Chapter 1

Fluids and Sodium Imbalance: Clinical Implications

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http://dx.doi.org/10.5772/intechopen.79121

Abstract

Fluids and electrolytes are basic components of the human body and essential for the survival of most species. Any imbalance can potentially lead to serious conditions and death. The replacement of fluids and electrolytes has been used since the ancient age. Modern medicine still requires certain degree of expertise in these areas, which ranges from simple replacement in patients with mild illness to a more complex management in critically ill or hospitalized patients. Training and education in the evaluation and management of patients with fluids and electrolyte abnormalities are fundamental for patient's outcomes. Severe sodium abnormalities are associated with increased morbidity and mortality, and they are markers of poor outcomes. This review presents a concise discussion of frequently asked questions in the evaluation and management of patients with fluids and sodium abnormalities.

Keywords: hypernatremia, hyponatremia, fluids, normal saline, ringer lactate, albumin

1. Introduction

The serum sodium (sNa) concentration and thus serum osmolality (sOsm) are closely controlled by water homeostasis, which is mediated by thirst, arginine vasopressin, and the kidneys. A disruption in this delicate balance is manifested as an abnormality in the sNa concentration—hyponatremia or hypernatremia and/or hemodynamic instability.

Fluid administration is an integral part of the clinician's armamentarium to manage a wide variety of clinical conditions, which range from mild dehydration to more life-threatening conditions like shock or trauma.

The goal of this review is to provide a concise discussion regarding fluids and sodium imbalance with an attempt to answer practical clinical questions on those areas. We focus in discussing basics physiological principles, and addressing the most common clinical challenges encountered by the practicing clinician.

1.1. Basic physiologic principle of fluids and sodium

The human body is composed of approximately 60% of water of which two-third are in the intracellular space and one-third in the extracellular space. The extracellular space is composed by the intravascular compartment (~8%), the interstitial compartment (~25%) and the transcellular compartment like cerebrospinal, pericardial fluid, which is very small [1, 2]. In the healthy individual, the extracellular fluid (ECF) and intracellular fluid (ICF) are in osmotic equilibrium, water moves from areas of greater solute concentration to establish equilibrium. Additionally, osmotically active substance shifts water from lower osmolarity to higher osmolarity areas. This is an important concept to understand when we administer intravenous fluids (IVF), as the distribution of fluids is based on the type of fluid administered.

There is a delicate and complicated transport system of water through cell membranes to maintain fluids and electrolyte balance. Sodium is the predominant cation in the extracellular compartment, which is electro-neutralized by chloride (Cl) and bicarbonate (HCO_3) as anions. In the intracellular space, potassium (K) is the major intracellular cation that is neutralized by many organic and nonorganic anions. The differential distribution of Na and K is tightly regulated by the sodium pump (Na-K ATPase) [1, 2]. Most osmotically active Na and K are dissolved and are sourced mostly from food intake. The body's ability to store sodium in tissues (bone, cartilage, connective tissue, etc.) prevents large fluctuations in the sNa levels despite erratic sodium intake [3, 4]. Most of the components in the intracellular compartment are too large to be able to cross membranes exerting little osmotic pressure.

Estimating the ECF volume based on sNa is highly prone to errors in clinical judgment. The volume in both, intracellular and extracellular fluids is primarily determined by the concentration of effective solutes that attract water by osmosis. Sodium and its attendant monovalent anions are the most prevalent effective solutes in ECF volume. The concentration of Na is determined by content of Na as well as volume of water. The primary tonicity receptor is located in the hypothalamic osmoreceptor, which is in charge to regulate the antidiuretic hormone (ADH) or vasopressin. The absence of ADH prevents aquaporin insertion on the luminal surfaces of collecting ducts in the nephrons forming hypotonic urine. The osmoreceptor is linked to both the thirst center and the vasopressin release center via nerve connections. There is a genetic susceptibility to hyponatremia linked to the gene coding for TRPV4 [2, 5–8]. Disease states releasing ectopic vasopressin or affecting vasopressin receptors will present with hyponatremia. Less prominent but important trigger for the regulation of vasopressin is large changes in effective arterial blood volume and blood pressure. Baroreceptors or stretch receptors in the carotid sinus and aortic arch are surrogates that detect changes in effective arterial blood volume. Nausea, pain, stress, and a number of other stimuli, including some drugs can also cause release of vasopressin [5].

2. Fluids

Intravenous fluids are one of the commonest used medications in hospitalized patients. They can be broadly categorized as crystalloids and colloids. Crystalloid solutions contain water, electrolytes with or without glucose. Colloids solutions contain albumin, starch, or other blood products. Fluids can be isotonic, hypotonic, or hypertonic.

Crystalloids: Common crystalloid solutions include 0.9%-normal saline (NS), 0.45%NS, lactated Ringers solutions (LR), Plasma-Lyte, and dextrose in water. Solutions with electrolyte compositions closer to that of plasma are called balanced fluids. Composition of commonly used crystalloids can be seen in **Table 1**.

Colloids: They can be divided into natural or synthetic. Natural colloidal solutions include red blood cells, fresh frozen plasma, and human albumin. Indications for the use of packed red cell and fresh frozen plasma are specific; they provide oxygen carrying capacity and clotting factors, respectively. Discussion regarding the use of red blood cells and plasma is beyond the scope of this review.

Synthetic colloidal solutions include hetastarch and dextran. They are used for volume expansion and include hetastarch and dextran.

Colloids can be categorized as hypo oncotic (e.g., gelatins, 4 or 5% albumin) and hyper oncotic (e.g., dextrans, hydroxyethyl starches (HES), and 20 or 25% albumin) solutions. **Table 2** describes the composition of commonly used colloids.

Indications for the use of either crystalloids or colloids depend of the clinical condition. Volume expansion by fluids is dependent on their osmolality and oncotic pressure. Isotonic fluids will distribute equally to all fluid compartments without a significant shift across

Solution	Na+ (mEq/L)	Cl− (mEq/L)	K+ (mEq/L)	Ca++ (mEq/L)	Lactate (mEq/L)	Glucose (g/l)	pH	Osmolarity (mOsm/L)
0.9%NS	154	154	0	0	0	0	pH 5.6 (4.5–7.0)	308
0.45 saline (1/2 saline)	77	77	0	0	0	0	5.0 (4.5–7)	154
3% saline	513	513	0	0	0	0	5.0 (4.5–7)	1026
Ringers lactate	130	109	4	3	28	0	6.5	272
Plasma-Lyte A*	140	98	5	0	8	0	7.4	294
5% dextrose	0	0	0	0	0	50	5.0	260

*Also contains magnesium 3 mEq/L, acetate 27 mEq/L, gluconate 23 mEq/L.

Table 1. Composition of crystalloids.

Fluid	Na+ (mEq/L)	Cl− (mEq/L)	Colloidal oncotic pressure (mm Hg)	Osmolarity (mOsm/L)
Albumin 5%	130–160	130–160	20	308
Albumin 25%	154	154	100	308
Hetastarch (6%)-NaCl	154	154	30	310
Gelatins (gelofusine 4%)	154	154	33	310
Dextran 70 + NaCl	154	154	60	310

Table 2. Composition of colloids.

cellular or vascular planes. However, hypertonic solutions will move fluids from intracellular and interstitial space into the intravascular compartment, while hypotonic fluids will result in shift of fluids from intravascular space to interstitial and intracellular compartments. Volume expansion of the intravascular compartment with colloids depends on the oncotic pressure.

The most common clinical indications for fluid administration are:

- Replacement of volume losses
- Maintenance of fluids and electrolyte balance
- Correction of electrolyte or acid-base disorders
- Persistent hypoglycemia or hyperglycemia
- Provision of a source of fuel (glucose)
- Intravenous administration of medication.

2.1. Question 1: which fluids are more effective—colloids or crystalloids?

Fluid resuscitation in critically ill patients in shock is the mainstay of therapy to maintain effective circulating blood volume. Timing of fluid resuscitation plays an important role in resuscitation and is based on the pathophysiology of shock [9, 10]. A long-standing controversy exists between proponents of colloids versus crystalloids for those patients. Supporters of crystalloids argue about risks of anaphylaxis, hemostasis impairment, and need for renal replacement therapy (RRT) with colloids as well as the potential to accumulate in tissues; whereas the colloid proponents argue with the risk of edema associated with crystalloids.

A recent Cochrane analysis concluded that there was no difference in mortality for hospitalized patients with trauma, burns, or following surgery when colloids were compared with crystalloids [11]. The use of HES may be associated with increased mortality; when they are compared to crystalloids, there was a higher incidence of adverse events and need for RRT [12, 13].

In the Crystalloid versus Hydroxyethyl Starch Trial (CHEST), involving 7000 adults in the ICU, the use of 6% HES (130/0.4), as compared with 0.9NS, was not associated with a significant difference in the rate of death at 90 days.

However, there was an increase in the rate of RRT and more adverse events in HES group [12]. The Colloids versus Crystalloids for the Resuscitation of the Critically Ill (CRISTAL) trial compared the effects of colloids versus crystalloids on mortality in patients presenting with hypovolemic shock [14]. There was no difference in mortality between the two groups at 28 days although 90-day mortality was lower in patients receiving colloids.

Low albumin levels are associated with all-cause mortality in both medical and surgical patients [15, 16]. Contrary to the belief that using albumin as a resuscitation fluid could improve mortality, a Cochrane review of 24 studies involving a total of 1419 patients, suggested that administration of albumin-containing fluids resulted in a 6% increase in the absolute risk of death when compared with use of crystalloid solutions [17]. This lead to the SAFE trial that showed similar outcomes between albumin and 0.9NS for resuscitation [18] No trial has consistently revealed superiority of albumin over crystalloids as resuscitative fluid.

In summary, there is no advantage of colloids versus crystalloids or vice versa. Considering the cost and adverse effect profile of colloids, crystalloids may be preferred over colloids. When colloids are used, care must be taken not to exceed recommended dose by regulatory agencies and avoid their use in patients with renal failure.

2.2. Question 2: are balanced fluids better than "0.9 normal saline?"

Normal saline is also referred as physiological or isotonic saline, neither of which is accurate. The sodium and chloride concentration of 154 mEq/L and the pH of 5.6 are certainly abnormal in "normal saline." The strong ion difference (SID) is the difference between the positively- and negatively-charged strong ions in plasma. Disturbances that increase the SID increase the blood pH while disorders that decrease the SID lower the plasma pH. This may also occur with volume resuscitation with 0.9NS (>30 cc/kg/h) due to excessive chloride administration impairing bicarbonate resorption in the kidneys resulting in hyperchloremic metabolic acidosis [19]. Other potential effects of 0.9NS include renal vasoconstriction with worsening renal function [20], increased postoperative complications, coagulation abnormalities [21], and an increased risk of death [22–24].

Lactated ringer, Plasma-Lyte, and Normosol are often called 'balanced fluids' as their electrolyte contents are closer to human plasma. These balanced crystalloids are also nearly isotonic but have a chloride concentration less than 110 mEq/L and a SID close to plasma.

Several trials comparing 0.9NS to balanced fluids have reported multiple outcomes. Outcomes have ranged from renal failure to mortality. Among critically ill adults with sepsis, resuscitation with balanced fluids was associated with a lower risk of in-hospital mortality [25]. In a meta-analysis of 11 RCTs (8 trials in operation room and 3 in ICU) involving 2703 patients, the in-hospital mortality, occurrence of acute kidney injury (AKI), and need for RRT was not different between balanced solutions and 0.9NS, irrespective of the location of the patients [26]. In a before and after trial comparing 0.9NS with LR solution, use of saline was a safe, viable alternative to LR in the trauma population [27]. In ICU patients requiring crystalloid fluid therapy, the use of a buffered crystalloid compared with saline did not reduce the risk of AKI or mortality [28]. Data regarding best fluid for the perioperative period is still inconclusive [29]. In patients undergoing renal transplants, balanced

electrolyte solutions were associated with less hyperchloremic metabolic acidosis compared to 0.9NS, but there were no difference in graft outcomes [30]. Among critically ill adults, the use of balanced crystalloids for IVF administration resulted in a lower rate of the composite outcome of death from any cause, new RRT or persistent renal dysfunction when compared to 0.9NS [31] Among noncritically ill adults treated with IVFs in the emergency department, there was no difference in hospital-free days between treatment with balanced crystalloids compared with saline [32].

Some myths about Ringers lactate:

1. *Ringers lactate in renal failure*: In a study comparing acid-base status in kidney transplant patients, LR compared with 0.9NS may lead to a lower serum potassium level and a lower risk of acidosis [33]. In a randomized, double-blind comparison of LR's solution and 0.9%NS during renal transplantation, LR was associated with less hyperkalemia and acidosis compared with 0.9NS [34].
2. *Ringers lactate in hepatic failure*: LR is avoided in patients with hepatic failure with the fear of inducing or worsening lactic acidosis. However, lactate is given as sodium lactate, which is a base rather than an acid. There are no data describing LR causing worse outcomes compared to saline in patients with hepatic dysfunction.

In summary, 0.9%NS is not superior to balanced fluids in volume resuscitation in both critically ill and noncritically ill patients, perioperative patients and posttrauma. Studies suggest that use of balanced crystalloids for IVF administration results in a lower rate of the composite outcome of death from any cause, new RRT, or persistent renal dysfunction than the use of 0.9%NS in critically ill patients. Balanced fluids are not harmful compared to 0.9%NS and seem to be the fluid of choice. However, caution is advised when balanced solutions are used in patients with renal failure and hyperkalemia. Normal saline is an ideal choice in patients with metabolic alkalosis and chloride deficits who are vomiting or have nasogastric tube to suction.

2.3. Question 3: what are the common indications for hypertonic saline?

The classical indication for 3% saline is symptomatic severe hyponatremia. This is discussed in detail later in this chapter. Other indication for hypertonic saline is resuscitation in patients with traumatic brain injury (TBI). In patients with TBI, osmotic agents to reduce cerebral edema are recommended [35]. Common osmotic agents are mannitol and hypertonic saline. Hypertonic saline decreases intracranial pressure (ICP), improves microcirculation, and acts as anti-inflammatory [36]. A retrospective study comparing effectiveness of mannitol versus hypertonic saline revealed that hypertonic saline given in boluses may be more effective than mannitol in lowering ICP but no difference was found in short-term mortality [37]. A comparison of effects in coagulation function or increase in the risk of intracranial rebleeding in patients with moderate TBI when using 3% hypertonic saline versus 20% mannitol for the control of ICP showed no differences [38]. A comparison of pharmacologic therapeutic agents used for the reduction of intracranial pressure after traumatic brain injury concluded that hypertonic saline exhibits beneficial advantages compared with the other medications as a first-line treatment of intracranial hypertension in patients with severe TBI [39]. Complications

of hypertonic saline use include hypernatremia, hyperchloremia, and renal failure. Mannitol and hypertonic saline in equiosmolar concentrations produced comparable effects on ICP reduction, brain relaxation, and systemic hemodynamic [40].

Hypertonic saline has been advocated in patients with volume loss after trauma, whereas TBI seems to be an indication to decrease cerebral edema, use of hypertonic saline in other situations is still unclear. In a meta-analysis, use of hypertonic saline showed no differences in clinical outcomes for hypotensive injured patients compared to isotonic fluid in the prehospital setting [41]. There is no evidence that hypertonic saline provides any additional benefit over isotonic crystalloid solutions for trauma resuscitation [42].

In summary, hypertonic saline can be used to decrease intra cranial pressure in patients with moderate to severe TBI. Care must be taken to avoid hypernatremia, hyperchloremia, and renal failure.

2.4. Question 4: how do we manage fluids in sepsis and septic shock?

In severe sepsis and septic shock, early volume resuscitation is indicated to save lives [43–45]; however, the best choice of fluids is unclear.

In a multicenter ICU trial of patients with severe sepsis randomly assigned to either 6% HES 130/0.42 or ringers acetate, patients receiving 6% HES 130/0.42 had a significant increase in the rate of death at 90 days and need for RRT. Several meta-analyses have shown that albumin does not provide a mortality benefit or decrease the need for RRT in critically ill patients, including those with hypoalbuminemia and sepsis [46–48]. A recent trial comparing albumin in addition to crystalloids versus crystalloids alone did not confer survival benefit in patients with severe sepsis or septic shock [49].

The early 2000s saw a resurgence in the use of hypertonic saline for sepsis resuscitation. Small volume resuscitation with hypertonic saline was postulated to achieve hemodynamic normalization by recruitment of fluid from the intracellular space, limiting interstitial edema [50]. Additional advantages included improved microcirculatory flow and favorable immunomodulatory effects. Two clinical trials have investigated the use of hypertonic saline in adult septic patients and there was no mortality difference [51, 52].

In the risk-adjusted inverse probability weighting analyses including 60,734 adults admitted to 360 ICUs across the United States between January 2006 and December 2010, the hospital mortality was 17.7% in the balanced fluid group, 19.2% in the 0.9%NS plus balanced fluids plus colloid group, 20.2% in the 0.9NS group ,and 24.2% in the saline plus colloid group. Balanced crystalloids were consistently associated with lower mortality. The authors concluded that when compared with exclusive use of 0.9%NS during resuscitation, coadministration of balanced crystalloids is associated with lower in-hospital mortality and no difference in LOS or costs per day. When colloids are coadministered, LOS and costs per day are increased without improved survival [53].

In summary, balanced fluids may be preferred over 0.9%NS in the resuscitation of patients with severe sepsis or septic shock without renal/liver or potassium issues. Hypertonic saline and other colloids including albumin are likely of no benefit over crystalloids. Use of starch is associated with adverse effects including increased need for RRT.

2.5. Question 5: fluid management in diabetic ketoacidosis

Patients with diabetic ketoacidosis (DKA) present with high anion gap metabolic acidosis, dehydration, and fluid deficits. Caution is advised in use of 0.9%NS due to two reasons. First, cerebral edema is a risk factor for death in patients with DKA. When a saline bolus is administered, it will distribute initially in the plasma that reaches the blood-brain barrier before equilibrating with the extracellular compartment. This has the potential to increase the interstitial volume of the brain ECF compartment and leads to cerebral edema. Second, chloride load in 0.9%NS can trigger nonanion gap metabolic acidosis.

A large bolus of 0.9%NS should be given only in emergent situations. It is advised to limit the amount of sodium ions infused in the first 120 min of therapy to about 3 mmol/kg body weight.

In a multicenter retrospective analysis of adults admitted for DKA to the ICU, which received almost exclusively Plasma-Lyte or 0.9%NS infusion up to 12 h, patients with PL had faster initial resolution of metabolic acidosis and less hyperchloremia, with a transiently improved blood pressure profile and urine output [54].

In summary: caution should be used using 0.9%NS in DKA and it is prudent to limit its use. If continued fluid resuscitation is needed, choice of fluids should be based on sNa levels. In patients with eunatremia or hypernatremia 0.45%NS is preferred and should be infused at 4–14 ml/kg/h, 0.9%NS is preferred in hyponatremia patients [55, 56].

2.6. Question 6: does my patient need maintenance fluids?

Maintenance fluid therapy is indicated in patients who are unable to eat for prolonged period of time in order to provide for fluids, electrolytes, and possibly some nutrition. The goal is to provide enough fluid and electrolytes to meet insensible losses and enable renal excretion of waste products. On an average, 2500 ml of water is ingested daily of which 60% is in form of fluids. Maintenance fluids should be a short-term measure since inappropriate therapy risks volume overload and electrolyte and acid-base disturbance. It is recommended to use 25–30 ml/kg/day water, 1 mmol/kg/day sodium, potassium, chloride, and 50–100 g/day glucose daily [57].

Higher insensible losses and hence higher maintenance of fluids needs to be considered in patients with ongoing losses, fever, burns, and third space losses especially in post-operative surgical patients. There is no evidence to use one kind of crystalloids over the other, hypotonic solutions should be avoided to avoid hyponatremia and avoidance of excessive sodium overload with 0.9%NS. Monitoring and avoidance of development of electrolyte imbalance is critical. Daily weights will prevent volume overload. Continuation of maintenance fluids should be critically reviewed in a daily bases.

2.7. Question 7: is there an ideal IV fluid?

An ideal resuscitative fluid should have an electrolyte composition close to plasma, should not accumulate in tissue, and must be completely metabolized. An ideal fluid does not exist and fluids should be treated as any other medication—indications, duration, effects, and adverse effects. Deciding which fluids are appropriate for each patient depends on the type

of fluid lost and the body compartment(s) that require additional volume. It is advisable to consider patients comorbid conditions, acid-base and electrolyte status, and the indication for fluids before making a final selection. Timing of therapy is based on clinical context, delayed resuscitation is not only resuscitation denied but could have a detrimental effect.

Education of use of fluids to the health care providers, especially those who usually initiate care on hospital admission is paramount to improve outcomes and decrease morbidity and mortality.

Pearls:

1. Treat IVF like medications and consider risks, benefits, alternatives, and risks of alternatives.
2. In most instances, balanced solutions may be adequate.
3. Normal saline is probably the fluid of choice in patients with metabolic alkalosis due to vomiting or gastrointestinal losses with volume and chloride deficits.
4. In critically ill adults, the use of 0.9%NS for IVF administration results in a higher rate of the composite outcome of death from any cause, new RRT, or persistent renal dysfunction.
5. In patients with DKA, use of 0.9%NS should be restricted to 1–1.5 L unless a compelling indication.
6. Hypertonic saline or colloids are fluids of choice in TBI with cerebral edema.
7. Role of hypertonic saline in trauma other than TBI, severe sepsis, septic shock, and hemorrhagic shock is uncertain.
8. HES is a risk factor for renal injury and need for RRT.
9. If a synthetic colloid is chosen, do not exceed the manufacturer recommended maximal dose.
10. Use maintenance fluids only when indicated and review need daily.

3. Disorders of sodium imbalance

3.1. Hyponatremia

3.1.1. Question 8: what is the importance of hyponatremia?

Hyponatremia is a common laboratory abnormality; it is usually defined as a sNa of less than 136 mmol/L. The sNa cut offs to define hyponatremia varies from 125 to 135 mmol/L depending on different studies [58, 59].

Hyponatremia have been reported in 8% of the general population and in up to 60% of hospitalized patients [60]. Patients in ambulatory setting have a lower rate compared with hospital or skill nursing facility setting. Miller et al. reported an 11% incidence of hyponatremia in the ambulatory setting among elderly population with a median age of 78 years [61, 62].

The importance of hyponatremia is related not only to the absolute sNa value, but to the underlying conditions leading to it; it can be the tip of a serious condition. Severity of

hyponatremia or its management can impact the patient's outcomes. Hyponatremia is not a disease, but a manifestation of an underlying disorder. The main focus of the management of hyponatremia is to elucidate the etiology and correction of laboratory abnormalities when levels are life threatening [59, 63].

Two major international guidelines attempted to address best practices in the management of this condition. The United States guidelines were published in 2013, however, they did not include grade of evidence due to scarce clinical evidence and resorted to expert panel recommendations [64]. In 2014, the European guidelines were published and included quality of evidence grades [65–67]. Rather than the absolute value of the sNa levels, the acuity of development of hyponatremia and its correction are of prime importance because the rate of change in sNa levels is associated with mortality, morbidity, and LOS [68, 69]. Mortality associated with hyponatremia has been reported as high as 30% [69].

A summary of relevant publications addressing prevalence of hyponatremia can be seen in **Table 3**. The serum cut off values for sodium in all those studies was between 130 and 138 and most of the studies were randomized control studies [58, 59].

3.2. Classification

Hyponatremia can be classified based in:

- Severity: this is based only in the absolute level of sNa. Mild 130–135 mmol/L, moderate 125–130 mmol/L, and severe when sNA is lower than 125 mmol/L.
- Time interval of development: acute-less than 48 h and chronic if more than 48 h. This information is occasionally difficult to obtain, but causes are usually different for acute and chronic hyponatremia.
- Measured osmolarity: it is fundamental to differentiate between the true hypotonic state from the isotonic and hypertonic state. Isotonic hyponatremia is usually due to pseudohyponatremia secondary to high plasma concentrations of triglycerides or proteins [70]. Expected changes in sNa in hypertriglyceridemia (TG) can be calculated as TG × 0.0002 = decrease in sNa in mEq/L; for plasma proteins (PP), PP in gm/dl – 8 × 0.25 = decrease in sNa in mEq/L.

  Commonest causes of hypertonic hyponatremia are hyperglycemia, administration of mannitol or other agents; the osmotic shift of water from ICF to ECF increases the total plasma volume diluting the sNa levels. Each increase in serum glucose levels by every 100 mg/dl after 150 mg/dl, decreases the sNa by approximately 1.6 mmol/L [71].
- Volume status: hypovolemia, euvolemia, and hypervolemia [72]. This is the most common classification used in the United States [64]. However, this classification is intrinsically flawed as there are no reliable, readily available and highly sensitive clinical tools to differentiate volume status, especially to differentiate hypovolemia from euvolemia [73–75]. Euvolemia itself is considered to be a misnomer as loss of sodium cannot happen without loss of water [2]. Clinical assessment is more reliable in cases of hypervolemia [2].

  Erroneous classification of patients into these categories can have detrimental outcomes [76].

Reference	Frequency (%)	Sample size	Outcome
Ambulatory setting			
Hawkins et al.	0.14	24,027	NA
Liamis et al.	7.7	5179	↑ Mortality
Gankam Kengne et al.	6	3551	↑ Mortality
Mohan et al.	2.5	14,697	NA
Hospital			
Hawkins et al.	42.6	43,249	NA
Hoorn et al.	30	5437	NA
Wald et al.	30	34,761	↑ Mortality
Wakar et al.	14.5	98,411	↑ Mortality
Congestive heart failure			
Gheorghiade	20	47,647	↑ Mortality
Liver cirrhosis			
Angeli et al.	49	997	↑ Mortality
Dawas	11	5152	↑ Mortality
HIV infection			
Tang	38	259	↑ Mortality
Cusano et al.	31	96	↑ Mortality
Non-dialysis kidney failure			
Covesdy et al.	13	655,493	↑ Mortality
Pneumonia			
Zilberberg et al.	8	7965	↑ Mortality

Modified from [58, 59].

Table 3. Prevalence and outcome of hyponatremia.

3.3. Clinical features

Symptoms of hyponatremia are initially subtle, nonspecifics, and difficult to recognize. They mostly manifest as neurological changes, which ranges from altered personality, lethargy and confusion to seizures, coma and death in severe cases [2, 77]. Symptomatic differences between acute severe and chronic hyponatremia have been reported. Symptoms of acute severe hyponatremia include nausea, vomiting, headache, seizure, coma, respiratory failure, and death, which are manifestations of brain edema. In chronic hyponatremia, main symptoms are fatigue, gait and attention deficit, osteoporosis, and fractures. Nausea and vomiting are seen in both, acute severe and chronic hyponatremia [78, 79]. Older patients with comorbid conditions tend to develop symptoms of hyponatremia at an earlier onset than young healthier patients. Premenopausal women are prone for cerebral edema from acute hyponatremia, it is hypothesized that this could be secondary to the action of estrogen and progesterone inhibiting Na+K+-ATPase and decreasing solute expel from brain cells; if not

recognized early, it will lead to neurological complications. The nonneurological manifestations are often due to the dysregulation in the volume status [5, 80].

3.3.1. Question 9: what are the causes of hyponatremia?

The best approach to evaluate causes of hyponatremia is to first decide if we are dealing with acute versus chronic hyponatremia.

Acute hyponatremia: the underlying etiological mechanism primarily causes large input of water. Normal individuals with intact thirst center and mental function develop aversion to large volume water intake. **Table 4** shows most common causes of acute hyponatremia.

Chronic hyponatremia: slow onset of hyponatremia, usually more than 48 h. The underlying etiology is lower rate of water excretion and involves release of vasopressin. In some case, decreased volume of filtered solute and residual water permeability play a role [5]. **Table 5** shows most common causes of chronic hyponatremia and **Table 6** shows the most common laboratory findings in the most common causes of hypotonic hyponatremia.

3.3.2. Question 10: how we evaluate a patient with hyponatremia?

Evaluation of hyponatremia still remains to some extent controversial and occasionally cumbersome.

In an attempt to avoid the pitfalls of volume evaluation recommended in the 2012 guidelines, the European guidelines were released in 2014. They prioritized the use of urine sodium (uNa) levels and urine osmolality (uOsm) over assessment of volume status [67]. Conditions leading to a false low or high uNa levels like low sodium diet or recent diuretic use and chronic kidney disease respectively were addressed [66, 81, 82].

Role of vasopressin and copeptin levels: measurement of vasopressin levels seems logical for the investigation of hyponatremia, but its unstable nature when not bound to plasma, low accuracy, and not readily available makes it use unsuitable. Moreover, uOsm is a readily available, accurate, and inexpensive surrogate [83]. Vasopressin is degraded into neurophysin and copeptin by enzymatic cleavage. Copeptin has been considered also a reasonable surrogate for

Ingestion of large volume of water	**Infusion of large volume of 5% dextrose**	**Infusion of large volume of hypotonic lavage fluid**	**Generation and retention of electrolyte-free water ("desalination")**
• Mood-altering drugs which blocks aversion to large water intake • Increased water intake to avoid dehydration • Beer potomania • Psychotic state	• Postoperative period (especially patients with a low muscle mass)	• Input of water and organic solutes, with little or no Na+ ions (e.g. post transurethral resection of prostate)	• Excretion of large volume of hypertonic urine caused by a large infusion of isotonic saline in a setting where vasopressin is present

Table 4. Causes of acute hyponatremia.

Lower rate of water excretion due to low volume of distal delivery of filtrate	Lower rate of water excretion due to vasopressin actions
• Very low glomerular filtration rate states • States with enhanced reabsorption of filtrate in the proximal collecting tubules caused by low effective arterial blood volume • Loss of Na+ and Cl− • Sweat: cystic fibrosis, marathon runner • Gastrointestinal tract: diarrhea • Renal: diuretics, aldosterone deficiency, renal or cerebral salt wasting • States with expanded extracellular fluid volume but low effective arterial blood volume (e.g., congestive heart failure, liver cirrhosis)	• Non-osmotic stimuli: pain, anxiety, nausea • Baroreceptor-mediated release of vasopressin due to very low EABV • Central stimulation of vasopressin: drugs like 3,4-methylenedioxymethamphetamine (MDMA), nicotine, morphine, carbamazepine, tricyclic antidepressants, serotonin reuptake inhibitors, antineoplastic agents • Pulmonary disorders: bacterial or viral pneumonia, tuberculosis • Central nervous system disorders: encephalitis, meningitis, brain tumors, subdural hematoma, subarachnoid hemorrhage, stroke • Release of vasopressin from malignant cells: small-cell carcinoma of the lung, oropharyngeal carcinomas, olfactory neuroblastomas • Administration of desmopressin • Glucocorticoid deficiency • Severe hypothyroidism • Activating mutation of the vasopressin 2 receptor: nephrogenic syndrome of inappropriate antidiuresis

Modified from [5].

Table 5. Causes of chronic hyponatremia.

Volume status	Clinical conditions	Urine Osm	Urine Na	Serum uric acid	FE_{NA}
Hypovolemic (appropriate ADH response)	Extrarenal losses	Elevated	<10–20	Elevated >4	<1
	Renal losses deficiency of mineralocorticoids	Elevated	>20	Elevated	>1
Hypervolemic (appropriate ADH response)	Heart failure, liver cirrhosis, nephrotic syndrome	Elevated	<20	Low/normal	<1
	Renal failure	Decreased	>20	Variable	>1
Euvolemia	Reset osmostat	Variable			
	SIADH	Elevated >100–300	>30–40	Decreased <4	>1
	Primary polydipsia	Decreased	Decreased	Low/normal	>1
	Hypothyroidism, deficiency of mineralocorticoids	Elevated	>20	Low/normal	>1

Table 6. Laboratory findings in most common causes of hypotonic hyponatremia.

vasopressin. Copeptin levels were reported to be increased in hypo and hypervolemic hyponatremia but not in syndrome of inappropriate secretion of antidiuretic hormone (SIADH). A ratio of serum copeptin to uNa with a cut off value of 30 pmol/mmol had an AUC of 0.88 in identifying hypovolemia from euvolemia [84].

Other biomarkers like apelin and midregional proatrial natriuretic peptide (MR-ProANP) have been evaluated in hyponatremia. Apelin counteract vasopressin in homeostasis. MR-ProANP increases to a larger extent in hypo or hypervolemic hyponatremia rather than in SIADH. The true diagnostic potential of these biomarkers are yet to be validated [85–88].

Based on existing guidelines and trying to overcome limitations of clinical evaluation of volume status, we suggest the following steps when evaluating a patient with hyponatremia:

1. Measurement of serum osmolarity to differentiate between hypotonic hyponatremia from iso- and hypertonic.
2. Hypotonic hyponatremia: clinical evaluation of volume status. In general, identification of hypervolemia is more accurate than differentiating between euvolemic and hypovolemic state.
3. Measurement of urine osmolarity (uOsm) and urinary sodium (uNa). This is conjunction with sOsm and examination should narrow down the diagnosis. For example, a threshold of uOsm of >100 mOsm/kg predicts the action of ADH on the collecting tubules, which in case of hyponatremia is not the appropriate response. This together with elevated uNa >20–30 mmol/L strongly suggests the presence of SIADH [2].
4. Needs to consider the presence of more than one disorder leading to hyponatremia [89].
5. Management should ideally address correction of sNa levels as well as the underlying condition leading to it.
6. Delayed or unavailability of sOsm is one of the major limiting factors during evaluation of hyponatremia as addressed by the United States guidelines, potentially leading to misclassification of patients based on clinical assessment of volume status.
7. Some experts suggest that a limited work up including sOsm, uNa, uOsm, and infusion of isotonic saline 1–2 l over 24 h may be sufficient for an accurate diagnosis in most cases of hypotonic hyponatremia [2]. Increase in sNa after trial of volume expansion suggests hypovolemic hyponatremia. However, this can be also seen in SIADH [75, 90–92].

Volume expansion should be cautiously done in certain conditions like immediate postoperative period, where isotonic saline can worsen the hyponatremia by a process called desalination, as presence of vasopressin makes the urine hypertonic by water resorption [93]. In addition, patients with hypervolemic states like heart failure or liver cirrhosis could deteriorate with the additional fluid administration.

Figure 1 shows a flow diagram for initial evaluation of hyponatremia.

3.3.3. Question 11: how do we manage hyponatremia?

Goal should ideally focus in the prevention of hyponatremia knowing its association with significant morbidity and mortality. There is no data available regarding the effects of treating asymptomatic mild to moderate hyponatremia [2, 94, 95].

http://dx.doi.org/10.5772/intechopen.79121

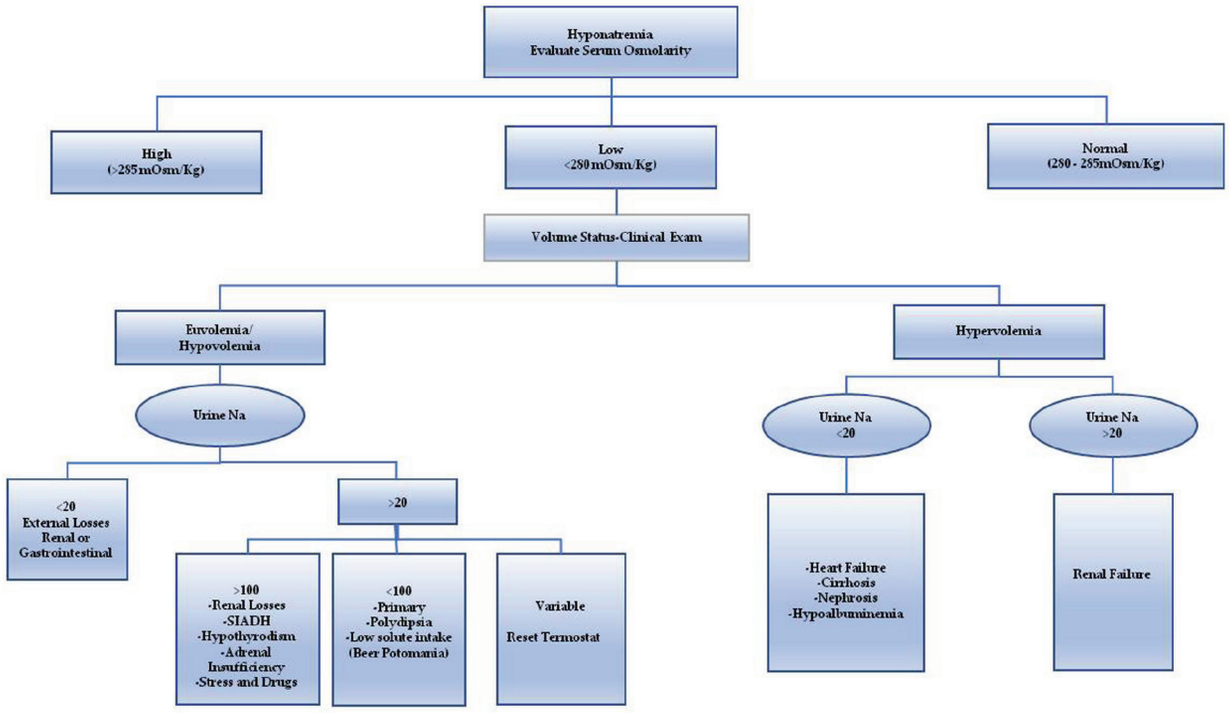

Figure 1. Algorithm for initial evaluation of hyponatremia. Based in the USA and European guidelines [64–67].

Patients presenting with severe, acute, or chronic hyponatremia should be treated in a monitor setting as those patients are at risk for adverse outcomes [2]. Acute respiratory failure from damage of the respiratory center or noncardiogenic pulmonary edema has been reported [96, 97]. Identification of patients at higher risk for osmotic demyelination remains a challenge during treatment; risks factors for development of osmotic demyelination include presence hypokalemia, alcoholism, malnutrition, and liver disease [64, 98]. **Table 7** shows basic management of patients presenting with hyponatremia and comparison of the two major existing guidelines.

Areas of concern with guidelines: caution must be excised when following guidelines. Areas of concern in the management of hyponatremia are:

- There is no clear evidence regarding the 48 h cut off to differentiate between acute and chronic hyponatremia, neither to clearly differentiate risk for osmotic demyelination in those patients.
- Clinically difficult to be certain regarding acuity of hyponatremia; in asymptomatic patients with hyponatremia, it could be assumed to be chronic.
- Limited evidence regarding the best and safer correction rate. A lower correction rate of 6 mEq/L/24 h could be safer.
- When to treat a patient with mild to moderate hyponatremia and none/minimal neurological symptoms remain a gray zone and depends on the clinical situation. Fluid restriction is the most common, cost effective, and safer modality of treatment [2, 72]. Fluid restriction of 500–1000 ml/day has been suggested and should be based in volume assessment. Urine Na to serum

electrolyte ratio (uNa + urine K/sNa) >1 indicates antidiuretic phase and a ratio <1 suggests aquaretic phase. Fluid restrictions to less than 500 ml/day in antidiuretic phase and 1000 ml/day in aquaretic phase have been recommended; however, adherence is a problem [72].

- Use of Vaptans. Vaptans are vasopressin type 2 receptor antagonist, present in the collecting duct and they induce excretion of hypotonic urine. Its use has been recommended in a subgroup of patients with hyponatremia secondary to excess vasopressin [99, 100]. There are many vaptans available including tolvaptan, satavaptan, lixivaptan, and conivaptan, which are been successful at increasing sNa and relieving symptoms in conditions like SIADH, congestive heart failure, and liver cirrhosis [101–103]. Sodium overcorrection is a concern and it was reported in 25% of 61 patients included in a study [103]. Side effects including liver injury, risk of overcorrection, and lack of long-term sodium improvement are some of limitations [101, 102, 104].
- Demeclocycline and lithium have low quality evidence to support front line management of hyponatremia. Demeclocycline is thought to inhibit adenylate cyclase activity upon binding of vasopressin to its receptor in the collecting tubule. The adverse effects associated with the drugs make them less desirable for treatment [2, 105].

3.3.4. Question 12: what are the complications and outcomes of hyponatremia?

Complications of hyponatremia can be divided in those caused by hyponatremia per se and those caused by the treatment of hyponatremia. In general, worse outcomes are associated with sNa levels of less than 115 mEq/L and with faster rate of fall in sNa [2].

3.4. Complications and outcomes of untreated hyponatremia

Complications of hyponatremia range from chronic debilitating symptoms like gait deficit and neuromuscular symptoms to a more severe and life-threatening presentation of brain edema. Chronic and mild-moderate hyponatremia have been associated with attention or gait deficits, increased risk of falls, and bone fractures. Bone is a reservoir for Na. Observational retrospective cross sectional and epidemiological surveys have established an association between chronic hyponatremia and osteoporosis and major osteoporotic fracture [106–111].

Unfortunately, there is a lack of evidence to suggest that osteoporosis is reversed with correction of hyponatremia [2].

The brain which is contained in the hard skull is not able to accommodate any swelling or increase in brain volume. This is evident especially in patients who develop acute hyponatremia. Cerebral edema occurs when cells within the brain swell, when there is an increase in extracellular fluid volume in the brain or both. Brain cells swell when there is a large osmotic force favoring an intracellular shift of water, owing to a higher effective osmolality in brain cells than the effective osmolality in plasma in capillaries near the blood–brain barrier [112–115]. The elevated intracranial pressure with the resultant acute cerebral edema can potentially lead to serious symptoms that ranges from seizures, coma to brain herniation causing irreversible midbrain damage and death [116, 117]. Incidence of fatal brain damage secondary to severe hyponatremia is unknown, majority of the cases have been reported during the perioperative period secondary to infusion of hypotonic fluids or self-water intoxication like marathon runners and psychiatric patients [118].

Conditions	General agreement in guidelines	Disagreement between guidelines
Acute or symptomatic hyponatremia—less 48 h	*Severe symptoms:* bolus 3% NaCl: 100–150 ml over 10–20 min × 2–3 as needed	Minimal—just in amount of fluids 50 ml difference
	Moderate symptoms: continuous infusion 3% NaCl 0.5–2 ml/kg/h or bolus 3% NaCl: 100–150 ml over 20 min × 1	
Chronic hyponatremia—more 48 h		
SIADH	First line: fluid restriction	None
	Second line: demeclocycline, urea, or vaptan	European guidelines do not recommend vaptans when sNa > 130 and recommend against when sNa > 125. Recommends against demeclocycline Suggest oral NaCl or loop diuretics
Hypovolemic hyponatremia	Isotonic saline or balanced crystalloid solution	Minimal/none
Hypervolemic hyponatremia	Fluid restriction—500—1 L/day Vaptans	European guidelines recommend against vaptan
Correction rates	Minimum-only USA guidelines: 4–8 mmol/L/day, 4–6 mmol/L/day in high risk of neurological complications	European guidelines have no minimum
	Limits: 10–12 mmol/L/day, 8 mmol/L/day in high risk patients	None
Management of overcorrection	Baseline sNa ≥ 120 mmol/L: probably unnecessary	European guidelines suggest to start once limit is exceeded
	Baseline sNa < 120 mmol/L: relower with electrolyte-free water or desmopressin after correction exceeds 6–8 mmol/L/day	Expert consultations recommended by European guidelines

Modified from [72].

Table 7. Management of hypotonic hyponatremia and comparison between existing guidelines.

Most cases of hyponatremia in the ambulatory setting are mild. An sNa of less than 125 mmol/L was seen in 0.14% in Hawkin et al. study [60]. The Dallas heart study, a large prospective multiethnic cohort study of 3551 ambulatory individuals with median age of 43 year/age and from diverse ethnicity, found that mild hyponatremia (median 133 mmol/L) was significantly associated with increased risk of death [119]. A large cross sectional observational study by the National Health and Nutrition Examination Survey in the United States with 15,000 individuals demonstrated that hyponatremia was an independent risk for increased mortality across age, gender, and comorbid conditions. Overall prevalence was around 2%. They also showed that prevalence of hyponatremia increased with age and was more frequent among women than men [120].

Others studies looking at the association of hyponatremia with specific comorbid conditions like heart failure, HIV, pneumonia, renal failure among others, concluded that hyponatremia is an independent risk factor for mortality regardless the levels of sNa [58, 121–129]. Among

patients presenting with acute pulmonary emboli, hyponatremia is common and several studies has shown to be an independent risk factor for increased short-term mortality. This result could be encountered as a variable in determining of pulmonary emboli severity and mortality [130, 131].

Among the hospitalized population, many studies have estimated the prevalence of hyponatremia from 8 to 40% [60, 69, 89, 132]. In Wald et al. study evaluating more than 50,000 patients, he established that irrespective of onset of hyponatremia-community, hospital aggravated or hospital acquired, all were associated with increased mortality, length of stay, and discharge to a facility; and this was independent of the underlying comorbid conditions. Mortality was increased among older patients. The operational definition for normal sNa in this study was 138–142 mEq/L. In patients with hospital acquired hyponatremia, the risk of mortality was 15 times higher among patients with first serum sodium level of 127 mEq/L or less [69]. A larger prospective study by Waiker and colleagues with approximately 100,000 individuals followed up to 5 years showed that irrespective of the severity of hyponatremia, presence of hyponatremia independently increased risk of dead with an odd ratio of 1.47, 1.32, and 1.33 at the time of admission, 1 and 5 year follow-up, respectively. It was more pronounced among patients admitted with cardiovascular disease, metastatic cancer, and those admitted for procedures related to the musculoskeletal system. They also showed that resolution of hyponatremia attenuated the increased risk of mortality [132].

3.5. Complications and outcomes of treatment of hyponatremia

There are no many studies evaluating outcomes of treatment of hyponatremia. Two studies evaluated the impact of treatment on mortality among patients with congestive heart failure and concluded that treatment confers no mortality benefit, however, there was symptomatic improvement and decreased length of stay [94, 95]. Other studies suggested that correction of mild hyponatremia could reverse attention and gait deficits [133, 134].

When hyponatremia develops over a slower rate, 24–48 h, the brain cells are able to adapt to expel enough of anions and organic solutes along with water to maintain its size. Rapid correction of hyponatremia can lead to inability to regain the organic solutes causing osmotic demyelination, a process still poorly understood [5].

Osmotic demyelination syndrome (ODS) and central pontine myelinolysis (CPM) are terms usually used interchangeably, but they represent separate, not well understood and highly feared complications of the treatment of hyponatremia. The effect of rapid correction of hyponatremia is termed as ODS and it is specific to the central nervous system and not always localized to the pontine region. Extrapontine myelinolysis is as frequent as CPM [135, 136]. Risk factors making patients more susceptible to the development of ODS include severity and chronicity of hyponatremia, the increment of sNa, the treatment used for sodium correction, concomitant hypokalemia, presence of liver disease and the nutritional status [98]. A small study of 33 patients showed that an increase in sNa to normal or hypernatremic levels in the first 48 h, a change in the sNa concentration of >25 mmol/L in the first 48 h, a hypoxic-anoxic episode, and an elevation of sNa to hypernatremic levels in patients with hepatic encephalopathy were associated with CMP. However, rate of correction was not associated with demyelination [118].

The clinical manifestations of ODS are variable depending on the location of demyelination. They range from pontine and bulbar symptoms such as dysarthria, dysphagia, and dystonia to more severe forms like locked-in state and coma [137]. In the past, prognosis of ODS and CMP was considered to be very poor; however, several studies have reported near complete neurological recovery. In addition, ODS/CMP are associated with other complications like aspiration pneumonia, urinary tract infection, deep venous thrombosis, and pulmonary embolism [137–139].

3.6. How can ODS be avoided?

In the absence of an absolute threshold for the rate of correction, it is well accepted that the safest rate of correction of hyponatremia is 6–8 mEq/L/day. Brain demyelination has been reported over a range of rate of sNa correction of 8–12–18 mEq/L/day [2, 72]. Some investigators in small, nonrandomized studies suggest concomitant use of desmopressin and hypertonic saline for better control of the rate of sNa correction in hyponatremia [140, 141]. Experiments on rats have shown little success with the combination regimen of D5W and desmopressin for the treatment of overcorrection of hyponatremia [142, 143]. The role of urea for ODS have not been well studied.

3.7. Hypernatremia

A difference of the complexity of hyponatremia, the finding of hypernatremia invariably denotes hypertonic hyperosmolality and always causes cellular dehydration. It is usually defined as a sNa of more than 145 mmol/L. It can be a frequent finding in hospitalized patients or high risk patients with poor access to water like the elderly, infants, patients on mechanical ventilation, and patients with altered mental status. In the elderly, a physiologic decrease in the thirst mechanism have been reported; however, there can be a pathological decrease in free water intake as well [60].

In general, clinical manifestations of hypernatremia correlate with the severity of sodium abnormalities and are related to central nervous system dysfunction and ranges from weakness, confusion to seizure and coma. In addition, sign of hypovolemia and hemodynamic abnormalities can be found on examination.

The complications of hypernatremia vary from mild to life threatening [144]. Brain shrinkage induced by hypernatremia can cause vascular rupture, with cerebral bleeding, subarachnoid hemorrhage, and permanent neurologic damage or death.

Causes of hypernatremia can be loose classified in two: either net water losses due to gastrointestinal or renal etiologies or hypertonic solution administration [144, 145].

3.7.1. Management of hypernatremia

The focus of management is addressing the underlying cause leading to hypernatremia and the correction of serum sodium. Initial evaluation includes evaluation of vital signs. In hemodynamically unstable patients, administration of isotonic 0.9% normal saline or balance fluids is advised, irrespective of sNa. Goal in those patients is fluid resuscitation hemodynamic

stabilization. Patient who are hemodynamically stable can be managed with oral or IVF replacement. The preferred route for fluid administration is the oral route or a feeding tube; otherwise IVF are required. Only hypotonic fluids are recommended, including pure water, 5% dextrose, and 0.2 or 0.45% sodium chloride. The more hypotonic the infusate, the lower the infusion rate required. An easy and efficient way to calculate this is by using Adrogue-Madias formula, which allows to calculate rate of infusate [144].

Correction rates: similar to management of hyponatremia, and to avoid sudden changes in tonicity, the target recommended fall in the sNa concentration is 8–10 mmol/L/day for patients with hypernatremia with a goal to reduce the sNa to 145 mmol/L [145, 146].

Pearls:

1. Serum sodium abnormalities are common and carry significant morbidity and mortality.
2. Evaluation of sodium abnormalities should focus in the underlying condition as well as management.
3. Following recommended algorithms for evaluation of hyponatremia is advised.
4. Evaluation of volume status in patients with sodium disorders can be a challenge.
5. Needs to keep in consideration the presence of more than one disorder.
6. Resuscitation of an unstable patient takes precedence over correction of sodium levels.
7. There is no rush to correct sNa levels, risk of overcorrection, or rapid increase in sNa can lead to serious complications.

4. Conclusion

We reviewed issues related to fluids and sodium disturbance and the clinical implications of these issues. The dysregulation of fluid and sodium homeostasis leads to many direct and indirect effects and carries significant morbidity and mortality in a wide variety of patients and clinical settings. Those range from mild cases of dehydration to more severe cases of patients in shock or with severe hypo- or hypernatremia.

Since the high prevalence of these disorders, clinicians in virtually every medical specialty will interact with patients requiring fluid administration and need for electrolyte evaluation and correction. Appropriate and timely administration of fluids and electrolyte correction with focus in avoidance of complications and improvement of outcomes is fundamental.

Conflict of interest

The authors have no conflict of interest.

Abbreviations

ECF	extracellular fluid
ICF	intracellular fluid
IVF	intravenous fluids
RRT	renal replacement therapy
HES	hydroxyethyl starches
SID	strong ion difference
TBI	traumatic brain injury

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