glucocorticoid medication is abruptly stopped, as the hypothalamus-adrenal axis is suppressed. This can be avoided if physicians provide thorough explanations about corticosteroid therapy and by continuous patients monitoring. Importantly, due to blockage of the steroidogenesis route, concurrent treatment of antifungal drugs (e.g., fluconazole, posaconazole), which are often used in hematologic patients, may maintain the axis suppressed for extended periods of time [103,104]. Adrenalitis and Addison's disease have been linked to nivolumab, as well as hypothyroidism and secondary adrenal insufficiency due to selective pituitary dysfunction [105]. Additionally, 20 years after treatment, long-term survivors of childhood ALL, who received a modest dose of cranial radiotherapy, shows some signs of central adrenal insufficiency [106].

- **Hyponatremia related to Kidney injury in Patients with Hematologic Diseases**

Hyponatremia is caused by a reduction in water excretion due to renal dysfunction reducing urine dilution capacity. Water retention is restricted in less severe renal diseases and excessive water consumption plays a crucial role in the

development of hyponatremia [107]. Kidney disease is a common occurrence in clinical practise. For example, bleeding, gastrointestinal losses, renal losses (e.g., osmotic diuresis), poor cardiac output, or decreased vascular resistance all can cause acute kidney injury (AKI) owing to prerenal azotemia (e.g., due to infections). Platinum-containing medicines, alkylating agents, and methotrexate are among the nephrotoxic agents used in haematological diseases. [108,109] In addition, contrast-induced kidney damage is prevalent, particularly in cancer patients [110]. AKI was shown to be 15.4 % common in hospitalised patients with haematological malignancies in a recent research, and blood sodium levels were found to be directly connected to AKI [111]. Intravascular hemolysis can be caused by hemoglobinopathies, complement abnormalities, and infections such as malaria [112]. A frequent consequence of hematopoietic stem cell transplantation (HSCT) is renal thrombotic microangiopathy, which results in decreased renal function [113]. Chemotherapy, radiation, sepsis, medications (e.g., antibiotics, calcineurin inhibitors), bone marrow toxicity, hepatic veno-occlusive disease, and GvHD are all possible causes of kidney damage after HSCT [114]. Renal impairment is highly prevalent in MM and other lymphoid malignancies and paraproteinemias [115]. Kidney damage in these individuals might be caused by hypercalcemia, hyperuricemia, dehydration, renal parenchymal involvement, ureteral obstruction, glomerulonephropathy, renal vascular compromise, and tumour lysis syndrome [116]. Furthermore, patients with MM are more susceptible to infections and frequently take non-steroidal anti-inflammatory drugs (NSAIDs) as pain relievers, both of which are risk factors for AKI [117]. A case of cryoglobulinemic glomerulonephritis linked to nodal and renal infiltration by T-cell lymphoma of the T-follicular helper phenotype is reported. [118]. Hemolytic uremic syndrome is the most common cause of AKI, although it can also happen in thrombotic thrombocytopenic purpura [119]. The release of free heme and iron due to intravascular hemolysis and subsequent hemoglobinuria, Fanconi syndrome, and possibly subclinical microvascular thrombosis are among the pathophysiological mechanisms that can cause both acute and chronic renal impairment in paroxysmal nocturnal hemoglobinuria (PNH) [120]. Furthermore, in sickle cell disease and sickle trait, chronic renal disease is a prevalent consequence. This is caused

by repeated bouts of sickling, which cause ischemia damage and microinfarctions, resulting in the destruction of the renal medulla's vascular architecture. Glomerular hyperfiltration and renal hyperperfusion, endothelial dysfunction, and the release of free heme owing to hemolysis are all contributing factors [121].

- **Hyponatremia related to Cardiac Disorders in Hematologic Patients**

Hyponatremia in heart failure (HF) is mostly caused by diuretic treatment or neurohormonal activation owing to effective circulation volume decrease [122]. Heart failure (HF) is a common side effect of a variety of hematologic illnesses and medicines used in clinical haematology. In the setting of persistent hemolysis and sickling, hemoglobinopathies, namely beta (β)-thalassemia and sickle cell disease are linked to HF. Chronic hemolysis causes anaemia, high-output HF and vasculopathy, whereas sickling causes both vasculopathy and myocardial ischemia. Furthermore, iron overload cardiomyopathy can be caused by repeated blood transfusions and increased iron absorption due to ineffective erythropoiesis in individuals with hemoglobinopathies [123]. Cardiomyopathy has been linked to the deposition of amyloid and iron in the heart in amyloid disease and hemochromatosis, respectively [124]. Treatment for a variety of haematological illnesses can compromise heart function. Thoracic radiation has been proven to produce irreversible dose-dependent cardiac damage and late-onset HF 5 to 30 years after first exposure [125], whereas anthracyclines have been found to cause irreversible dose-dependent cardiac damage and late-onset HF [126]. Anthracyclines have been linked to the development of HF in survivors of childhood and adult-onset malignancies, as well as in patients with HL or aggressive NHL [127]. Cardiovascular problems, particularly HF, have been linked to alkylating drugs such cyclophosphamide, fluoropyrimidines, and tyrosine kinase inhibitors [128]. Chimeric antigen receptor (CAR) T-cell treatment has the potential to harm the myocardial and potentially cause HF due to excessive cytokine release [129]. Immune checkpoint inhibitors have also been linked to the development of myocarditis [130].

- **Hyponatremia related to Liver Diseases in Hematologic Patients**

Hyponatremia is common in hepatopathies, particularly cirrhosis, due to

decreased effective arterial blood volume and other associated causes. The chief causes of pseudohyponatremia are significant hyperlipidemia (hypertriglyceridemia and hypercholesterolemia) and hypergammaglobulinemia, both of which are prevalent characteristics of liver illnesses [43]. Liver involvement can occur as a result of a variety of hematologic diseases, potentially leading to hyponatremia. In beta (β)-thalassemias, cirrhosis can result from hemosiderosis caused by iron excess from transfusions. Repeated episodes of arterial occlusion that damage the liver in sickle cell disease can compromise its function. Autoimmune hemolytic anaemia and autoimmune hepatitis are two conditions that can occur together. Hepatic vein blockage (Budd–Chiari syndrome) is a complication of polycythemia vera or other myeloproliferative disorders, PNH, and bone marrow transplantation [131]. Liver infiltration (e.g., lymphoma, leukaemia, multiple myeloma) can cause a wide range of problems, from asymptomatic elevated liver function tests to abrupt hepatic failure [132]. Importantly, several disorders (e.g., hemochromatosis, Wilson disease) might have both hepatic and hematologic symptoms, whereas some hematologic comorbidities or sequelae (e.g., DM, HF, HBV, HCV) have been linked to the development of hepatic cirrhosis. Cirrhosis can be caused by DM-related non-alcoholic fatty liver disease, but HF can cause hepatic fibrosis (also known as "heart cirrhosis") [43]. Cirrhosis can also occur as a result of HBV and HCV infections following numerous blood transfusions in hematologic individuals.

• **Hyponatremia related to Pharmacological Agents used in the treatment of Blood Diseases**

Low blood sodium concentration has been linked to a number of medicines routinely used to treat haematological illnesses. SIADH is the most prevalent cause of drug-induced hyponatremia. Nausea, a typical chemotherapy side effect, is a powerful inducer of ADH secretion. Vinca alkaloids like vincristine cause hyponatremia by inducing SIADH [133]. It is important to highlight that taking vincristine and azoles at the same time is not recommended, as it blocks vincristine metabolism and as a result, may increase the drug's side effects, such as neurotoxicity and hyponatremia [134,135]. Hyponatremia can be caused by CD19 + CAR T-cells used to treat relapsed/refractory ALL because of hypercytokinemia and increased IL-6, which

induces the hypothalamus to produce ADH inappropriately [136]. Methotrexate can cause hyponatremia at high dosages, most likely owing to toxic effects on the cerebrum's neurosecretory regions, activation of natriuretic peptides, or changes in the distribution of body fluid volumes [109,137]. Hyponatremia is caused by cyclophosphamide when it is given in high dosages with a significant amount of hypotonic fluids to prevent hemorrhagic cystitis. However, when cyclophosphamide is administered at lower dosages, hyponatremia can occur [138]. It should be noted that cyclophosphamide and vincristine are co-administered in certain lymphoma chemotherapy protocols, such as hyper-CVAD (cyclophosphamide, vincristine sulfate, doxorubicin hydrochloride, dexamethasone, methotrexate, cytarabine) and CODOX-M/IVAC (cyclophosphamide, vincristine, doxorubicin, high-dose methotrexate/ifosfamide, etoposide, high-dose cytarabine). Both regimens have a > 20% risk of febrile neutropenia, and antifungal drugs like azoles are frequently used in combination, raising the risk of hyponatremia, as previously indicated. Selinexor, an oral selective inhibitor of nuclear export that is now being tested in clinical trials for relapsed refractory multiple myeloma, has been reported to produce hyponatremia in nearly 30% of patients [139]. Ibrutinib, a drug often used to treat chronic lymphocytic leukaemia, mantle cell lymphoma, and WM, has been proven to cause hyponatremia in up to 6% of patients [140]. Due to the concomitant administration of high quantities of hypotonic fluids to prevent nephrotoxicity, platinum-based antineoplastic medicines may also reduce sodium levels [109]. In patients using cisplatin, both SIADH and CSWS have been identified as underlying causes of hyponatremia [141,142,143]. On the other hand, hyponatremia is less common with oxaliplatin than with cisplatin [144]. Rise in urinary N-acetyl β -glycosaminidase, a proximal tubule lysosomal enzyme, within 24–48 hours after cisplatin treatment has been postulated as a predictor of hyponatremia caused by this medication [142,145]. Because of the translocational impact of sucrose's osmotic burden, intravenous delivery of sucrose-containing immunoglobulin can produce genuine hyponatremia [146]. In the context of renal dysfunction, maltose-containing IVIG can cause translocational (hyperosmolar) hyponatremia. Maltose, which is metabolized by maltase in the proximal renal tubules, accumulates in the extracellular fluid in this situation, raising serum

osmolality and diluting blood levels. Another cause of hyponatremia after IVIG is aseptic meningitis-associated SIADH [45]. Most tyrosine kinase inhibitors (TKIs) including imatinib, nilotinib, dasatinib, and bosutinib, have been linked to hyponatremia in a dose-dependent manner, mostly owing to SIADH [147,148]. But ponatinib has no linked to hyponatremia. Tricyclic antidepressants, selective serotonin re-uptake inhibitors, proton

pump inhibitors, antiepileptic medications, trimethoprim-sulfamethoxazole, NSAIDs, tramadol and other opioid analgesics all are associated with hyponatremia in patients treated for haematological diseases. [45,149] Drugs used for the treatment of hematological diseases and their associated mechanisms for hyponatremia are shown in Table 3.

Drug	Disease	Mechanism
Cyclophosphamide, ifosfamide [138,150,151,152]	Multiple myeloma, lymphomas	SIADH, hypotonic fluids to prevent hemorrhagic cystitis
Imatinib and other TKIs [147,148]	CML, ALL	SIADH
Entospletinib [153]	In development	SIADH
Vincristine [141,133,154]	Lymphomas, ALL	SIADH
Methotrexate [155]	Lymphomas, ALL	SIADH and CSWS
mTOR inhibitors (everolimus) [156]	In development	Aldosterone resistance
Tacrolimus [59]	Post AlloSCT	SIADH
Selinexor [139]	In development	Unknown
Cytarabine, Elacytarabine [157]	Lymphomatous meningitis, AML	Unknown
Hydroxyurea [158]	Myeloproliferative neoplasms, sickle cell disease	CSWS
Ibrutinib [140]	CLL, mantle cell lymphoma, Waldenstrom's macroglobulinemia	Unknown
Nivolumab, Pembrolizumab [159,160,161]	Hodgkin lymphoma	Primary adrenal insufficiency, Diabetes mellitus
Rituximab plus lenalidomide [162]	Follicular lymphoma	Unknown
Pentostatin [163]	HCL	Unknown
Cyclosporine A [164]	Immunosuppression post AlloSCT	SIADH
Desmopressin [165,166]	Bleeding disorders	Unknown
Intravenous immunoglobulin (IVIG) [146]	ITP	Translocational effect of the osmotic load of sucrose and IVIG nephropathy
Bortezomib [167]	Multiple myeloma	SIADH
CD19+ chimeric antigen receptor (CAR) T-cells [136]	ALL, DLBCL, PMBCL	Elevated IL-6→ SIADH
Platinum compounds (cisplatin, carboplatin, oxaliplatin) [141,142,143]	Relapsed or refractory lymphomas	SIADH, CSWS, hypotonic fluids
Interferon [168]	HCL, CML, multiple myeloma, follicular lymphoma	SIADH

Melphalan [169]	Multiple myeloma	SIADH
Busulfan [109]	Prior to SCT	SIADH

Table 3: Drugs used for the treatment of hematological diseases and their associated mechanisms for hyponatremia

(ALL: acute lymphocytic leukemia, AlloSCT: allogeneic stem cell transplantation, AML: acute myeloid leukemia, CML: chronic myeloid leukemia, CLL: chronic lymphocytic leukemia, CSWS: cerebral salt wasting syndrome, DLBCL: diffuse large B-cell lymphoma, HCL: hairy cell leukemia, ITP: immune thrombocytopenia mTOR: mammalian target of rapamycin, PMBCL: primary mediastinal B-cell lymphoma SIADH: syndrome of inappropriate secretion of antidiuretic hormone, TKIs: tyrosine kinase inhibitors)

❖ **Evaluation of Hyponatremia**

Hyponatremia patients commonly have significant neurologic consequences as a result of cerebral edema. Rapid correction of hyponatremia may result in the development of central demyelinating lesions, particularly in the pons (a condition known as central pontine myelinolysis or osmotic demyelination syndrome (ODS)), which can cause major neurologic disabilities or even death [170]. As a result, early identification of the underlying causes of hyponatremia is critical for proper care and avoidance of therapeutic hazards that can lead to hyponatremia under or over treatment. Figure 1 displays a step-by-step diagnostic assessment of hyponatremia in hematologic patients.

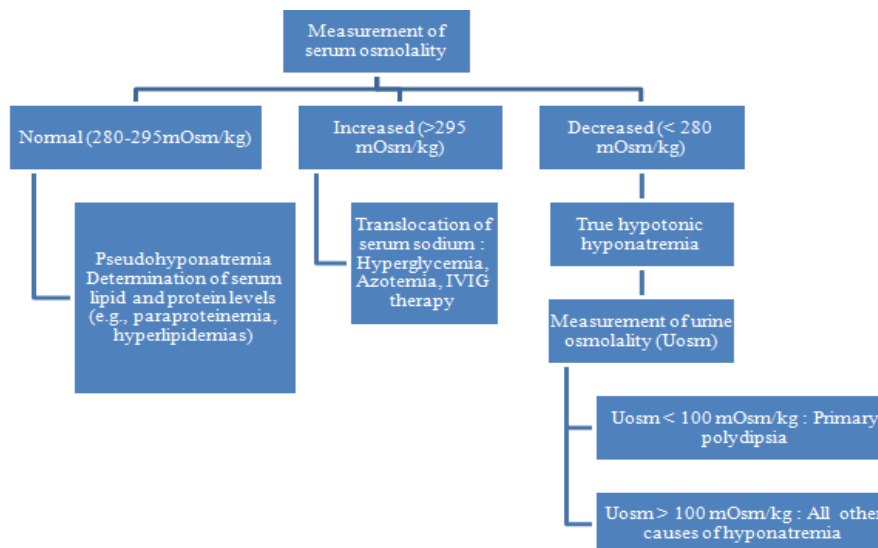


Figure 1: Approach to a patient with hyponatremia with hematologic disease. (IVIG: Intravenous Immunoglobulin, mOsm: milliosmole, Uosm: urine osmolality)

Concentration of sodium in urine (UNa) in a random urine sample is crucial for the diagnostic process. Low effective arterial blood volume or SIADH are indicated by values less than or greater than 30 mEq/L, respectively. However, diuretic treatment, osmotic diuresis, salt-losing nephropathy, primary adrenal insufficiency and metabolic alkalosis all can cause UNa > 30 mEq/L. UNa < 30 mEq/L, can be seen in individuals with chronic SIADH who are on a reduced salt diet or

anorexia. A low urine chloride concentration (UNa < 25 mEq/L) is a reasonable marker of extracellular volume depletion in the presence of metabolic alkalosis [43]. Hyponatremia caused by SIADH and CSWS has been reported in hematologic disorders with intracranial involvement [171]. Later with SIADH, this represents a similar laboratory profile where hypouricemia with a fractional excretion of uric acid (FEUA) > 11%, UNa > 30 mmol/L, and Uosm > 100 mOsm/kg.



However, due to the varying volume status in these illnesses, the therapy is not same (i.e., normovolemia in the case of SIADH versus hypovolemia in the case of CSWS). In clinical practise, it can be difficult to distinguish between CSWS and SIADH since extracellular volume is commonly assessed in a way that is inaccurate for clinical reasons. In reality, CSWS usually lacks overt signs of volume depletion such as hypotension, reduced skin turgor, raised hematocrit and higher blood urea nitrogen to creatinine ratio. Fluid restriction, loop diuretics, and vaptans (ADH antagonists) are used to treat SIADH should be avoided in a seemingly normovolemic patient with hyponatremia associated with "intracranial disease," as they may deteriorate both hypovolemia and hyponatremia, leading to cerebral edema and even seizures in the case of CSWS. [172] Hypertonic saline should be given in such conditions. Given that FEUA normalises SIADH but stays 11% in CSWS, the calculation of FEUA after treating hyponatremia is regarded as a valuable tool for making the right diagnosis. Isotonic saline should be avoided if the U_{osm} is higher than the serum osmolarity (particularly in situations of $U_{osm} > 530$ mOsm/kg) as it may exacerbate hyponatremia due to SIADH [171,173]. Hypopituitarism with subsequent adrenal insufficiency is another neglected cause of

hyponatremia that frequently manifests with a SIADH like appearance (euvoletic hyponatremia, low serum uric acid, and urea levels, $U_{Na} > 30$ mmol/L, $U_{osm} > 100$ mOsm/kg). Additionally, it can be challenging to distinguish between primary and secondary adrenal insufficiency as latter this may not exhibit the typical symptoms associated with mineralocorticoid shortage. In fact, hypovolemia as determined by a clinical assessment may not be evident whereas hyperkalemia may be absent in 30 to 50 % of Addison's disease patients. Certain diagnostic procedures (cortisol determination and adrenocorticotropic hormone (ACTH) stimulation test) may be necessary to diagnose hypothalamic–pituitary–adrenal axis problems in such circumstances [15]. Finally, hypothyroidism-induced hyponatremia is quite uncommon, occurring most likely only in severe hypothyroidism ($TSH > 50$ mIU/L). Before attributing low blood sodium levels to hypothyroidism, other probable causes and superimposed variables of hyponatremia (e.g., medicines, infections, adrenal insufficiency) should be examined [174]. In Figure 2, a recommended method for treating a patient with hypotonic hyponatremia, $U_{osm} > 100$ mOsm/kg, and hematologic disease is depicted.

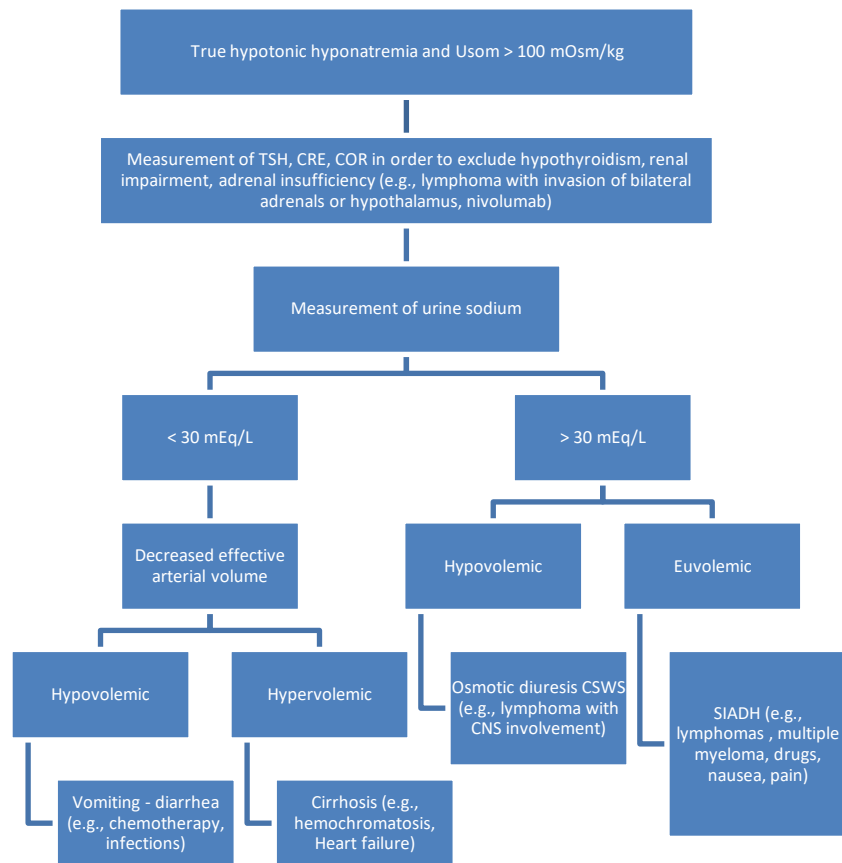


Figure 2: Approach to a patient with hypotonic hyponatremia, Uosm > 100 mOsm/kg, and hematologic disease (Uosm: urine osmolality, TSH: thyroid-stimulating hormone, CRE: creatinine, COR: cortisol, CSWS: cerebral salt wasting syndrome, SIADH: syndrome of inappropriate antidiuretic hormone secretion, CNS: central nervous system)

❖ **Treatment of Hyponatremia**

The major goal of hyponatremia treatment is to minimise the potentially fatal neurologic consequences that might emerge during or after overcorrection of this electrolyte imbalance. Correction of hyponatremia should be done at a rate of < 8–10 mEq/L/24 h [170,175]. The optimal rate of correction should be limited to 4–6 mEq/L/24 h in the presence of circumstances that predispose individuals to develop ODS (i.e., hypokalemia, malnutrition, liver illness, alcoholism, and serum sodium levels ≤ 105 mEq/L) [170,175,176]. Hyponatremia’s therapeutic approaches are generally focused on the length of the condition, as well as the patient’s symptoms and extracellular volume status [17,177]. A bolus infusion of 100–150 mL of hypertonic saline (3 % NaCl) over 20 minutes, up to three times, is advised in situations with severe neurological symptoms owing to hyponatremia [175,176]. To

correct the symptoms of hyponatremic encephalopathy, the objective is to elevate serum sodium concentration by 4–6 mEq/L within the first 4–6 hours, without exceeding the aforementioned limits. For mild symptoms, a continuous infusion of 3 % NaCl (0.5–2 mL/kg/hour) might be utilised [175,176,178,179]. In the treatment of hypovolemic hyponatremia, the underlying causes of hyponatremia (e.g., infections, hyperglycemia, primary adrenal insufficiency) must be addressed, as well as the use of diuretics. To restore intravascular volume, normal saline or Ringer’s lactate solution should be used [176,180]. To minimise an extremely fast increase in sodium concentration when volume status is restored, close monitoring of serum sodium levels (every few hours) and urine output is strongly suggested. In this situation, a sudden drop in ADH secretion and a following sharp rise in diuresis are seen. Noteworthy, any potassium deficiency should be rectified in hypovolemic situations. Potassium

chloride should be administered to hypotonic fluids in such circumstances. Normal saline with potassium chloride (i.e., a hypertonic solution) should be avoided because it raises the risk of hyponatremia overcorrection, volume overload and pulmonary edema, particularly in the elderly or in patients with HF [180]. In the case of hyponatremia caused by SIADH, fluid restriction is the first line treatment. Treatment of other superimposed variables (e.g., infection, discomfort, nausea) is also necessary after discontinuation of the offending drugs. Water clearance can be increased by increasing solute intake (such as salt tablets or urea) and using loop diuretics. On the other hand, treatment for hypervolemic hyponatremia involves

limiting fluid consumption and giving patients loop diuretics to reduce their body's excess sodium and water. Vaptans increase water diuresis. So, it is recommended as a second-line treatment for hyponatremia caused by SIADH, whether it is hypervolemic or euvolemic hyponatremia [177]. Due to case reports of concomitant ODS; vaptans should not be administered in hypovolemic hyponatremia or in combination with hypertonic saline solution [175,176,181]. Dialysis is required for edematous hyponatremia in the context of severe acute or chronic renal damage. Table 4 represents the basic principles of hyponatremia management.

- Determination of time onset of hyponatremia (acute < 48 h and chronic > 48 h)
- Proper correction rate < 8–10 mEq/L/24 h
- Proper correction rate of 4–6 mEq/L/24 h in high risk conditions for ODS
- Hypokalemia, malnutrition, advanced liver disease, alcoholism, serum sodium \leq 105 mEq/L
- In acute symptomatic hyponatremia, administration of hypertonic saline solution (3% sodium chloride) is prudent
- In patients with SIADH, fluid restriction, furosemide, or vaptans are the major treatment options
- In hypovolemic patients and CSWS, fluid restriction, furosemide, and vaptans are contraindicated. Instead, isotonic saline solution may be administered

Table 4: Basic principles of hyponatremia management

(CSWS: cerebral salt wasting syndrome, h: hours, ODS: osmotic demyelination syndrome, SIADH: syndrome of inappropriate secretion of antidiuretic hormone)

II. CONCLUSIONS

Hyponatremia, which is often multifactorial, is common in individuals with hematologic diseases and may exacerbate their already precarious clinical situation. Because of its non-specific clinical characteristics, which can be wrongly assigned to other clinical entities such as neutropenic sepsis, chemotherapy side effects, CNS involvement, or disease-related fatigue, the severity of this condition is frequently overestimated. To understand the fundamental causative processes and appropriately individualise therapy, further care should be taken. Co-administration of medications that modify each other's metabolism should be avoided if hyponatremia is already present, since this may worsen it. Aside from

treating hyponatremia according to its duration, symptoms and extracellular volume status, the therapeutic approach should include stopping any offending drugs and managing any other conditions (e.g., infectious, cardiac, renal, or endocrine) that may be contributing to the disorder. Overall, haematologists should become familiar with the early detection and treatment of hyponatremia.

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