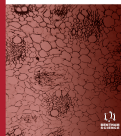**REVIEW ARTICLE**

Hyperglycemic Hyperosmolar State: A Pragmatic Approach to Properly Manage Sodium Derangements

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Abstract: ***Introduction***: Although hypovolemia remains the most relevant problem during acute decompensated diabetes in its clinical manifestations (diabetic ketoacidosis, DKA, and hyperglycemic hyperosmolar state, HHS), the electrolyte derangements caused by the global hydroelectrolytic imbalance usually complicate the clinical picture at presentation and may be worsened by the treatment itself.

Aim: This review article is focused on the management of dysnatremias during hyperglycemic hyperosmolar state with the aim of providing clinicians a useful tool to early identify the sodium derangement in order to address properly its treatment.

Discussion: The plasma sodium concentration is modified by most of the therapeutic measures commonly required in such patients and the physician needs to consider these interactions when treating HHS. Moreover, an improper management of plasma sodium concentration ($_pNa^+$) and plasma osmolality during treatment has been associated with two rare potentially life-threatening complications (cerebral edema and osmotic demyelination syndrome). Identifying the correct composition of the fluids that need to be infused to restore volume losses is crucial to prevent complications.

Conclusion: A quantitative approach based on the comparison between the measured $_pNa^+$ ($_pNa^+_M$) and the $_pNa^+$ expected in the presence of an exclusive water shift ($_pNa^+_G$) may provide more thorough information about the true hydroelectrolytic status of the patient and may therefore, guide the physician in the initial management of HHS. On the basis of data derived from our previous studies, we propose a 7-step algorithm to compute an accurate estimate of $_pNa^+_G$.

1. INTRODUCTION

Hypovolemia is one of the most relevant clinical problems during acutely decompensated diabetes mellitus, irrespective of whether it is Diabetic Ketoacidosis (DKA) or Hyperglycemic Hyperosmolar State (HHS). Moreover, different electrolyte derangements may coexist with hypovolemia at the onset or may be caused by fluid replacement itself, if the composition of the infused saline solution is not appropriate.

Therefore, a careful evaluation of plasma osmolality ($_pOsm$), sodium ($_pNa^+$) and potassium concentrations ($_pK^+$) and of acid-base status is crucial to determine the correct composition of fluids to be administered.

This review is focused on the management of $_pNa^+$ during HHS. Particularly, we will discuss the potential role of a quantitative approach to dysnatremias in identifying the proper amount of Na^+ and K^+ that need to be infused in order to prevent harmful derangements in $_pOsm$ as well as two associated life-threatening complications: cerebral edema and Osmotic Demyelination Syndrome (ODS).

2. PATHOPHYSIOLOGY

In HHS the Extracellular Volume (ECV) effective osmolality (tonicity) is increased due to the elevation in the plasma glucose concentration ($_pG$) according to the following formula:

Effective osmolality (mOsm/kgH$_2$O) = 2 × $_pNa^+$ (mmol/L) + 2 × $_pK^+$ (mmol/L) + $_pG$ (mg/dL) / 18

Blood urea nitrogen is not included in this particular formula since it does not affect the osmotic gradient across cell membranes, being permeable through them [1, 2].

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The restriction of glucose to the ECV generates an osmotic gradient which shifts water from the Intracellular Volume (ICV) to the ECV, leading to a dilutional fall in $_pNa^+$ [3]. In the absence of preexisting or associated electrolyte derangements, this process causes hypertonic hyponatremia since, despite a low $_pNa^+$, $_pOsm$ rises, usually above 320 mOsm/kg due to the high $_pG$.

Obviously, this is not a static condition and other variables affect the process.

First of all, hyperglycemia causes an osmotic diuresis which increases renal excretion of water in excess of that of Na^+ and other ions. This large electrolyte-free water output tends to raise both $_pNa^+$ and $_pOsm$ [4-6]. Water intake is consequently one of the main determinants of the clinical presentation and the laboratory findings of hyperglycemic crisis: in fact, in those patients who are able to compensate the volume lost through osmotic diuresis with oral water intake, the rise in $_pOsm$ can be dampened, while $_pNa^+$ tends to be even lower. On the contrary, as HHS usually develops in elderly patients with an impaired thirst mechanism and/or a reduced access to water [7], volume depletion is often prevailing, such that the measured $_pNa^+$ can be normal or even increased (averaging 149 mEq/L in some studies [2, 8]).

A further crucial issue is K^+ replacement. In the first phases of treatment, a high infusion rate of K^+ salts may be required to prevent insulin-induced hypokalemia (even up to 10-20 mmol/h [9]). However, K^+ administration leads to a rise in $_pNa^+$, since all millimoles of K^+ infused should be considered as molar Na^+ equivalents; this means that K^+ administration induces an increase in $_pNa^+$ comparable to that observed when the same amount of Na^+ is infused [10, 11]. Therefore, the amount of K^+ administered has to be carefully considered during fluid infusion in order to avoid an overly rapid correction of hyponatremia or even the onset of hypernatremia [12].

The process is further enhanced by the simultaneous administration of insulin that promotes K^+ entry into cells in several tissues (mainly liver, skeletal muscle, cardiac muscle and adipose tissue) [13, 14]. This effect is mediated by many transport pathways, particularly by the Na^+/K^+ ATPase [15], which pumps Na^+ out of the ICV in exchange for K^+, thus contributing to the increase in $_pNa^+$.

Other important elements that should be taken into account during fluid replacement are vomiting and nasogastric suction, which can increase water, solute and hydrogen ion losses.

3. QUANTITATIVE APPROACH

Over the years many correction factors have been proposed in order to help the physician to calculate $_pNa^+$ expected in the presence of hyperglycemia.

Until 1973, clinicians estimated a fall in $_pNa^+$ of 2.8 mmol/L for every 100 mg/dL increase in $_pG$ that occurred above a concentration of 100 mg/dL [16]. In 1973 Katz suggested that the water shift should stop before the normal ECV osmolality is restored, thus producing hyperosmolality in both compartments; on this basis, he mathematically cal-

culated a correction factor of 1.6 mmol/L [17]. Later, in 1999, Hillier *et al.* demonstrated that the higher is $_pG$, the more inaccurate is the correction factor proposed by Katz; a correction factor of 2.4 mmol/L was then introduced in clinical practice, although the Authors themselves admitted that it still underestimates the reduction in $_pNa^+$ for $_pG > 400$ mg/dL and that, above this cut-off, a correction factor of 4 mmol/L is more reliable [18].

Although in the following years, a large number of studies have analyzed and reviewed the proposed correction factors [19], even now there is no consensus on which one should be considered the most accurate: for example, the American Diabetes Association (ADA) guidelines for the treatment of DKA and HHS [9] report the one proposed by Katz and then re-evaluated by Nguyen *et al.* (1.6 mmol/L) [20], while Spasovski *et al.* report in their clinical guidelines for the treatment of hyponatremia the value suggested by Hillier *et al.* (2.4 mmol/L) [21].

However, although the Literature seems deeply focused on this essentially mathematical aspect, it is important to highlight that the Δ_pNa^+/Δ_pG ratio is affected by many variables that cannot be included in the simplified equations proposed, such that this ratio can widely vary depending on the magnitude of the concomitant solute and/or water depletion. We already demonstrated this effects in previous works using a computer simulation model [22-24].

Another challenging issue is the estimate of volume status; although these patients are almost always dehydrated, an accurate estimate of volume status is very important in order to avoid adverse events related to an incorrect treatment. Excluding invasive techniques (such as transpulmonary thermodilution [25]), that are not applicable to this kind of patients, non-invasive methods (based on echocardiography [26], changes in the pulse oximeter waveform [27] or biomarkers as copeptin [28]), although effective in identifying fluid overload, are not widely available and, at the moment, give unreliable results from the quantitative point of view. For these reasons we based our model on anthropometric measurements; we previously set up a mathematical model that allowed us to estimate both the ECV and the glucose excess [29]. We then computed the $_pNa^+$ expected on the basis of the water shift caused by hyperosmolality ($_pNa^+_G$). The difference between the $_pNa^+_G$ and the measured $_pNa^+$ ($_pNa^+_M$) stratified patients into 3 groups:

- $_pNa^+_M \approx _pNa^+_G$: in this situation, the measured $_pNa^+$ is comparable to that predicted by the water shift; this means that no changes in either water or Na^+ content occurred, and that hyponatremia is completely explained by the dilution of Na^+ content caused by water flows across cell membranes;

- $_pNa^+_M < _pNa^+_G$: in this situation the measured $_pNa^+$ is lower than the expected one; it means that Na^+ deficit is greater than water losses;

- $_pNa^+_M > _pNa^+_G$: in this situation the measured $_pNa^+$ is higher than the expected one; it means that either an absolute water deficit is present or that it prevails over the associated Na^+ loss.

This classification is useful in clinical practice and helps the physician to choose the correct initial fluid treatment.

4. TREATMENT

The first goal in treating HHS is to restore the water deficit, which averages 100-200 mL/kg (about 10.5 L in a typical 70-kg man) because of the massive losses due to the osmotic diuresis [30]. Water deficit is usually larger in HHS compared to DKA. In fact, while the relative lack of insulin allows the development of higher $_pG$ during the longer time course, the total lack of insulin in type 1 diabetes mellitus leads to earlier ion and acid-base derangements (euglycemic DKA also exists [31]) that call for earlier attention, as they are invariably fatal if left untreated. Fluid treatment is meant to expand the circulating volume, thus improving renal perfusion and function. It has been also demonstrated that this reduces the counter-regulatory hormone release and insulin resistance [32]. As already stated, selecting the proper fluid to be infused is important to avoid treatment complications. Isotonic saline (0.9% NaCl) is usually suggested as the first choice in emergency conditions: it is recommended to administer 1000-1500 mL in the first hour and then to reduce the infusion rate according to the hemodynamic and clinical response [9, 33]. Infusion rates should always be made compatible with the patients' cardiac function, although the overall water deficit should be corrected within the first 24 hours of treatment [9]. However, as soon as hemodynamic stability has been achieved, it is important to switch to other solutions according to the corrected $_pNa^+$ ($_pNa^+_G$) with the aim to avoid treatment-related dysnatremias. The classification we previously presented [22] can reasonably guide this choice:

- If $_pNa^+_M < _pNa^+_G$, isotonic saline is the appropriate choice in order to compensate the Na^+ deficit due to osmotic diuresis;

- If $_pNa^+_M > _pNa^+_G$, a hypotonic fluid should be given in order to simultaneously administer a larger amount of water coupled to a lower amount of Na^+, avoiding to worsen or to generate hypernatremia;

- If $_pNa^+_M \approx _pNa^+_G$, both 0.9% and 0.45% NaCl solutions can be appropriated, and their relative amounts are usually determined by the consideration that $_pNa^+$ will gradually rise along with insulin treatment (since the glucose shift from the ECV to the ICV reverses the osmotic gradient and drags water to the ICV, thus concentrating the ECV Na^+ content).

As already stated, the molar equivalence existing between Na^+ and K^+ implies that 1 millimole of KCl will raise the $_pNa^+$ exactly as 1 mmol of NaCl will. Therefore, the need to give supplemental K^+ together with fluid replacement must be considered in choosing the adequate solution. For example, in the last case presented above ($_pNa^+_M \approx _pNa^+_G$), if K^+ supplementation is required, hypotonic fluids should be preferred in order to avoid an overly rapid or even excessive increase in $_pNa^+$ and its associated risks. Particularly, ADA recommends to administer supplemental K^+ when:

- $_pK^+ < 3.3$ mmol/L before insulin infusion is started;

- $3.3 \leq _pK^+ \leq 5.2$ mmol/L during insulin infusion.

K^+ supplementation is not safe, and often unnecessary, when $_pK^+ > 5.2$ mmol/L, but $_pK^+$ has to be closely monitored (usually every 2 hours) during continuous insulin infusion [9]. As already described, this latter recommendation is explained by the K^+ transport into cells promoted by the hormone, mainly through the activation of Na^+/K^+ ATPase [15]. Because of the constriction imposed by electrical neutrality, this molecular mechanism requires that Na^+ shifts from cells to interstitium, such that a further rise in $_pNa^+$ must be expected.

On the other hand, it is important to be aware that the infusion of hypotonic solutions becomes necessary when $_pG$ falls below 300 mg/dL: in fact, glucose supplementation is required in order to keep $_pG$ within the 200-300 mg/dL range, so that glycogen stores can be gradually rebuilt [9]. The administration of such a large amount of electrolyte-free water has the obvious consequence to dampen the rise in $_pNa^+$ related to previous and simultaneous treatments (saline, insulin infusions, K^+ supplementation).

Because of a large number of variables that affect the $_pNa^+$ variation in time (related both to the above mentioned treatments and to free water renal excretion), it is recommended to check electrolytes (together with venous pH, glucose and creatinine) at least every 2-4 hours in order to guide therapy [9].

To guide treatment, Table **1** reports the composition of the most common solutions available in clinical practice, including Ringer's and glucose solutions.

4.1. Treatment Complications

It has been demonstrated that brain cells are partially permeable to glucose regardless of insulin action because of a selective expression of transport proteins [34]. Therefore, hypertonicity exclusively due to hyperglycemia is physiologically dampened in the Central Nervous System (CNS). On the other hand, hypertonicity due to hypernatremia has a greater impact on the CNS and it has been suggested that the $_pNa^+$ is a better predictor of neurological impairment than the $_pG$ itself, since severely hyperglycemic patients can be fully asymptomatic in the absence of hypernatremia [35].

However, when the development of hypernatremia-related hypertonicity is gradual, brain cells can activate an adaptation mechanism based on the accumulation of both inorganic osmolytes (basically electrolytes) and organic osmolytes (the so-called *idiogenic* osmoles) in order to reduce the osmotic transmembrane gradient, preventing an excessive water shift from cells and the related brain shrinking [36].

Treatment-related complications occur when these pathophysiological processes are ignored.

Clinically apparent cerebral edema causes a symptomatology characterized by headache, insisted vomiting, seizures, papilledema, abnormal pupillary response, cranial nerves palsies, altered mental status and impaired consciousness, sphincter incontinence, rising blood pressure with inappropriate bradycardia up to respiratory arrest [37-39]. Overt cerebral edema is uncommon in HHS and in adults [40], predominantly occurring in children with DKA (0.3-

Table 1.   Composition of the most common solutions available in clinical practice.

Solution	Na$^+$ (mEq/L)	K$^+$ (mEq/L)	Cl$^-$ (mEq/L)	Glucose (g/L / mM)	Osmolarity (mOsm/L)	pH
0.9% NaCl (Normal saline)	154	0	154	0	308	5
0.45% NaCl (½ Normal saline)	77	0	77	0	154	5
0.22% NaCl (¼ Normal saline)	39	0	39	0	78	5
Ringer's solutions *	130	4	109	0	273	6.5
5% Glucose in water †	0	0	0	50 / 278	278 †	5
10% Glucose in water †	0	0	0	100 / 556	556 †	5
5% Glucose in 0.45% NaCl †	77	0	77	50 / 278	406 †	5

*The table reports the typical composition of Ringer's solutions, but the content of each component may slightly vary among different producers.
†Since glucose is rapidly absorbed into the cells as a result of insulin action, the solutions of glucose in water can be considered hypotonic (although 5% is actually isotonic and 10% hypertonic); similarly, the final tonicity of the solutions of glucose in saline depends on the sodium chloride concentration (usually 0.45%).

1.0% of DKA episodes in children [41], with a 21-24% mortality rate [42]). However, studies involving computerized tomography, electroencephalography and magnetic resonance diffusion-weighted imaging have demonstrated that the development of subclinical cerebral edema is frequent during the first 24 hours of treatment of hyperglycemic emergencies [4, 43-45]. The most accredited theory claims that cerebral edema is caused by an overly rapid reduction in $_P$Osm [46]: brain cells, which previously adapted to hypertonicity by accumulating idiogenic osmoles, become hypertonic when the $_P$Osm falls, because the elimination of organic osmolytes is a slow process compared to the quick changes in $_P$G during treatment [4]: thus, the reverse osmotic gradient generates a water shift into brain cells. However, new evidences from recent clinical studies question the pivotal importance of this mechanism, as the pathogenesis of cerebral edema during hyperglycemic emergencies seems to be vasogenic rather than cytotoxic [47]: in fact, different rehydration protocols were not related to different rates of subclinical cerebral edema in a randomized clinical trial [48]. These findings may prove the role of other less reputed mechanisms, such as hypoxia, ischemia/reperfusion-like injury, inflammation and impaired ion transport [9]. Anyway, the only measure suggested to prevent cerebral edema in such patients is still a gradual reduction of $_P$Osm, that should be obtained by avoiding an excessive rehydration, by gradually decreasing the $_P$G (the recommended rate is 50-75 mg/dL/h) and then by using glucose infusions to keep the $_P$G within a 200-300 mg/dL range as long as the $_P$Osm is being normalized and the patient remains mentally alert [9].

ODS is a life-threatening complication typically associated with the overly rapid correction of a hypotonic state (typically, chronic hyponatremia) [49]. The clinical syndrome, characterized by the development of neurological impairment (confusion, drowsiness, altered mental status up to respiratory arrest or a so-called *locked-in syndrome*) even a few days after the correction of the hypotonic condition, is produced by an acute shrinking in brain cells with a secondary blood-brain barrier damage which triggers an inflammatory response, mainly complement-mediated [50]. This phenomenon, which is pathophysiologically related to adapta-

tion mechanisms to hypotonicity, is more likely to occur in encephalic areas where cells are less prone to eliminate idiogenic osmoles, such as the central part of basal pons (central pontine myelinolysis) [51]. ODS is not typically associated to HHS: only a few case reports have been published since 1989, some of them reporting the neurological impairment at presentation (suggesting a possible role of hyperglycemia in the development of brain damage [52]), others as a complication of treatment [53]. Pathophysiologically, an overly rapid correction of Na$^+$ deficit (in those with $_P$Na^+_M < $_P$Na^+_G) or a further increase in the $_P$Na$^+$ (in those with $_P$Na^+_M > $_P$Na^+_G or $_P$Na^+_M ≈ $_P$Na^+_G) can cause rapid fluctuations in $_P$Osm, essentially identical to the conditions that produce ODS while treating hyponatremia [54]. This complication explains why it is so important to evaluate the Na$^+$ content of the infused fluids and to consider the effect of K$^+$ and insulin on the $_P$Na$^+$. The occurrence of a catastrophic ODS when treating HHS remains infrequent, but an overly rapid development of iatrogenic hypernatremia may still worsen the patient's neurological status and must be avoided.

5. EXAMPLES

Figs. (**1** and **2**) give a schematic representation of the changes produced by hyperglycemia in total body water (TBW), ICV, ECV and their respective concentrations of Na$^+$, Cl$^-$, other (than chloride) anions (OAN) and osmolality. The same starting condition (**A**), modified by the same glucose addition, can evolve towards different clinical features according to different adaptive responses. Fig. (**1**) exemplifies the two extreme clinical patterns:

- In **B** (the typical HHS presentation) osmotic diuresis produces massive water losses, which are larger than solute losses and are not completely compensated by water intake, thus producing a higher $_P$G, a higher $_P$Osm and either normonatremia or hypernatremia;

- In **C** free water intake is higher (mainly because thirst and consciousness are preserved) and the effects of the osmotic diuresis are partially compensated, thus producing a lower water deficit, a proportionally higher

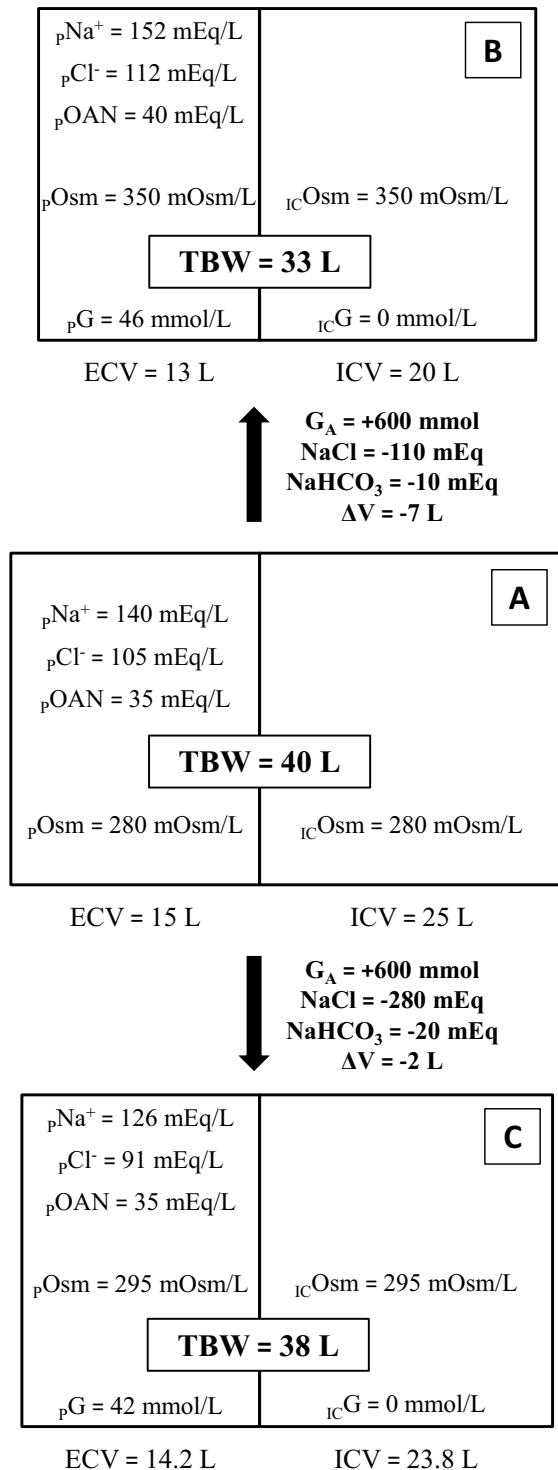solute loss and, consequently, a lower $_pG$, a lower $_pOsm$ and either hyponatremia or normonatremia.

Fig. (1). The same baseline condition (**A**), modified by the same amount of G_A (600 mmol) can evolve towards two opposite clinical presentation depending on whether or not the patient compensate osmotic diuresis with water intake (respectively **B** and **C**).

46 mmol/L = 830 mg/dL; 42 mmol/L = 758 mg/dL.

Fig. (**1**) reports two extreme examples in which the proper fluid to be infused would be easy to identify. How-

ever, in less striking cases, the correct choice may not be clearly evident. Therefore, once hemodynamic stability is ensured, it is mandatory to obtain information about the patient's volume status through the physical examination (blood pressure, heart rate and their orthostatic changes; skin and mucous hydration, jugular or peripheral veins distension or collapse); additionally, body weight and its recent changes may give valuable information, but these data are hardly ever available, especially in the Emergency Department.

Laboratory tests needed to set the proper treatment include $_pOsm$, $_pG$, $_pNa^+$, $_pK^+$ and $_pCl^-$. These data allow the clinician to compute the amount of water and cations to be administered in order to restore volume deficit and correct electrolyte derangements. The formulas we propose (reported in Table **2**) are taken from our previous work, where the boundary conditions for their applicability were also identified: $_pOsm_1 > 280$ mOsm/L (a necessary requirement in HHS) and $_pCl_1/_pNa_1 \neq 0.75$ [24].

Table 2. Step-by-step algorithm to calculate $_pNa^+_G$. The required variables are $_pOsm_0$ and $_pOsm_1$, normal body weight (needed to compute TBW_0 and then ECV_0), $_pNa^+_0$, $_pNa^+_1$ and $_pG_1$.

-	Step-by-step Algorithm to Compute $_pNa^+_G$
1. Compute the first estimate of the variation in total body water	$\Delta V_{FE} = (\Delta_P Osm \times TBW_0) / {}_pOsm_1$
2. Compute the first estimate of the variation in Na^+ content	$\Delta Na^+_{FE} = ({}_pNa^+_1 - {}_pNa^+_0) \times \Delta V_{FE}$
3. Compute the final extracellular volume	$ECV_1 = [({}_pNa^+_0 \times ECV_0) - \Delta Na^+_{FE}] / {}_pNa^+_1$
4. Compute the amount of glucose in extracellular volume	$G_A = {}_pG_1 \times ECV_1$
5. Compute the $_pOsm_G$ (rise in $_pOsm$ exclusively due to G_A)	$_pOsm_G = [({}_pOsm_0 \times TBW_0) + G_A] / TBW_0$
6. Compute the extracellular volume expected in the presence of exclusive osmotic water shift	$ECV_G = TBW_0 - [({}_pOsm_0 \times ICV_0) / {}_pOsm_G]$
7. Compute the $_pNa^+$ expected in the presence of exclusive osmotic water shift	$_pNa^+_G = ({}_pNa^+_0 \times ECV_0) / ECV_G$

Fig. (**2**) presents laboratory data from four hypothetical example patients along with the respective computed $_pNa^+_G$.

We think that these formulas can represent a valuable tool for the physician when fluids treatment of HHS needs
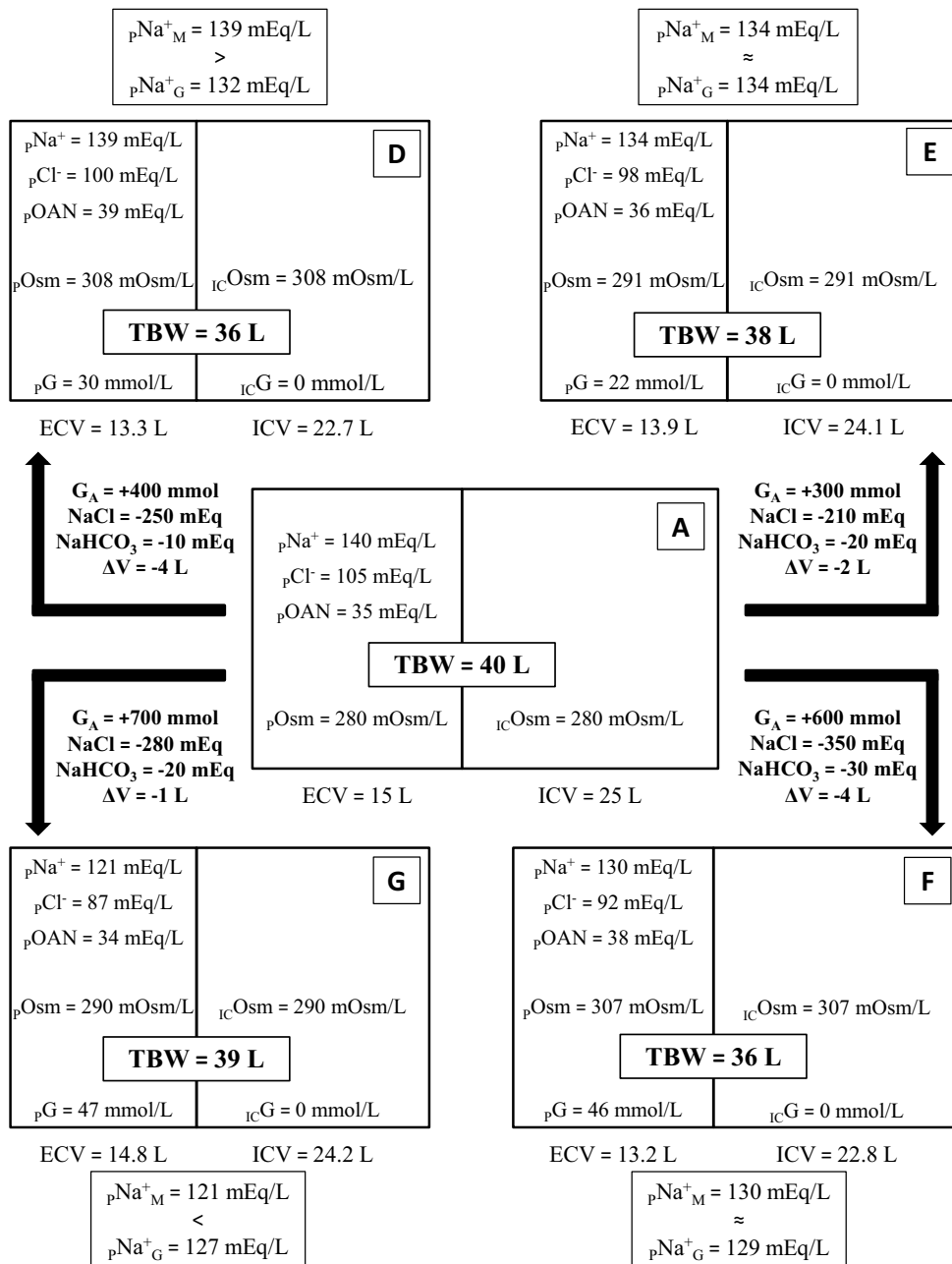
$_pNa^+{}_M$ = 139 mEq/L
\>
$_pNa^+{}_G$ = 132 mEq/L

$_pNa^+$ = 139 mEq/L **D**
$_pCl^-$ = 100 mEq/L
$_pOAN$ = 39 mEq/L

$_pOsm$ = 308 mOsm/L $_{IC}Osm$ = 308 mOsm/L

TBW = 36 L

$_pG$ = 30 mmol/L $_{IC}G$ = 0 mmol/L

ECV = 13.3 L   ICV = 22.7 L

$_pNa^+{}_M$ = 134 mEq/L
≈
$_pNa^+{}_G$ = 134 mEq/L

$_pNa^+$ = 134 mEq/L **E**
$_pCl^-$ = 98 mEq/L
$_pOAN$ = 36 mEq/L

$_pOsm$ = 291 mOsm/L $_{IC}Osm$ = 291 mOsm/L

TBW = 38 L

$_pG$ = 22 mmol/L $_{IC}G$ = 0 mmol/L

ECV = 13.9 L   ICV = 24.1 L

G_A = +400 mmol
NaCl = -250 mEq
$NaHCO_3$ = -10 mEq
ΔV = -4 L

$_pNa^+$ = 140 mEq/L **A**
$_pCl^-$ = 105 mEq/L
$_pOAN$ = 35 mEq/L

TBW = 40 L

$_pOsm$ = 280 mOsm/L $_{IC}Osm$ = 280 mOsm/L

ECV = 15 L   ICV = 25 L

G_A = +300 mmol
NaCl = -210 mEq
$NaHCO_3$ = -20 mEq
ΔV = -2 L

G_A = +700 mmol
NaCl = -280 mEq
$NaHCO_3$ = -20 mEq
ΔV = -1 L

G_A = +600 mmol
NaCl = -350 mEq
$NaHCO_3$ = -30 mEq
ΔV = -4 L

$_pNa^+$ = 121 mEq/L **G**
$_pCl^-$ = 87 mEq/L
$_pOAN$ = 34 mEq/L

$_pOsm$ = 290 mOsm/L $_{IC}Osm$ = 290 mOsm/L

TBW = 39 L

$_pG$ = 47 mmol/L $_{IC}G$ = 0 mmol/L

ECV = 14.8 L   ICV = 24.2 L

$_pNa^+$ = 130 mEq/L **F**
$_pCl^-$ = 92 mEq/L
$_pOAN$ = 38 mEq/L

$_pOsm$ = 307 mOsm/L $_{IC}Osm$ = 307 mOsm/L

TBW = 36 L

$_pG$ = 46 mmol/L $_{IC}G$ = 0 mmol/L

ECV = 13.2 L   ICV = 22.8 L

$_pNa^+{}_M$ = 121 mEq/L
\<
$_pNa^+{}_G$ = 127 mEq/L

$_pNa^+{}_M$ = 130 mEq/L
≈
$_pNa^+{}_G$ = 129 mEq/L

Fig. (2). The same baseline condition (**A**), modified by different combinations of G_A, Na^+ lost and volume lost, can produce different clinical presentations. The ratio between $_pNa^+{}_G$ and $_pNa^+{}_M$ can help the physician to estimate whether volume losses prevail over Na^+ losses (**D**), Na^+ losses prevail over volume losses (**G**) or the two actually balance and the reduction in $_pNa^+$ can be approximated to that exclusively produced by water shift (**E, F**). $_pNa^+{}_G$ has been calculated with the formulas reported in Table **2**.
30 mmol/L = 543 mg/dL; 22 mmol/L = 388 mg/dL; 46 mmol/L = 830 mg/dL; 47 mmol/L = 849 mg/dL.

to be started. However, since the computing algorithm includes different steps with a number of variables, in order to simplify its use in clinical practice, we are setting up an easily available calculation tool that instantly provides the $_pNa^+{}_G$ and other data that, together with a careful clinical examination, help the physician to choose the correct treatment.

CONCLUSION

Although hypovolemia remains the most relevant problem in HHS and requires immediate correction, electrolyte derangements and particularly dysnatremias usually complicate and worsen the global clinical picture. Most of the therapeutic measures routinely necessary in HHS (fluids infusion, insulin infusion, K^+ supplementation) affect $_pNa^+$. The physician needs to be aware of this as well as of the underlying pathophysiological mechanisms in order to predict the change in $_pNa^+$ and prevent the potential complications of improper treatments. The quantitative approach we propose on the basis of our previous works can provide more accurate information about the patient's hydroelectrolytic status and guide the physician in the choice of the proper

composition of the fluids that need to be infused to restore volume losses.

LIST OF ABBREVIATIONS

DKA	=	Diabetic Ketoacidosis
HHS	=	Hyperglycemic Hyperosmolar State
$_pOsm$	=	Plasma Osmolality
$_pNa^+$	=	Plasma Sodium Concentration
$_pK^+$	=	Plasma Potassium Concentration
ODS	=	Osmotic Demyelination Syndrome
ECV	=	Extracellular Volume
$_pG$	=	Plasma Glucose Concentration
ICV	=	Intracellular Volume
$_pNa^+_G$	=	Plasma Sodium Concentration Expected in the Presence of Exclusive Osmotic Water Shift
$_pNa^+_M$	=	Measured Plasma Sodium Concentration
CNS	=	Central Nervous System
TBW	=	Total Body Water
$_pCl^-$	=	Plasma Chloride Concentration
$_pOAN$	=	Plasma Concentration of Anions other than Chloride
G_A	=	Amount of Glucose in Extracellular Volume
ΔV_{FE}	=	First Estimate of the Variation in Total Body Water
ΔNa^+_{FE}	=	First Estimate of the Variation in Na^+ Content
$_pOsm_G$	=	Rise in Plasma Osmolality Exclusively Due to the Amount of Glucose Diluted in Extracellular Volume
ECV_G	=	Extracellular Volume Expected in the Presence of Exclusive Osmotic Water Shift

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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