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Sodium Disorders in Multiple Myeloma: Beyond Pseudohyponatremia to Clinical Pitfalls and Mechanistic Insights

In depth review

Elena Tanzarella[1], Michele Paolisi[1], Martina Catania[1], Francesca Tunesi[1], Liliana Italia De Rosa[1], Pierpaolo Bianca[1], Kristiana Kola[1], Alessandro Barruscotti[2], Rodolfo Fernando Rivera[3], Paolo Manunta[1,2], Giuseppe Vezzoli[1,2], Maria Teresa Sciarrone Alibrandi[2]

1 Vita Salute San Raffaele University, 20132 Milan, Italy
2 O.U. Nephrology and Dialysis, San Raffaele Scientific Institute, 20132 Milan, Italy
3 Nephrology and Dialysis Unit, Pio XI Hospital, ASST Brianza, Via Mazzini 1, Desio (MB)


Elena Tanzarella

Corresponding author:
Liliana Italia De Rosa
UO Operativa Nefrologia e Dialisi Ospedale IRCCS San Raffaele Milano
Via Olgettina 60 20132 Milano
Tel 0226435330 Fax 0226432384
E-mail: derosa.liliana@hsr.it

ABSTRACT
Hyponatremia is a relatively frequent finding in multiple myeloma (MM) and may result from either pseudohyponatremia, due to marked hyperproteinemia, or true hyponatremia from genuine sodium-water imbalance. Differentiating between these two entities is essential, as they differ in pathogenesis, clinical relevance, and management.
Pseudohyponatremia, observed in approximately 15–20% of MM patients, is a measurement artifact occurring with indirect ion-selective electrode techniques when plasma water fraction is reduced by high M protein levels. Serum osmolality remains normal, and no sodium correction is required.
True hyponatremia (<135 mEq/L with hypo-osmolality) is less common but clinically significant, often associated with worse prognosis. Mechanisms include renal impairment (cast nephropathy, Fanconi syndrome, light chain deposition), hypervolemia from advanced renal failure, hypovolemia from gastrointestinal losses or diuretics, drug-induced effects (notably bortezomib, cyclophosphamide), and paraneoplastic SIADH. Alterations in electroneutrality and strong ion difference (SID) from highly cationic M protein may further lower sodium, usually mildly.
Pseudohyponatremia is managed by controlling the underlying myeloma and reducing paraproteinemia. True hyponatremia treatment is etiology-specific: isotonic saline for hypovolemia, fluid restriction ± solute supplementation for SIADH, careful diuretic adjustment for hypervolemia, and withdrawal of causative drugs when possible. Optimal control of the plasma cell clone, through modern triplet or quadruplet regimens prevents recurrence.
A structured diagnostic approach integrating volume status, laboratory evaluation, and medication review is critical to distinguish pseudo from true hyponatremia, prevent inappropriate interventions, and address the underlying disease.

KEYWORDS: Multiple Myeloma, Hyponatremia, Pseudohyponatremia

Introduction

Multiple myeloma (MM) is a malignant plasma cell disorder characterized by clonal proliferation within the bone marrow and overproduction of a monoclonal immunoglobulin, commonly referred to as M protein. This abnormal protein production and the associated tumor burden contribute to a wide range of clinical manifestations and complications [1, 2].

Epidemiology

Globally, MM accounts for an estimated 160,000 new cases and over 100,000 deaths annually. In the United States, it represents approximately 1.8% of all newly diagnosed cancers. The median age at diagnosis is around 70 years, with a slightly higher incidence in men than in women. African American individuals have an increased risk compared with other ethnic groups [1–3].

Pathogenesis and Risk Factors

The pathogenesis of MM is multifactorial and incompletely understood. Established risk factors include advanced age, male sex, African ancestry, and family history of plasma cell disorders. Environmental and occupational exposures, such as to benzene and certain pesticides, have been suggested as possible contributors [1, 4–6].

M Protein Characteristics

M protein is most frequently of the IgG subtype (~55% of cases) or IgA (~20%), and 40% of patients present with Bence Jones proteinuria due to excess free monoclonal κ or λ light chains in the urine. A subset (15–20%) secrete only Bence Jones protein without detectable serum M protein. Rare variants include IgM, IgD, and IgE myeloma, as well as non-secretory forms detected only by serum free light chain assays [1, 4, 7].

Clinical Features and Complications

MM can present insidiously, with fatigue, bone pain, recurrent infections, or biochemical abnormalities. Major complications include [1, 4, 7, 8]:

- Osteolytic lesions and fractures – due to osteoclast activation and osteoblast inhibition
- Hypercalcemia – present in ~30% of newly diagnosed cases, resulting from bone resorption, increased osteoclast-activating cytokines, and reduced renal calcium excretion
- Renal impairment – caused by light chain deposition, hypercalcemia, amyloidosis, or nephrotoxic agents
- Amyloidosis (AL) – develops in 10–20% of patients due to light chain deposition in organs such as kidney, heart, and liver
- Anemia – from bone marrow infiltration, renal dysfunction, or nutritional deficiencies
- Infections – secondary to immunoparesis and treatment-related immune suppression.

Therapeutic Approach

Treatment of MM is tailored to patient age, comorbidities, cytogenetic risk, and transplant eligibility. Modern regimens integrate multiple drug classes [9–11]:

- Proteasome inhibitors (e.g., bortezomib, carfilzomib, ixazomib)
- Immunomodulatory and anti-angiogenic drugs (e.g., lenalidomide, pomalidomide). Monoclonal antibodies – notably daratumumab (anti-CD38), which has significantly improved response depth and survival in both transplant-eligible and -ineligible patients, and

is used in induction, consolidation, and relapse settings, often in triplet or quadruplet combinations

- Corticosteroids (e.g., dexamethasone)
- Alkylating agents (e.g., cyclophosphamide, melphalan), especially in conditioning before autologous stem cell transplantation.

For transplant-eligible patients, induction regimens such as D-VTd (daratumumab, bortezomib, thalidomide, dexamethasone) or D-VRd (daratumumab, bortezomib, lenalidomide, dexamethasone) are now widely adopted, followed by high-dose melphalan and autologous stem cell transplantation. Maintenance therapy, typically with lenalidomide, prolongs progression-free survival [11].

Hyponatremia in multiple myeloma

Hyponatremia, defined as a serum sodium concentration <135 mEq/L, is a relatively frequent laboratory abnormality in patients with multiple myeloma (MM) and may occur as pseudohyponatremia or true hyponatremia. Correct classification is critical, as these conditions differ substantially in their pathogenesis, clinical significance, and management strategies [12–14].

Pseudohyponatremia

Pseudohyponatremia is the artifactual lowering of measured serum sodium in the presence of normal serum osmolality (275–295 mOsm/kg). Pseudohyponatremia can also occur with increased serum OSM (e.g., in hyperglycemia). In MM, this occurs due to marked hyperproteinemia from excess monoclonal immunoglobulin (M protein) production. The high protein content increases the non-aqueous fraction of plasma, thereby reducing the proportion of plasma water, the compartment in which sodium resides [15, 16]. When sodium is measured by indirect ion-selective electrode (ISE), which requires sample dilution, the reduced water fraction leads to underestimation of sodium concentration, despite normal osmotic activity. Direct ISE, performed on undiluted serum or plasma, avoids this artifact.

Pseudohyponatremia is not an uncommon finding in patients with multiple myeloma. Several studies have documented its occurrence in approximately 15–20% of cases (Figure 1). This prevalence highlights how frequently the condition can be encountered in clinical practice, particularly in patients with markedly elevated levels of monoclonal protein [17–19]. From a clinical standpoint, pseudohyponatremia has no osmotic consequences, as the actual sodium concentration in the plasma water compartment remains normal. Therefore, no corrective measures targeting sodium levels are required. The key lies in recognizing the condition promptly, in order to avoid inappropriate therapeutic interventions and to focus instead on managing the underlying myeloma and reducing paraproteinemia.

True Hyponatremia

True hyponatremia in MM is defined by:

- Serum sodium <135 mEq/L
- Hypo-osmolality (<275 mOsm/kg)

Although less common than pseudohyponatremia, the estimates remain uncertain, although more data indicate that its prevalence is around 8% (Figure 1), it carries greater clinical significance, as it may contribute to neurological symptoms ranging from mild confusion to seizures and coma, and it is associated with worse overall prognosis. The pathogenesis of true hyponatremia in MM is multifactorial, with several mechanisms often coexisting in the same patient [13, 14, 20] (Figure 2).

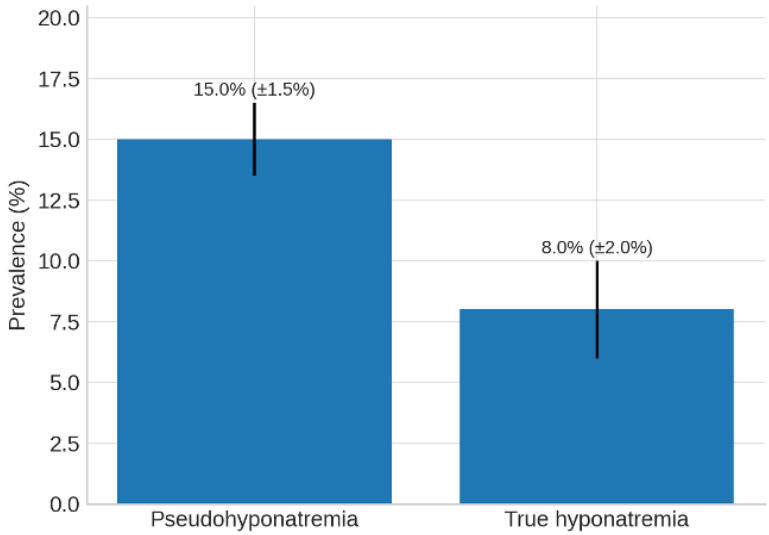

Figure 1. Hyponatremia in MM – Pseudo vs True.

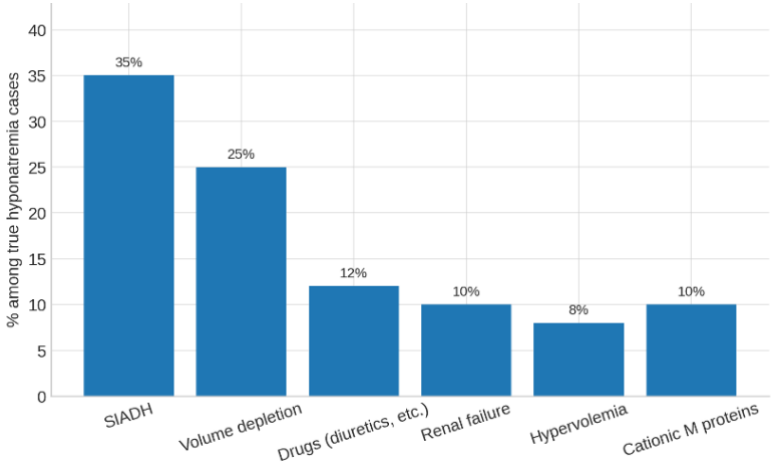

Figure 2. Causes of true hyponatremia in MM.

Pathophysiological Mechanisms of True Hyponatremia in Multiple Myeloma According to Volume Status

Hypovolemic Hyponatremia

a. Gastrointestinal and Extrarenal Losses

Gastrointestinal sodium and water losses are frequent in MM patients due to chemotherapy-induced vomiting and diarrhea, poor oral intake, or infections. The ensuing extracellular fluid volume depletion activates baroreceptor-mediated ADH release, promoting renal water reabsorption. Since water is retained in excess of sodium, serum sodium concentration declines further. In these cases, the urine sodium is typically low (<20 mmol/L) because the kidneys avidly retain sodium to defend effective arterial blood volume [21].

b. Renal Salt-Wasting: Fanconi Syndrome and Tubular Injury

Excess light chains are taken up by proximal tubular cells via endocytosis. Inside the cells, they may precipitate and cause lysosomal rupture, leading to cellular injury. This impairs the reabsorption of bicarbonate, phosphate, glucose, uric acid, amino acids, and sodium. The resultant bicarbonate loss produces a normal anion gap metabolic acidosis, while chronic proximal tubular injury leads to

natriuresis and mild to moderate volume depletion, both of which may exacerbate hypovolemic hyponatremia [22–25].

Loop and thiazide diuretics, frequently used in MM to manage hypercalcemia or fluid overload, can further promote renal sodium loss and worsen hypovolemia. Thiazides, in particular, impair urinary dilution in the distal tubule, creating a setting in which ADH-induced water retention can more easily cause hyponatremia [26].

In summary, when sodium loss (gastrointestinal or renal) exceeds water loss and stimulates non-osmotic ADH release, true hypovolemic hyponatremia ensues.

Euvolemic Hyponatremia

a. Paraneoplastic SIADH

Although rare, MM may be associated with ectopic ADH production by malignant plasma cells or cells in the tumor microenvironment. More commonly, cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) – produced in abundance in MM – can potentiate the renal tubular response to ADH, lowering the threshold for water reabsorption. This leads to water retention, low serum osmolality, and high urine osmolality despite hyponatremia, in the absence of overt edema or signs of volume depletion, i.e. a euvolemic state [13, 27].

b. Drug-Induced SIADH (Bortezomib and Cyclophosphamide)

Bortezomib and cyclophosphamide have both been implicated in the development of SIADH. Potential mechanisms include direct stimulation of hypothalamic ADH release, increased sensitivity of renal collecting ducts to ADH, and indirect effects through inflammatory cytokine release or oxidative stress (Figure 3). In these cases, urine sodium is typically elevated (>20 mmol/L) and urine osmolality is inappropriately high for the degree of hyponatremia, while the patient appears clinically euvolemic [28–31].

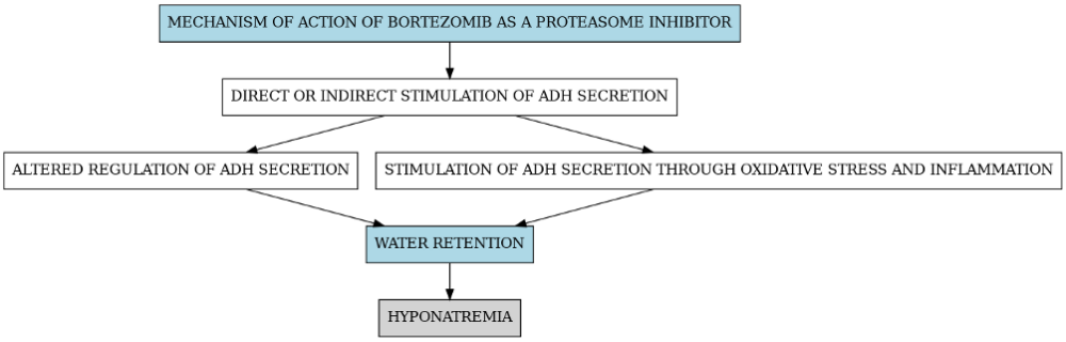

Figure 3. Mechanism by which bortezomib induces hyponatremia.

c. Electroneutrality and Strong Ion Difference Alterations

According to Stewart's physicochemical model of acid–base balance, plasma sodium concentration is not only a reflection of sodium intake and excretion but also depends on the Strong Ion Difference (SID) – the net balance between fully dissociated cations (Na^+, K^+, Ca^{2+}, Mg^{2+}) and anions (Cl^-, lactate, sulfate) [32, 33].

M protein, especially when highly cationic, contributes to the pool of strong cations in plasma. To maintain electroneutrality, a compensatory reduction in sodium (and sometimes potassium) may occur, often accompanied by an increase in chloride concentration. This can lead to a lower anion gap, which, if unrecognized, may be mistakenly attributed to other causes [20, 33]. When SID alterations predominate in otherwise hemodynamically stable patients, the resulting hyponatremia is usually mild and euvolemic, but it may compound other mechanisms such as SIADH.

Unlike pseudohyponatremia, this is not a laboratory artifact – serum osmolality is genuinely reduced because the decrease in plasma sodium within the aqueous compartment is real.

Hypervolemic Hyponatremia

MM-Related Advanced Renal Failure

In multiple myeloma, monoclonal free light chains are freely filtered by the glomerulus. In the distal tubules, they interact with Tamm–Horsfall protein to form obstructive casts. These casts block tubular flow, trigger local inflammation, and damage the tubular epithelium. Beyond cast formation, free light chains may deposit within the renal interstitium, provoking inflammation, fibrosis, and even acute tubular necrosis. The cumulative effect of these lesions is a progressive fall in glomerular filtration rate (GFR) with impaired sodium and water handling. As GFR declines, the kidney progressively loses its ability to excrete electrolyte-free water, so that even modest fluid intakes cannot be fully eliminated. In parallel, activation of neurohormonal systems (renin–angiotensin–aldosterone system, sympathetic nervous system, and non-osmotic ADH release) promotes renal retention of sodium and water to defend effective arterial blood volume. However, the defect in free water clearance is relatively greater than the defect in sodium excretion, resulting in a disproportionate accumulation of water over sodium. The net effect is expansion of the extracellular fluid volume with edema and congestion, but a fall in serum sodium concentration due to dilution – the typical picture of hypervolemic hyponatremia in advanced MM-related kidney disease [20, 22, 34–36].

Table 1 outlines the pathogenetic mechanisms underlying true hyponatremia.

Volume status	Main causes in MM	Predominant mechanism
Hypovolemic	Chemotherapy-related vomiting and diarrhea; infections; poor oral intake; Fanconi syndrome; loop or thiazide diuretics; other tubular salt-wasting lesions	Loss of sodium and water with relatively greater sodium loss → reduced effective arterial blood volume, non-osmotic ADH release, impaired free water excretion
Euvolemic	Paraneoplastic SIADH; bortezomib- or cyclophosphamide-induced SIADH; predominant SID/electroneutrality changes from highly cationic M protein	Inappropriate ADH secretion or increased renal sensitivity to ADH; in selected cases dominant physicochemical (SID) effects → water retention without overt edema
Hypervolemic	Advanced MM-related renal failure due to cast nephropathy, light chain interstitial deposition, and chronic tubulointerstitial damage	Impaired free water clearance with retention of sodium and water, but proportionally greater water retention → edema and dilutional hyponatremia

Table 1. Pathogenesis of true Hyponatremia in MM.

Clinical Approach

Step 1 – History and Physical Examination

Document disease status, renal function history, fluid intake, medications, and gastrointestinal losses.

Assess neurological symptoms (confusion, seizures, coma) and volume status:

- Hypovolemia: dry mucous membranes, orthostatic hypotension, tachycardia;
- Hypervolemia: edema, ascites, jugular venous distension.

Step 2 – Laboratory Work-Up

Serum Sodium concentration

Serum osmolality (distinguish true vs pseudo)

Renal function (urea, creatinine)

Serum protein electrophoresis and M protein quantification

Free light chain assay

Thyroid and adrenal function (TSH, cortisol)

Urine

Urinary sodium:

- <20 mmol/L → hypovolemia with sodium retention
- >20 mmol/L → SIADH or renal salt wasting

Urine osmolality:

High in SIADH despite hyponatremia

Diagnostic Key Points

Always confirm hypo-osmolality to classify true hyponatremia.

In MM, pseudohyponatremia is more frequent, but true hyponatremia requires cause-specific intervention.

Avoid sodium correction in pseudohyponatremia – focus on treating the underlying myeloma and reducing paraproteinemia.

In true hyponatremia, tailored therapy to the mechanism: volume repletion for hypovolemia, fluid restriction for SIADH, careful diuretic management in hypervolemia, and drug review.

Figure 4 depicts the diagnostic algorithm for differentiating pseudohyponatremia from true hyponatremia in multiple myeloma.

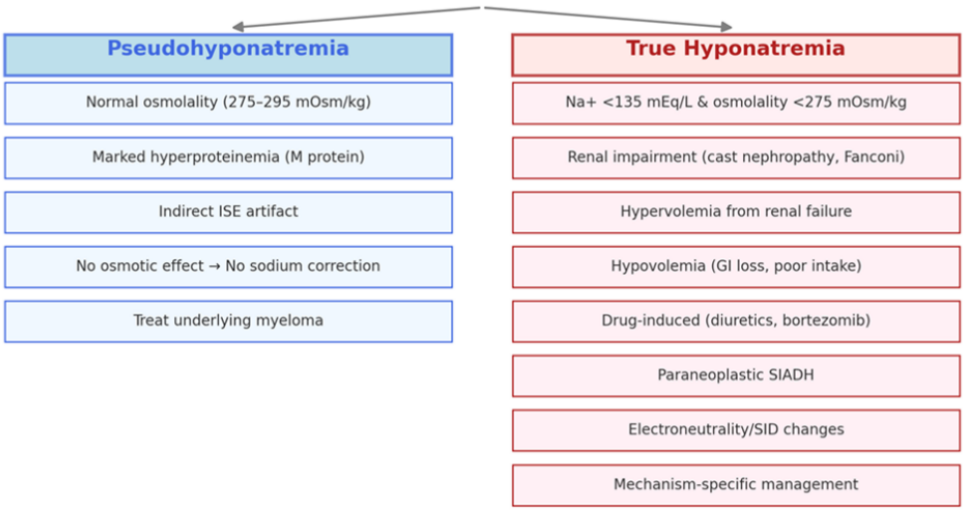

Figure 4. Pseudohyponatremia vs true Hyponatremia.

Therapeutic Considerations

The treatment of hyponatremia in multiple myeloma (MM) hinges on two critical steps: accurate classification into pseudohyponatremia or true hyponatremia, and precise identification of the underlying mechanism in the latter.

Pseudohyponatremia

Because pseudohyponatremia represents a measurement artifact rather than a genuine disturbance in sodium-water balance, no specific sodium correction is warranted. In fact, attempts to raise serum sodium in this setting may be not only unnecessary but also potentially harmful, especially if hypertonic saline is used. The therapeutic focus must instead be directed at controlling the myeloma itself – through reduction of the M protein burden – thereby normalizing plasma water content and resolving the laboratory abnormality. Transitioning to direct ion-selective electrode measurement can prevent repeated misclassification.

True Hyponatremia

Management must be individualized, as multiple pathophysiological processes may coexist [37]. In addition to classifying true hyponatremia according to volume status (hypovolemic, euvolemic, or hypervolemic), treatment should be guided by an assessment of effective osmolality and osmotic load. Measurement of urine osmolality together with urinary sodium and potassium concentrations allows an approximate estimation of daily osmolar excretion and electrolyte-free water clearance. When urinary osmolality is high and osmolar excretion is low (e.g., in patients with poor oral solute intake), even relatively small amounts of hypotonic fluids may worsen hyponatremia. In this setting, the correction strategy must balance fluid restriction with an increase in osmotic load (oral sodium chloride or urea), as emphasized in onconephrology literature on hyponatremia and electrolyte disorders in cancer patients [38].

Hypovolemic hyponatremia (e.g., from gastrointestinal losses or renal salt-wasting due to Fanconi syndrome or diuretics) requires cautious volume repletion, ideally with isotonic saline, correcting sodium gradually to avoid osmotic demyelination [37]. In these patients, low urine sodium (<20 mmol/L) indicates appropriate renal sodium conservation, whereas higher values suggest ongoing renal losses (e.g., diuretics, tubular injury). Restoration of effective arterial blood volume downregulates non-osmotic ADH release, increases electrolyte-free water clearance, and allows serum sodium to normalize.

Hypervolemic hyponatremia from advanced MM-related renal failure benefits from sodium and fluid restriction, judicious diuretic use, and optimization of renal support; dialysis may be necessary in refractory cases [37]. In this context, total body sodium and water are both increased, but water retention is relatively greater because of impaired free water clearance and persistent ADH activity. Estimating osmolar excretion helps to define how stringent fluid restriction must be and whether additional osmotic load (e.g., hypertonic dialysis baths or carefully titrated loop diuretics combined with salt and albumin, when appropriate) is needed to enhance aquaresis without further worsening congestion.

In euvolemic, SIADH-related hyponatremia – whether paraneoplastic or drug-induced (e.g., bortezomib, cyclophosphamide) – the cornerstone of treatment is reduction of effective water intake relative to the patient's osmolar output. Fluid restriction, increased solute intake (oral salt or urea), and in selected cases vasopressin receptor antagonists are used to raise sodium by enhancing electrolyte-free water excretion [37–39]. The required degree of fluid restriction can be estimated from urine osmolality: when urine is highly concentrated and osmolar excretion is low, very strict fluid restriction may be necessary unless osmotic load is increased. Discontinuation or dose adjustment of the offending drug should be considered whenever feasible, balancing oncologic efficacy with electrolyte stability [37–39].

Drug-induced natriuresis from thiazide or loop diuretics, when it presents as hypovolemic hyponatremia, warrants withdrawal or dose reduction, along with electrolyte repletion [37]. In contrast, in hypervolemic patients with advanced renal failure, loop diuretics may be used

strategically to increase sodium and water excretion and thereby improve congestion and serum sodium, provided that blood pressure and renal perfusion are carefully monitored.

Electroneutrality-related sodium depression from highly cationic M protein is generally mild; here, management focuses on myeloma-directed therapy, as sodium levels typically normalize with paraprotein reduction [20]. In these patients, hyponatremia often coexists with other mechanisms (e.g., SIADH or renal failure), and the same principles of osmolality-based management and volume-status–oriented therapy apply.

Figure 5 outlines the treatment approach to hyponatremia in multiple myeloma.

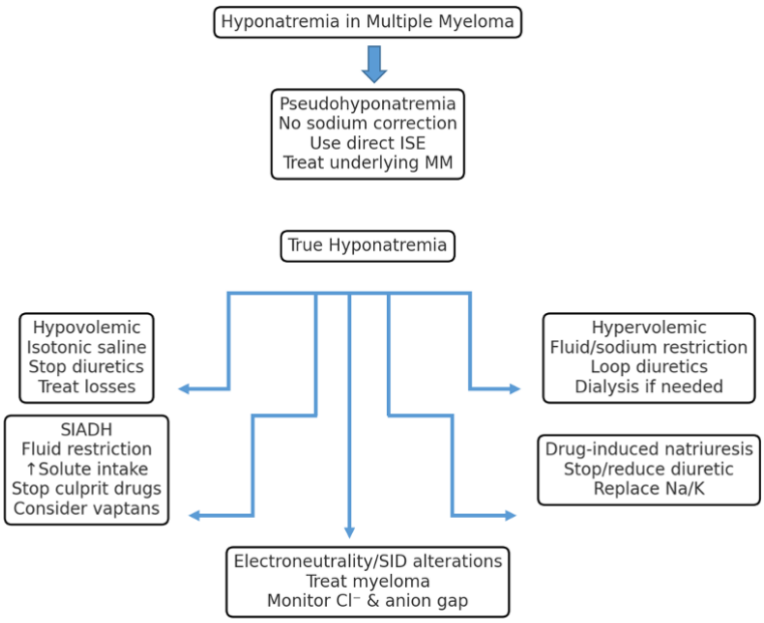

Figure 5. Treatment of Hyponatremia in Multiple Myeloma

Conclusions

Hyponatremia in MM is a multifaceted clinical problem that may arise from either laboratory artifact (pseudohyponatremia) or genuine disturbances in sodium and water homeostasis (true hyponatremia). Pseudohyponatremia – driven by marked hyperproteinemia from excessive monoclonal immunoglobulin production – is common, occurring in up to one fifth of patients, and requires recognition to avoid unnecessary and potentially harmful sodium correction. In contrast, true hyponatremia, although less frequent, carries important prognostic implications and is typically the result of overlapping mechanisms including renal impairment, hypovolemia, drug-induced effects, and, in rare cases, paraneoplastic SIADH. Additional contributions from physicochemical alterations, such as strong ion difference shifts due to cationic M protein, may further modulate sodium balance.

A structured diagnostic approach – integrating volume status assessment, serum and urine studies, and careful medication review – is essential to differentiate between pseudo and true hyponatremia and to guide targeted interventions. Ultimately, optimal management hinges on addressing the underlying myeloma, correcting reversible contributors, and individualizing fluid and electrolyte therapy to the patient's pathophysiological profile.

KEY CLINICAL MESSAGES

- Differentiate pseudo from true hyponatremia – confirm serum hypo-osmolality before initiating sodium correction; pseudohyponatremia is common in MM and should not be treated with sodium supplementation.
- Recognize high prevalence – pseudohyponatremia occurs in up to 15–20% of MM patients, often in the setting of marked hyperproteinemia from monoclonal immunoglobulin excess.
- Identify overlapping mechanisms in true hyponatremia – renal impairment, hypovolemia, drug effects (diuretics, bortezomib, cyclophosphamide), and paraneoplastic SIADH can coexist, amplifying severity.
- Consider physicochemical factors – cationic M protein may alter the strong ion difference, subtly lowering sodium concentration and reducing the anion gap.
- Tailor treatment to etiology – volume repletion for hypovolemia, fluid restriction for SIADH, cautious diuretic use in hypervolemia, and always address the underlying myeloma to reverse contributing factors.

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