Current Trends in Internal Medicine
Alosaimi MM and Hassan H. Curr Trends Intern Med 8: 214.
www.doi.org/10.29011/2638-003X.100114
www.gavinpublishers.com

Review Article

Hyponatremia, a Concise Practical Review

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Citation: Alosaimi MM, Hassan H (2024) Hyponatremia, a Concise Practical Review. Curr Trends Intern Med 8: 214. DOI: 10.29011/2638-003X.100114

Received Date: 05 January 2024; **Accepted Date:** 11 January 2024; **Published Date:** 15 January 2024

Abstract

Hyponatremia, defined as serum sodium below 135mmol / L, is the most common electrolyte abnormality. Its causes can be divided into hypovolemic, euvolemic and hypervolemic according to volume status, and to hypoosmolar, pseudo-hyponatremia and hyperosmolar according to plasma osmolality.

Hyponatremia can be life-threatening if acute or severe. Similarly, inappropriate treatment can lead to significant morbidities. Frequent monitoring and timely interventions are essential to prevent complications.

Hyponatremia symptoms and duration dictate the treatment pace. Hyponatremia with moderate to severe CNS symptoms requires immediate treatment with hypertonic intravenous fluid. The aggressive treatment of chronic hyponatremia, however, increases the risk of osmotic demyelination syndrome. Water restriction and treatment of the underlying cause are the primary management of hyponatremia in edematous patients or are caused by syndrome-inappropriate antidiuresis.

Total Body Water and Osmolality Regulation

In adults, water accounts for 45 to 60% of body weight [1]. It is distributed between intracellular fluid (ICF) and extracellular fluid (ECF) compartments. About 2/3 of total body water (TBW) is in the ICF and 1/3 in the ECF compartment [2]. The volume of each compartment is determined by its osmolality (osmolality is the number of dissolved particles in a kilogram of water). The cell membrane is freely permeable to water, but not most other intracellular and extracellular constituents. As a result, water moves through the cell membrane until the osmotic gradient dissipates and the osmolality across the cell membrane equalizes. A rapid decrease in extracellular osmolality will lead to a shift of water to the intracellular compartment, cell swelling, and a reduction in ECF volume [3].

Plasma sodium is the major extracellular cation and is the primary determinant of plasma osmolality. Therefore, maintaining a steady sodium concentration is an essential physiological process. Thirst, arginine vasopressin (AVP) and the kidneys are responsible for maintaining plasma osmolality. The hypothalamus senses changes in osmolality and regulates synthesis and secretion of AVP [4-6]. It also regulates hypoosmolality-mediated thirst [7]. AVP acts on V2 receptors in the kidney collection ducts and increases water absorption. This is achieved by inserting aquaporin-2 (AQP2) water channels into the luminal surface of the principal cells [8].

Brain cells adapt within hours to hypoosmolality by loss of electrolytes (rapid adaptation) and to chronic hypoosmolar ECF by loss of organic osmolytes (slow adaptation) [9]. Overly aggressive correction of chronic hyponatremia leads to shrinkage of brain cells and irreversible damage (osmotic demyelination syndrome (ODS) [10].

Clinical Manifestations of Hyponatremia

Manifestations of hypotonic hyponatremia are primarily related to dysfunction of the central nervous system and are more evident when the drop in sodium concentration is significant or rapid (i.e. within hours). Headache, nausea, vomiting, muscle cramps, lethargy, restlessness, disorientation, and depressed reflexes can be observed. Severe and rapidly evolving hyponatremia can cause seizure, coma, brain- stem herniation, respiratory arrest, and death.

Causes of Hyponatremia

Hyponatremia is the most common electrolytes disturbance in hospitalized patients and the general population [11-13]. It is caused by excessive water gain in relation to sodium, excessive sodium loss in relation to water, or a trans-cellular water shift. Hyponatremia does not always represent a hypoosmolar state but can be associated with normal or even high osmolality. It is useful

to clinically divide the causes of hyponatremia into hypovolemic, euvolemic and hypervolemic hyponatremia, table1.

The most common causes of severe hyponatremia are thiazide diuretics and the syndrome of inappropriate anti-diuretic hormone secretion (SIAD). Excessive water intake can lead to hyponatremia if the excretory capacity for the free water of the kidney is overwhelmed (primary polydipsia). Hyperglycemia is the most common cause of translocational hyponatremia. An increase of 100 mg per deciliter (5.6 mmol) in serum glucose concentration reduces serum sodium by 2.4 mmol/L and leads to an increase in serum osmolality of 2.0 mOsm / kg of water.14 Common causes of hyponatremia are listed in table 1.

Decreased volume of ECF	Increased volume of ECF	Normal volume of ECF
Renal sodium loss - Diuretics - Osmotic diuresis (glucose, urea, mannitol) - Adrenal insufficiency - Salt-wasting nephropathy - Renal tubular acidosis Extrarenal sodium loss - Diarrhea - Vomiting - Blood loss Fluid sequestration - Bowel obstruction - Peritonitis - Pancreatitis - Muscle trauma - Burns	Congestive heart failure Liver cirrhosis Nephrotic syndrome Kidney failure (acute or chronic) Pregnancy	Thiazide Hypothyroidism Adrenal insufficiency Syndrome of inappropriate antidiuretic hormone secretion Exercise induced hyponatremia

Table 1: Common Causes of Hyponatremia.

Evaluation of Hyponatremia

It is essential to first exclude pseudo-hyponatremia and hyperosmolar state in evaluating hyponatremic patients. Pseudohyponatremia is a laboratory error that results from using an indirect method to measure serum sodium (which involves sample dilution) in patients with hyperlipidemia or hyperproteinemia [15]. Indirect methods (e.g. indirect ion-selective electrode potentiometry) do not take into account that large volume of plasma is occupied by proteins or lipids in these patients. Measuring plasma osmolality or sodium using an ion-specific electrode (i.e., a blood gas analyzer) confirms hypotonic hyponatremia.

When plasma contains an excess of osmotically active molecules (such as glucose and mannitol), free water moves from intracellular to extracellular compartments down the osmotic gradient and dilutes serum sodium. This can be confirmed by correcting sodium levels for hyperglycemia or by measuring plasma osmolality.

The other essential aspect of hyponatremia assessment is its duration. Hyponatremia of unknown duration should be considered chronic.

Typical laboratory workup for hyponatremia includes:

- Serum osmolality, plasma glucose
- Urine osmolality (surrogate of vasopressin activity), and urine sodium
- Total protein and triglycerides
- Assessing hypothyroidism, hypoadrenalism
- Confirming SIAD
- Imagine looking for the cause of SIAD.
- During correction, serum sodium every 2-4 hours, urine electrolytes and osmolality (especially if the urine output exceeds 100ml/h).

Investigations should not be exhaustive if the cause is evident from clinical assessments (such as acute gastroenteritis, congestive heart failure, and a recent start of thiazide diuretics).

Management of Hyponatremia

Treatment of hyponatremia requires balancing the risk of hypotonicity (brain edema) and rapid sodium correction (ODS). The severity of symptoms and the duration of hyponatremia determine the correction rate.

Adrogué and Madia's equation can be used to estimate the effect of giving 1 liter of IVF on a patient's serum sodium by assuming a closed system, i.e. no net water or electrolytes gain or loss other than the IVF given [16].

The effect of one liter of any IVF on serum sodium can be calculated as follows:

$$\text{Change in serum sodium} = \frac{\text{Infusate sodium} - \text{patient's sodium}}{\text{TBW} + 1}$$

The equation can be used to guide both hyponatremia and hypernatremia management. The sodium concentration of common IVF is as follows: D5water: 0, 0.45sodium chloride: 77 mmol/L, Ringer's lactate: 130 mmol/L, 0.9 sodium chloride: 154 mmol/L, 3% sodium chloride: 513 mmol/L.

For example, an 80 kg elderly patient presented with hyponatremia, [Na^+] = 115 mmol/L and seizure. The management plan was to administer 3% sodium chloride to raise serum sodium by 5 mmol and to give lorazepam. To calculate how much fluid is needed to raise serum sodium 5 mmol/L:

Effect of one liter 3% sodium chloride $=\frac{513 - 115}{40 + 1}$=9.7mmol

Using simple calculation: the volume of 3% sodium chloride needed = 5/9.7=0.515 liter= 515 ml. As mentioned earlier, this calculation does not consider the electrolytes-free water diuresis, insensible, and ongoing GI water losses.

Symptomatic Hypotonic Hyponatremia

For patients with severe symptoms or serum sodium below 115-120 mmol/L, treatment with hypertonic sodium chloride is recommended. This can be administered as boluses or continuous infusion. A bolus of 100-150 ml of 3% sodium chloride, repeated 2-3 times as needed, should be given. A continuous 3% sodium chloride infusion at 0.5 to 2 ml/kg/h is an alternative for those with moderate symptoms [17]. Compared to the 3% sodium chloride infusion, boluses are easier to administer and do not lead to more sodium over-correction [18]. Raising serum sodium by a few mmol (5 mmol) is adequate to reverse the CNS manifestations and permit further and slower correction [19]. Patients with seizures also require immediate anticonvulsant drug therapy.

In managing patients with chronic (>48 hours) hyponatremia, it is crucial to monitor serum sodium frequently (20 minutes after the hypertonic fluid boluses and every 2 to 4 hours) and strictly monitor urine output. The 24-serum sodium correction should not exceed 8 mmol in the first 24 hours. Clinically significant ODS has been mainly reported upon correcting hyponatremia by more than 12mmol/24h [20]. Other risk factors for ODS include initial serum sodium <110 mmol/L, alcoholism, malnutrition, chronic liver disease, hypokalemia, and female gender [21,22]. By contrast, rapid correction of acute hyponatremia (< 24 hours duration) carries no risk of ODS [23]. Also, hyponatremia that accompanies edematous states carries minimal risk of ODS, as the prevailing defect is impaired water excretion (unless AVP blocker has been used) [16].

A 50-100 ml of 8.4% sodium bicarbonate (contains 1 mmol/ml sodium) can be used if the 3% sodium chloride is not readily available. 8.4% sodium bicarbonate is not commonly used to treat severe hyponatremia. However, it is easily and timely accessible, raise the serum sodium [24,25] and decrease intracranial pressure similar to the 3% sodium chloride [26].

The rate of hyponatremia correction depends not only on the IVF rate and sodium concentration, but also on the kidney response. As most hyponatremic conditions are associated with elevated AVP, rapid correction could occur when hypovolemia is corrected, AVP stimulation abates, and the urine becomes hypotonic relative to the plasma (free water diuresis). In case of overcorrection, a hypotonic fluid (relative to the urine) should be given. Overcorrection can be prevented by giving desmopressin 2 to 4 micrograms subcutaneously or IV to prevent hypotonic diuresis [27-29]. The rapid correction of hyponatremia should be stopped when life-threatening manifestations seize, and other symptoms improve, or achieving a serum sodium 125 to 130 mmol/L (or even lower if the initial serum sodium is below 100 mmol/L).

Mildly Symptomatic/Asymptomatic Hyponatremia

There is no consensus about the optimal treatment of hyponatremia with mild symptoms. Nevertheless, correction should be sufficient to reverse the manifestations of hypotonicity, but not so rapid to pose a risk of developing ODS. The correction rate should not exceed 8-10 mmol/L on any day of treatment.

Water restriction is the mainstay of long-term management for edematous patients with hyponatremia. Optimization of hemodynamics in severe heart failure by several measures can increase the excretion of electrolyte-free water. Also, loop diuretics reduce urine concentration and increase excretion of electrolyte-free water. In heart failure, treatment with AVP V2 receptor antagonists improves the serum sodium, and augments diuresis [30]. However, this was not translated into improved survival or decreased heart failure morbidities [31].

Syndrome of Inappropriate Antidiuresis (SIAD)

The syndrome of inappropriate antidiuresis (SIAD) is a common cause of hyponatremia [32]. SIAD is caused by inappropriate secretion of AVP, which is not suppressed by plasma hypoosmolality, secretion of AVP at lower osmotic setpoint (reset osmostat), or abnormal water retention by the kidney. The causes of SIAD can be categorized as related to malignant diseases, pulmonary diseases, central nervous system disorders, and drug-induced, table 2.

Malignant Diseases	Pulmonary Disorders	Disorders of the CNS	Drugs	Other Causes
Carcinomas (lung, GI, Genitourinary) Thymoma Ewing's sarcoma Lymphoma	Infections Asthma Cystic fibrosis Respiratory failure with positive pressure ventilation	Infection Bleeding and masses Multiple sclerosis Guillain Barre syndrome Delirium tremens	Drugs that stimulate AVP release - Chlorpropamide - SSRIs - Tricyclic antidepressants - Clofibrate - Carbamazepine - Nicotine - Narcotics - Antipsychotics AVP analogues - Desmopressin - Oxytocin	Heriditary (gain of function mutation of V2 receptor) Acute intermittent porphyria Endurance exercise General anesthesia Nausea Pain Stress

Table 2: Common causes of SIAD.

The hallmark of SIAD is plasma hypoosmolality and inappropriately concentrated urine. Criteria for the diagnosis of SIAD are summarized in table 3 [33].

Management of SIAD should be directed to prevent hyponatremia (post-operative), treatment of the underlying cause, and amelioration of hypotonicity. Administration of isotonic instead of hypotonic maintenance fluid can prevent post-operative hyponatremia [34]. Water restriction is the mainstay of management hyponatremia in SIAD. If this is unsuccessful, sodium chloride with/without loop diuretics can be tried. If these measures fail, an AVP V2-receptor antagonist (such as Tolvaptan) can be used [35]. Initially, a low dose should be started, and the patient's sodium level should be monitored. Also, treatment with urea is associated with improvement of hyponatremia and is well-tolerated [36].

Essential features
- Decreased effective osmolality (<275 mOsm/kg of water) - Urinary osmolality >100 mOsm/kg of water during hypotonicity - Clinical euvolemia - Urinary sodium >40 mmol/liter with normal dietary salt intake - Normal thyroid and adrenal function - No recent use of diuretic age
Supplemental features
- Plasma uric acid <4 mg/dl - Blood urea nitrogen <10 mg/dl - Fractional sodium excretion >1%; fractional urea excretion >55% - Failure to correct hyponatremia after 0.9% saline infusion - Correction of hyponatremia through fluid restriction - An abnormal result on the test of water load (<80% excretion of 20 ml of water per kilogram of body weight over a period of 4 hours), or inadequate urinary dilution (<100 mOsm/kg of water) - Elevated plasma ADH levels despite the presence of hypotonicity and clinical euvolemia

Table 3: Criteria for SIAD diagnosis [26].

Cerebral Salt Wasting

Cerebral salt wasting (CSW) is a disorder characterized by natriuresis and AVP activation due to insult to the CNS [37]. Distinguishing CSW from SIAD is difficult, as both disorders can be caused by CNS disease and characterized by hypoosmolality and inappropriately concentrated urine. Contracted volume status (orthostatic hypotension, dry mucous membranes, decreased jugular venous pressure, and weight loss), high urea and creatinine, and improvement with isotonic saline expansion helps differentiate CSW from SIAD.

Conclusions

Hyponatremia is common in clinical practice. It can be caused by excessive water gain, excessive sodium loss or a shift in water between compartments. Careful history and physical examination will determine the cause in most cases. The severity and duration of hyponatremia determines the treatment approach. In the case of severe hyponatremia with symptoms of central nervous system dysfunction, immediate treatment with hypertonic intravenous fluids is required. For hyponatremia associated with edema or syndrome of inappropriate antidiuretic hormone secretion, the primary management strategies include water restriction and the treatment of the underlying disease.

References

1. Watson PE, Watson ID, Bait RD (1980) Total Body Water Volumes for Adult Males and Females Estimated from Simple Anthropometric Measurements. 33: 27-39.
2. Bedogni G, Borghi A, Battistini N (2003) Body water distribution and disease. In: Acta Diabetologica. 40: S200-202.
3. Grantham J, Linshaw M (1984) The Effect of Hyponatremia on the Regulation of Intracellular Volume and Solute Composition. 54: 5.
4. Verbalis JG (2007) How does the brain sense osmolality?. Journal of the American Society of Nephrology 18: 3056-3059.
5. Majzoub JA, Rich A, Van Boom J, Habener JF (1983) Vasopressin and oxytocin mRNA regulation in the rat assessed by hybridization with synthetic oligonucleotides. Journal of Biological Chemistry 258: 14061-14064.
6. Nowycky MC, Seward EP, Chernevskaya NI (1998) Excitation-secretion coupling in mammalian neurohypophysial nerve terminals. Cell Mol Neurobiol 18: 65-80.
7. McKinley MJ, Johnson AK (2004) The Physiological Regulation of Thirst and Fluid Intake. News in Physiological Sciences 19: 1-6.
8. Nielsen S, Chout CL, Marples D, Christensen EI, Kishoret BK, et al. (1995) Vasopressin Increases Water Permeability of Kidney Collecting Duct by Inducing Translocation of Aquaporin-CD Water Channels to Plasma Membrane. 92: 1013-1017.
9. Sterns RH, Silver SM (2006) Brain Volume Regulation in Response to Hypo-osmolality and Its Correction. Am J Med 119: S12-S16.
10. Martin RJ (2004) Central pontine and extrapontine myelinolysis: The osmotic demyelination syndromes. Neurology in Practice 75: iii22-28.
11. Upadhyay A, Jaber BL, Madias NE (2006) Incidence and prevalence of hyponatremia. Am J Med 119: S30-35.
12. Liamis G, Rodenburg EM, Hofman A, Zietse R, Stricker BH, et al. (2013) Electrolyte Disorders in Community Subjects: Prevalence and Risk Factors. Am J Med 126: 256-263.
13. Tazmini K, Nymo SH, Louch WE, Ranhoff AH, Øie E (2019) Electrolyte imbalances in an unselected population in an emergency department: A retrospective cohort study. PLoS One 14: e0215673.
14. Hillier TA, Abbott RD, Barrett EJ (1999) Hyponatremia: evaluating the correction factor for hyperglycemia. Am J Med 106: 399-403.
15. Weisberg LS (1989) Pseudohyponatremia: a reappraisal. Am J Med 86: 315-318.
16. Adrogué HJ, Madias NE (2000) Hyponatremia. N Engl J Med 342: 1581-1589.
17. Hoorn EJ, Zietse R (2017) Diagnosis and treatment of hyponatremia: Compilation of the guidelines. Journal of the American Society of Nephrology 28: 1340-1349.
18. Baek SH, Jo YH, Ahn S, et al. (2021) Risk of Overcorrection in Rapid Intermittent Bolus vs Slow Continuous Infusion Therapies of Hypertonic Saline for Patients With Symptomatic Hyponatremia: The SALSA Randomized Clinical Trial. JAMA Intern Med 181: 81-92.
19. Spasovski G, Vanholder R, Allolio B, Annane D, Ball S, et al. (2014) Clinical practice guideline on diagnosis and treatment of hyponatraemia. Nephrol Dial Transplant 29 : i1-i30.
20. Sterns RH, Riggs JE, Schochet SS (1986) Osmotic demyelination syndrome following correction of hyponatremia. N Engl J Med 314: 1535-1542.
21. King JD, Rosner MH (2010) Osmotic demyelination syndrome. Am J Med Sci 339: 561-567.
22. Aegisdottir H, Cooray C, Wirdefeldt K, Piehl F, Sveinsson O (2019) Incidence of osmotic demyelination syndrome in Sweden: A nationwide study. Acta Neurol Scand 140: 342-349.
23. Cheng JC, Zikos D, Skopicki HA, Peterson DR, Fisher KA (1990) Long-term neurologic outcome in psychogenic water drinkers with severe symptomatic hyponatremia: the effect of rapid correction. Am J Med 88: 561-566.
24. Gutierrez R, Schlessinger F, Oster JR, Rietberg B, Perez GO (1991) Effect of hypertonic versus isotonic sodium bicarbonate on plasma potassium concentration in patients with end-stage renal disease. Miner Electrolyte Metab 17: 297-302.
25. Kim HJ (1996) Combined effect of bicarbonate and insulin with glucose in acute therapy of hyperkalemia in end-stage renal disease patients. Nephron 72: 476-482.
26. Bourdeaux C, Brown J (2010) Sodium bicarbonate lowers intracranial pressure after traumatic brain injury. Neurocrit Care 13: 24-28.
27. Perianayagam A, Sterns RH, Silver SM, Grieff M, Mayo R, Hix J, et al. (2008) DDAVP is effective in preventing and reversing inadvertent overcorrection of hyponatremia. Clin J Am Soc Nephrol 3: 331-336.
28. Gankam Kengne F, Soupart A, Pochet R, Brion JP, Decaux G (2009) Re-induction of hyponatremia after rapid overcorrection of hyponatremia reduces mortality in rats. Kidney Int 76: 614-621.
29. Rafat C, Schortgen F, Gaudry S, Bertrand F, Miguel-Montanes R, et al. (2014) Use of desmopressin acetate in severe hyponatremia in the intensive care unit. Clinical Journal of the American Society of Nephrology 9: 229-237.
30. Gheorghiade M, Gattis WA, O'Connor CM, Adams Jr KF, Elkayamet U, et al. (2004) Effects of tolvaptan, a vasopressin antagonist, in patients

hospitalized with worsening heart failure: a randomized controlled trial. JAMA 291: 1963-1971.

31. Konstam MA, Gheorghiade M, Burnett JC, Grinfeld L, Maggioni AP, et al. (2007) Effects of oral tolvaptan in patients hospitalized for worsening heart failure: the EVEREST Outcome Trial. JAMA 297: 1319-1331.
32. Berghmans T, Paesmans M, Body JJ (2000) A prospective study on hyponatraemia in medical cancer patients: epidemiology, aetiology and differential diagnosis. Support Care Cancer 8: 192-197.
33. Ellison DH, Berl T (2007) Clinical practice. The syndrome of inappropriate antidiuresis. N Engl J Med 356: 2064-2072.
34. Moritz ML, Carlos Ayus J (2007) Hospital-acquired hyponatremia--why are hypotonic parenteral fluids still being used?. Nat Clin Pract Nephrol 3: 374-382.
35. Schrier RW, Gross P, Gheorghiade M, Berl T, Verbalis JG, et al. (2006) Tolvaptan, a Selective Oral Vasopressin V2-Receptor Antagonist, for Hyponatremia. 355: 2099-2112.
36. Rondon-Berrios H, Tandukar S, Mor MK, Ray EC, Benderet FH, et al. (2018) Urea for the Treatment of Hyponatremia. Clin J Am Soc Nephrol 13: 1627-1632.
37. Palmer BF (2000) Hyponatraemia in a neurosurgical patient: syndrome of inappropriate antidiuretic hormone secretion versus cerebral salt wasting. Nephrol Dial Transplant 15: 262-268.