
بسم الله الرحمن الرحیم
بنام خداوند بخشاینده مهربان
In the name of Allah the Beneficent the Merciful

Na disorders

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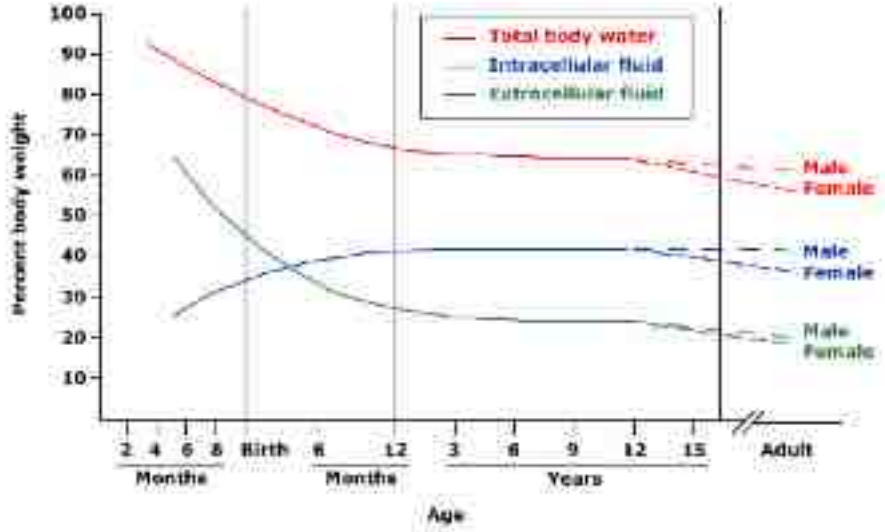
Total body water and its major subdivisions as a function of age

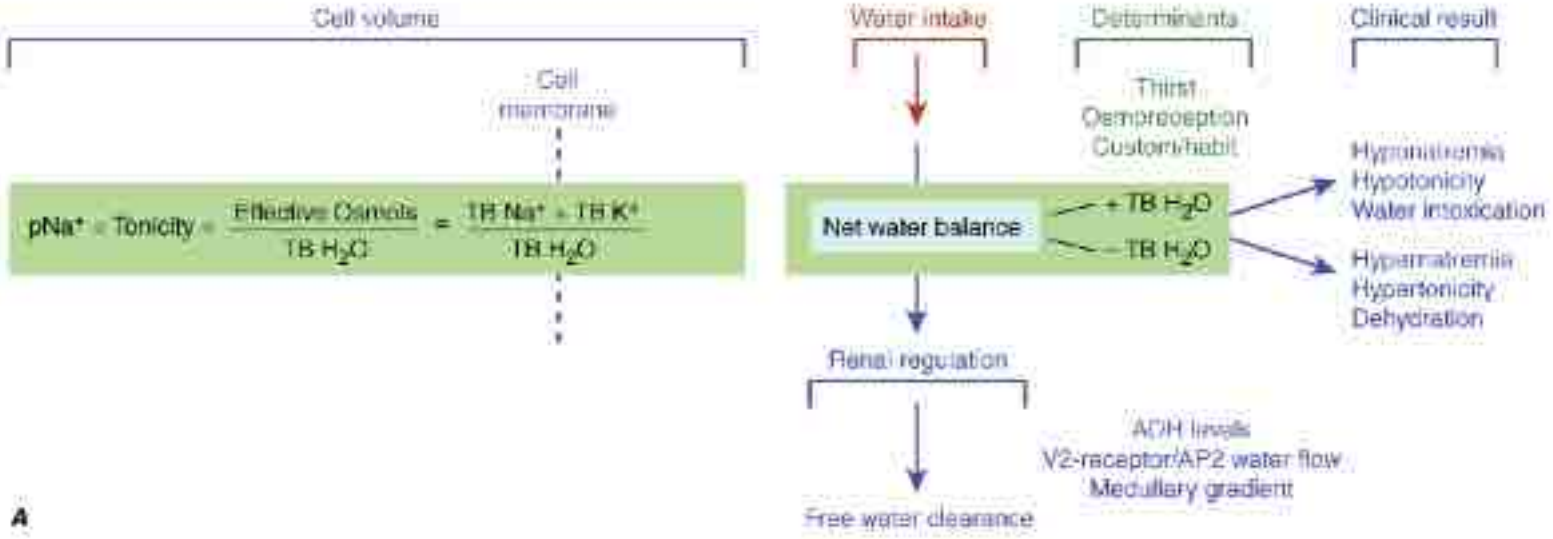


Osmoregulation vs volume regulation

- The body wants to maintain its extracellular sodium concentration in a narrow range by osmoregulation (135-145 mEq/L).
- Also it will maintain extracellular fluid volume (ECFV) within an acceptable range by volume regulation.

- In clinical practice, consider cases of abnormal Na concentration as problems with water control.
- Problems with ECV size are related to problems with the Na control mechanisms.

HypoNa
HyperNa

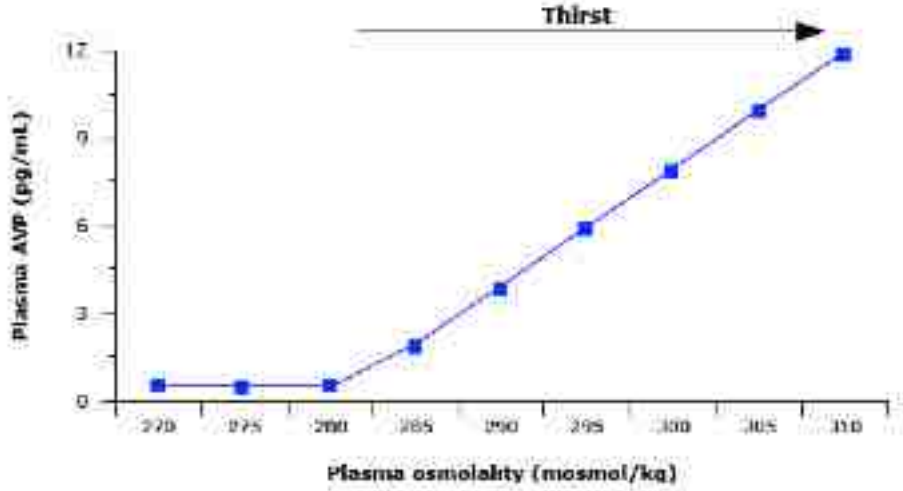


Osmoregulation vs volume regulation

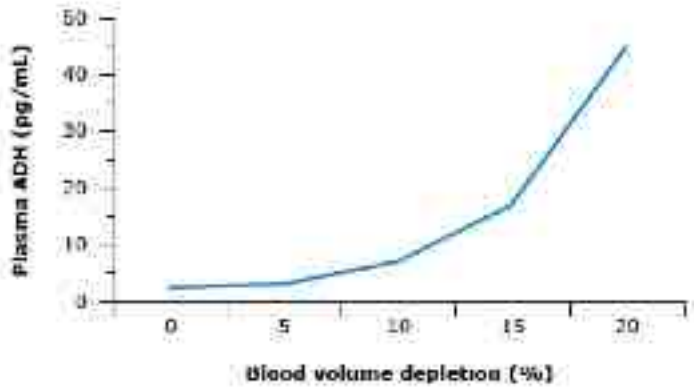
Differences between osmoregulation and volume regulation

	Osmoregulation	Volume regulation
What is being sensed	Plasma osmolality	effective circulating volume
Sensors	Hypothalamic osmoreceptors	Carotid sinus
		Afferent glomerular arteriole
		Atria
Effectors	ADH	Sympathetic nervous system
		Renin-angiotensin-aldosterone
		Natriuretic peptides
		Pressure natriuresis
		ADH
What is affected	Water excretion (via ADH)	Sodium excretion
	Water intake (via thirst)	

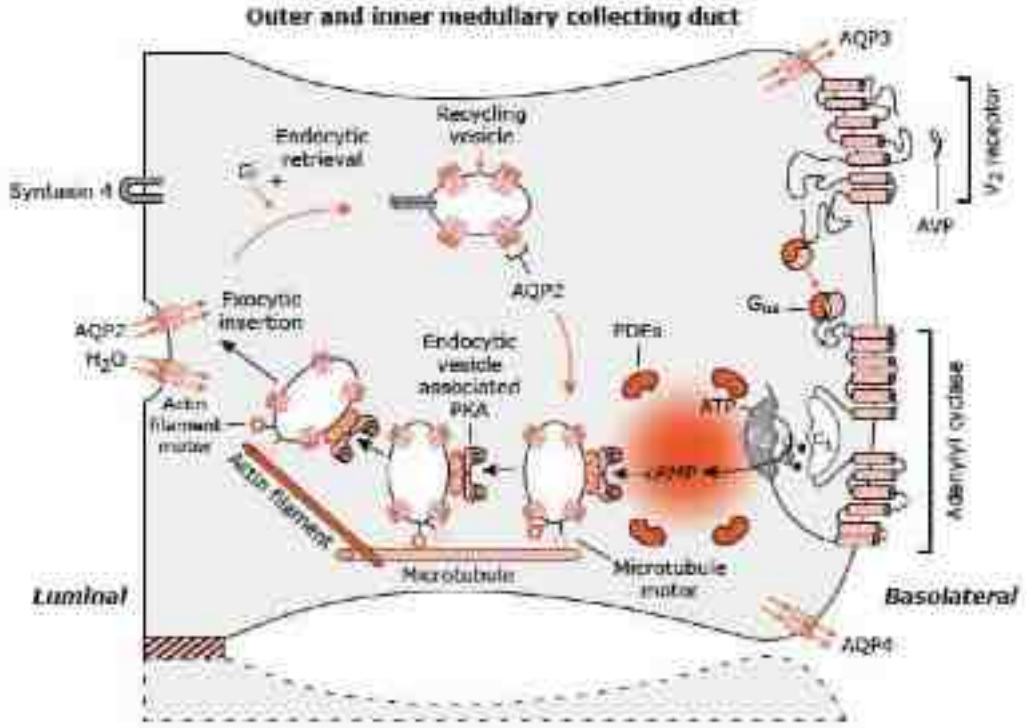
Osmoregulation of thirst



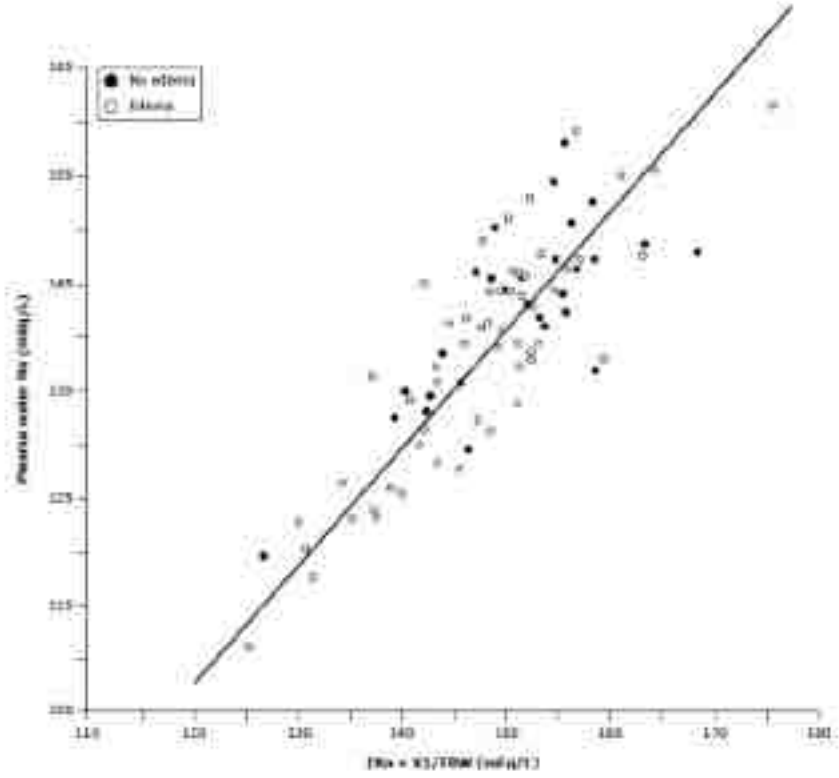
Hypovolemic stimulus to ADH release



Effect of arginine vasopressin on water permeability in the collecting duct



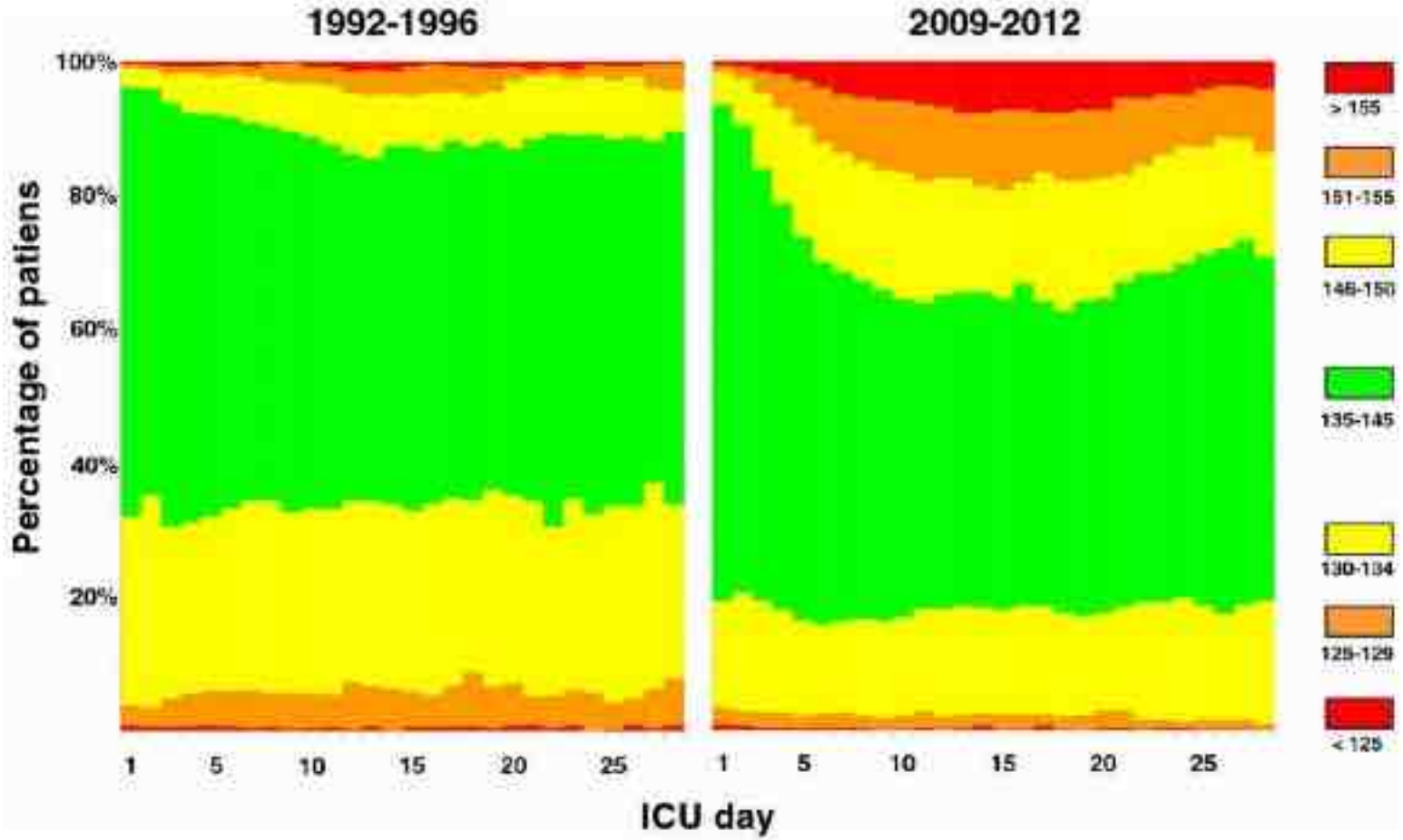
Determinants of the plasma sodium concentration



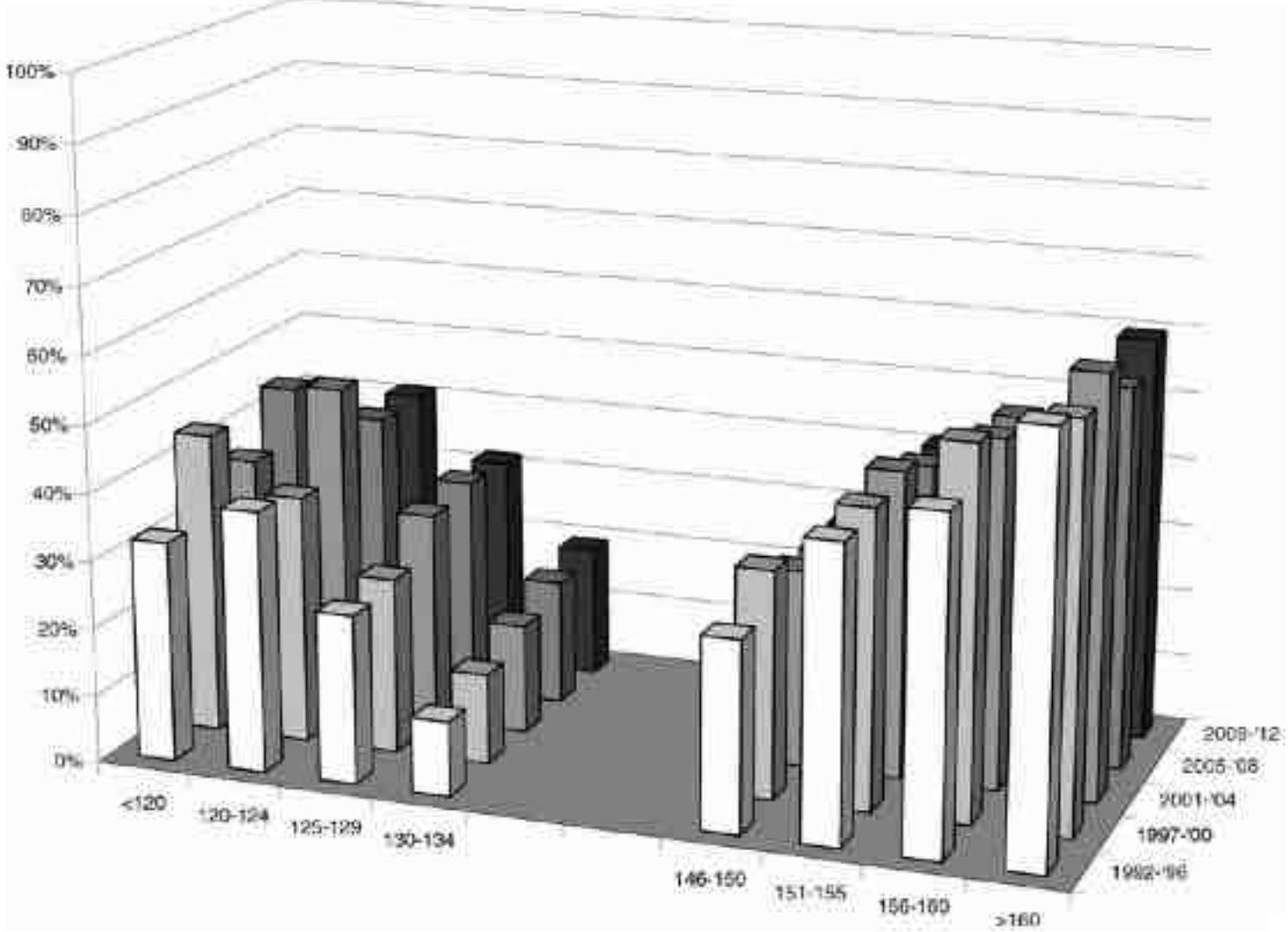
- Hyponatremia (too much water or overhydration).
- •Hypernatremia (too little water or dehydration).
- •Hypovolemia (too little sodium, the main extracellular solute or volume contraction).
- •Hypervolemia (too much sodium, the main extracellular solute, with expansion of the effective arterial blood volume and hypertension).
- •Edema or hypervolemia (too much sodium with associated water retention in interstitial spaces).

- Hyponatremia is independently associated with mortality which may be due to a direct causal relationship.

Shift from HypoNa to HyperNa in ICU



DysNatremia and mortality in ICU



An independent mortality risk rising with increasing severity of both hyponatremia and hypernatremia

- Odds ratios and 95% confidence interval (CI) for borderline, mild, moderat and severe hyponatremia were 1.32 (1.25–1.39), 1.89 (1.71–2.09), and 1.81 (1.56–2.10), respectively.

- Funk, GC., Lindner, G., Druml, W. et al. Incidence and prognosis of dysnatremias present on ICU admission. Intensive Care Med 36, 304–311 (2010). https://doi.org/10.1007/s00134-009-1692-0

- HypoNa are associated with all-cause mortality.*
- HypoNa is a major risk factor for mortality in advanced liver cirrhosis*
- HypoNa increased mortality, rehospitalizations, prolonged hospital stays, and major cardiovascular events in patients with heart failure*
- HypoNa asociated with higher risk for all-cause mortality in non-dialysis CKD and maintenance dialysis patients
- Development of hyponatremia before, upon, or during admission indicates worse prognosis in any given patient.*

[illegible]
[illegible]

Journal of Translational Medicine

RESEARCH **Open Access**

Intensive care unit-acquired hyponatremia in critically ill medical patients

[illegible]

Abstract

Background: Previous research has focused on intensive care unit (ICU)-acquired hypernatremia; however, ICU-acquired hyponatremia has frequently been overlooked and has rarely been studied in surgical or mixed ICUs. The aim of this study is to investigate the incidence of ICU-acquired hyponatremia, the risk factors associated with its development, and its impact on outcomes in critically ill medical patients.

Methods: We conducted a retrospective cohort study based on the prospective registry of all critically ill patients admitted to the medical ICU from [illegible] to December [illegible]. Baseline characteristics and management variables were compared between ICU-acquired hyponatremia and normonatremia patients.

Results: [illegible]

Conclusions: ICU-acquired hyponatremia is not uncommon in critically ill medical patients. Increased volume balance is associated with its development. ICU-acquired hyponatremia is related to increased use of renal replacement therapy but not to mortality.

Keywords: Acute kidney injury, Critical care, [illegible], Hyponatremia, Intensive care unit

Background

Hyponatremia, defined as a serum sodium concentration less than [illegible] mmol/L, is a common electrolyte abnormality found in critically ill patients [1]. More than one-sixth to one-fourth of patients have hyponatremia on intensive care unit (ICU) admission, and these patients have increased risk of mortality and prolonged ICU length of stay (LOS) [illegible]. Indeed, sodium level is a significant prognostic factor and is included in ICU scoring systems [illegible]. These previous studies evaluated hyponatremia at the time of ICU admission, although new onset hyponatremia is easily detected in clinical practice.

ICU-acquired dysnatremia is the disturbance of sodium level in patients whose sodium concentration was initially normal on ICU admission. Traditionally

[illegible]

Table 4 Clinical Outcomes

Outcomes	ICU-acquired hyponatremia (n = 217)	Normonatremia (n = 1008)	*P* value
ICU mortality	33 (15.2)	145 (14.4)	0.751
28-day mortality	45 (20.7)	215 (21.3)	0.927
ICU length of stay	5.3 (3.0–10.9)	4.9 (3.0–9.3)	0.216
Renal replacement therapy[a]	29 (13.4)	75 (7.4)	0.007
CRRT	25 (11.5)	70 (6.9)	0.035
Intermittent hemodialysis	9 (4.1)	16 (1.6)	0.029
Time to renal replacement therapy (days)	3.0 (2.0–9.0)	5.0 (3.0–9.0)	0.262

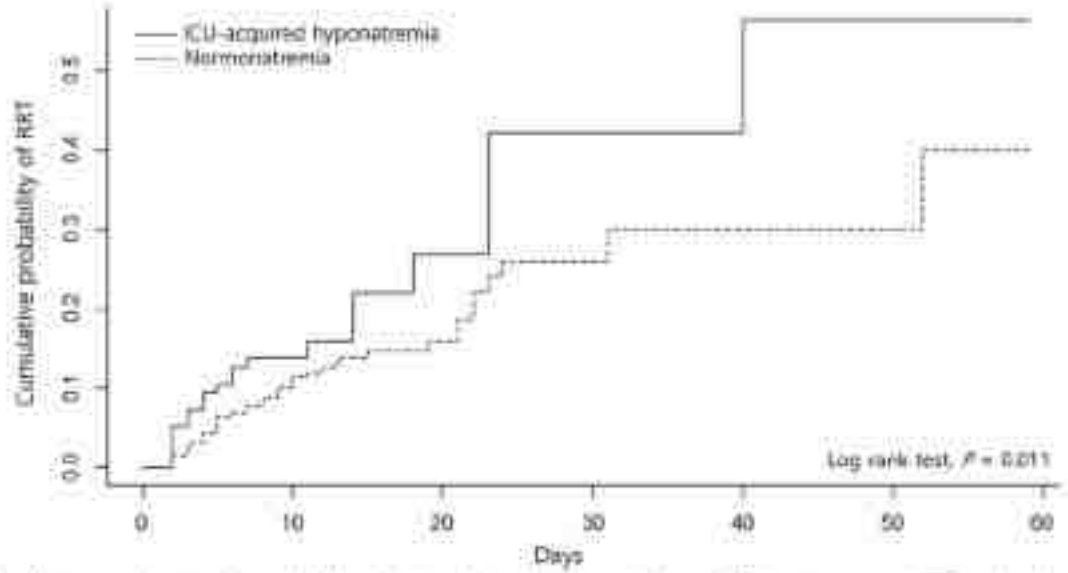
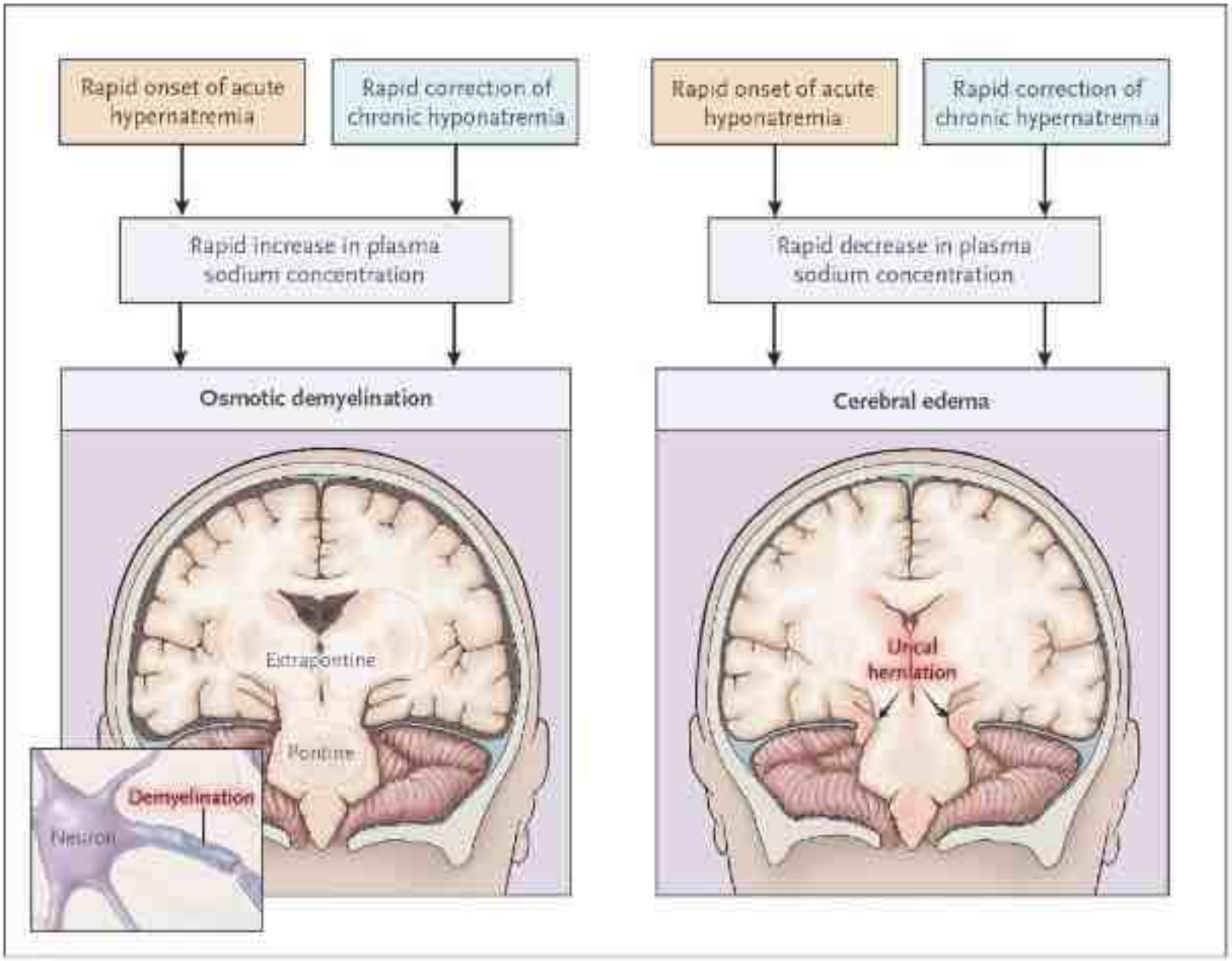


Fig. 2 Kaplan–Meier curves showing the probability of initiation of renal replacement therapy. *ICU* intensive care unit, *RRT* renal replacement therapy

- Hypotonic hyponatremia is the most common electrolyte disorder encountered in clinical practice.
- post-operative hyponatremic encephalopathy is equally likely in both genders but women of menstruating age were 25 times more likely to die or develop permanent brain damage than either men or postmenopausal women.
- Female sex hormon inhibit the activity of Na-K ATPase

- HypoNa represent excess water in relation to water
- Duration: acute vs chronic (<48 hrs vs≥ 48 hrs)
- Severity: 130-134, 120-129, < 120 mmol/lit.
- Symptoms: severe=seizures, obtundation, coma, and respiratory arrest. Mild to mod=headache, fatigue, lethargy, nausea, vomiting, dizziness, gait disturbances, forgetfulness, confusion, and muscle cramps.
- Asymptomatic: subtle impairments in mentation and gait and an increased risk of falls and fractures.

- Concurrent hypoxemia can exacerbate hyponatremia-induced cerebral edema.


Rapid onset of acute hypernatremia
Rapid correction of chronic hyponatremia
Rapid increase in plasma sodium concentration
Osmotic demyelination
Extrapontine
Pontine
Demyelination
Neuron
Rapid onset of acute hyponatremia
Rapid correction of chronic hypernatremia
Rapid decrease in plasma sodium concentration
Cerebral edema
Uncal herniation

Rapid or overcorrection

- ODS occurs especially in the pons (central pontine myelinolysis), although extrapontine myelinolysis affecting the basal ganglia, cortex, lateral geniculate body and internal capsule can also occur.

- Risk of ODS increases in serum Na< 105 mEq/L and those with hypokalemia, alcohol use disorder, malnutrition, liver disease, and possibly, hypophosphatemia.
- Reuptake of the myoinositol and other organic osmolytes occur more rapidly in the uremic environment which explains the low risk of ODS in uremic subjects.*

Osmotic demyelination syn.

Impairment in Short-Term Memory
Attention deficit
Dysarthria
Dysphagia
Flaccid Quadriparesis
Oculomotor abnormalities
Ataxia
Mutism
Parkinsonism
Catatonia
Dystonia
Tremor
"Locked-in" syndrome
Seizures
Coma

ODS

- Quadriparesis, dysarthria, dysphagia, and other pseudobulbar symptoms, pseudobulbar palsy, seizures, locked-in syndrome, coma and even death.
- ODS may occur several days after the correction of hyponatremia.
- ODS may be asymptomatic or mildly symptomatic.
- Symptoms of ODS may or may not be reversible.

Goal of correction in acute HypoNa

- In sever symptomatic 4-6 mmol/lit in first 24hr
- No more than 10-12 mmol/l/24 hrs and 18mmol/l/48 hrs must be corrected.
- Acute asymptomatic hypoNa, Na<130mmol/lit, 50 ml bolus of NaCl 3% IV
- In acute symptomatic hypoNa, Na<130 mmol/l, 100 ml bolus of NaCl 3% IV in 10 min. can repeat up to 300 ml(in European organization 150 ml NaCl 3% in 20 min and repeat once if necessary.
- Goal is ↑Na by 4-6 mmol/lit in few hrs.

Chronic HypoNa

- Mild to moderate W/O symptoms no emergent therapy is needed.
- D.C drugs than can induce HypoNa.
- Sever HypoNa, Na<120 mmol/lit, NaCl 3% ,15-30 ml/ hr or 1ml/kg (max. 100 ml) Q6h IV inf ± dDAVP.
- dDAVP is recommended as 1 to 2mcg, IV or SC Q6-8hr for a period of 24 to 48 hrs (or until the serum sodium has been increased to at least 125 mEq/L).

Rapidly reversible causes of hyponatremia

- True volume depletion
- Adrenal insufficiency
- SIAD(H)
- Thiazide-associated hyponatremia
- In these condition dDAVP can prevent rapid correction of HypoNa and reduces risk of ODS.
- dDAVP is not recommended In edematous states such as heart failure and cirrhosis or recurrent HypoNa due to chronic SIAD(H) .

General measures in chronic HypoNa

- Stop medication that could cause HypoNa.
- Restrict electrolyte free or hypotonic fluids.
- Increase salt intake(4-6gr/day) + loop diuretics.
- Identify and treat cause of HypoNa.
- Vaptans?
- Isotonic saline
- Hypotonic fluids?

- The United States guidelines recommended the use of hypertonic saline in patients with acute (<48 h) hyponatremia with moderate to severe symptoms* while the European guidelines based its recommendations to use hypertonic saline on the severity of symptoms rather than the duration.*

ARTICLE

Severe Hyponatremia Is Often Drug Induced: 10-Year Results of a Prospective Pharmacovigilance Program

Elena Ramírez[1,2,*], Amelia Rodríguez[1], Javier Queiruga[2], Irene García[1], Lucía Díaz[1], Lucía Martínez[1], Raúl Muñoz[1], María Muñoz[1], Hoi Y. Tong[1], José Carlos Martínez[1], Alberto M. Borobia[1], Antonio J. Carcas[1] and Jesús Frías[1,*]

We conducted a prospective evaluation of drug-induced severe hyponatremia (adverse drug reaction (ADR)) through the Prospective Pharmacovigilance Program from Laboratory Signals at Hospital over a period of 10 years. Cases of serum sodium (NaS) < 116 mM were recorded from July 2007 to June 2017 (first period). Also cases of NaS 116–122 mM were recorded from July 2012 to June 2017 (second period). Drugs were the primary cause of severe hyponatremia. The incidence rate of NaS < 116 mM by drugs was increased threefold over the decade. Compared with other causes of hyponatremia, patients with adverse drug reaction–serum sodium (ADR-NaS) in the first period were older (79 years (interquartile range (IQR) 69.6–89 vs. 65 years (IQR 49–81); P < 0.001) and were more often women (70.8% vs. 48.9% men, P < 0.001). In the second period were also older (79 years (IQR 65.3–89) vs. 49 years (IQR 46–80.6); P < 0.001) and were more often women (70% vs. 53%; P = 0.002), and ADR-NaS occurred more often in summer. The most frequent therapeutic groups of culprit drugs were the cardiovascular system and nervous system. The 65.3% in the first period and 71.2% in the second period of the ADR-NaS cases responded to hydration and had been diagnosed with hypovolemic hyponatremia.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

[illegible]

WHAT QUESTION DID THIS STUDY ADDRESS?

[illegible]

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

[illegible]

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

[illegible]

[illegible]

[illegible]

Drug induced sever HypoNa

Table 1 Breakdown by diagnosis of severe hyponatremia recorded at La Paz University Hospital by periods: first period (from July 2007 to June 2012), second period (from July 2012 to June 2017)

Signal category	Causes	N of cases	% of cases	Incidence rate* (per 10,000 patients)	Poisson 95% confidence interval of incidence rate (per 10,000 patients)	P value
First period Hyponatremia < 116 mM	Hemorrhage or masses CNS	76	20.2	5.15	1.08–8.77	0.860
	Neoplasia	74	19.7	5.11	1.08–8.77	1.000
	Drugs	**72**	**19.2**	**3.02**	**1.08–8.77**	**ref.**
	Heart failure or cirrhosis	38	10.1	1.58	0.24–6.57	0.071
	Pulmonary infection	27	7.2	1.13	0.24–6.57	0.012
	Gastrointestinal losses	25	6.7	1.05	0.24–6.57	0.005
	Advanced renal failure	21	5.6	0.88	0.03–3.89	0.002
	Endocrine disorders	15	4.0	0.63	0.03–3.89	<0.001
	Primary polydipsia	9	2.4	0.38	0.03–3.89	<0.001
	Pseudohyponatremia	7	1.9	0.29	0.03–3.89	<0.001
	Low dietary solute intake	2	0.5	0.08	0.03–3.89	<0.001
	Exercise associated	2	0.5	0.08	0.03–3.89	<0.001
	Other	8	2.1	0.34	0.03–3.89	<0.001
	Total	375	100.0	15.78	10.67–27.22	
Second period Hyponatremia < 122 mM	**Drugs**	**333**	**36.8**	**14.74**	**8.40–23.49**	**ref.**
	Heart failure or cirrhosis	111	12.3	4.91	1.63–10.24	<0.001
	Gastrointestinal losses	93	10.3	4.12	1.63–10.24	<0.001
	Advanced renal failure	79	8.7	3.50	1.09–8.77	<0.001
	Neoplasias	71	7.8	3.14	1.09–8.77	<0.001
	Hemorrhage, CNS masses	65	7.2	2.88	0.62–7.23	<0.001
	Endocrine disorders	38	4.0	1.68	0.24–6.57	<0.001
	Pulmonary infection	34	3.8	1.51	0.24–6.57	<0.001
	Primary polydipsia	25	2.8	1.11	0.24–6.57	<0.001
	Low dietary solute intake	14	1.6	0.62	0.03–3.89	<0.001
	Exercise associated	12	1.3	0.53	0.03–3.89	<0.001
	Pseudohyponatremic	10	1.1	0.44	0.03–3.89	<0.001
	Other	23	2.5	1.02	0.24–6.57	<0.001
	Total	908	100.0	40.11	29.42–54.47	<0.001

Values of drug induced hyponatremia are bold

CNS, central nervous system; ref., reference

*Excluding 129 and 115 errors (preanalytical errors) in hyponatremia < 116 mM and hyponatremia < 122 mM, respectively

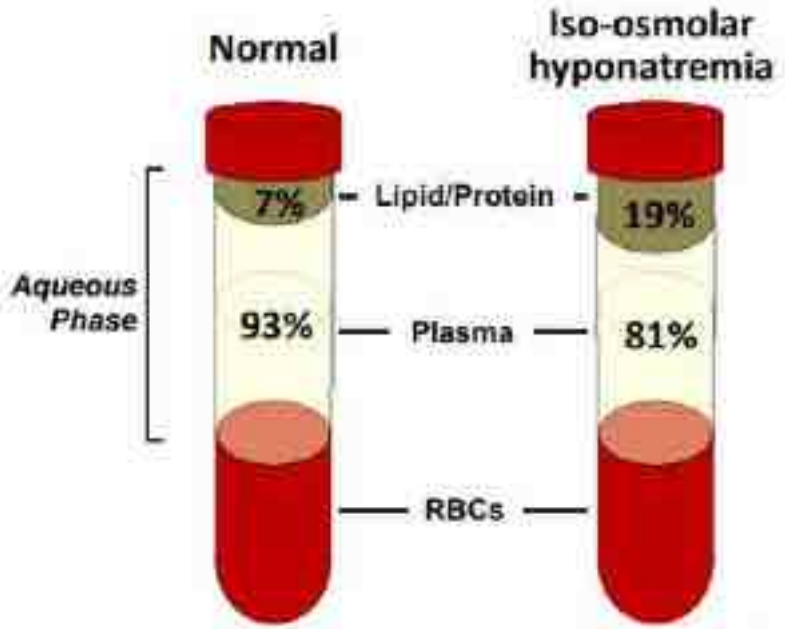
Mechanisms of THZ induced HypoNa

Table 2. Mechanisms of thiazide-induced hyponatremia.

Renal (Primary)
NCC inhibition-related
Sodium loss leading to GFR reduction and enhanced proximal tubular fluid reabsorption
Impaired urinary dilution
Independent of NCC inhibition
AQP2 upregulation in the collecting duct
Direct effect
Prostaglandin E2-mediated
Extrarenal (subsidiary)
Insufficient solute intake
Excessive water intake
Coexistent hypokalemia leading to transcellular cation exchange

AQP2, aquaporin-2; GFR, glomerular filtration rate; NCC, Na-Cl cotransporter.

Isosmolar or pseudoHypoNa



[Na^+] in plasma aqueous phase	**154 mEq**	**154 mEq**
Plasma % of aqueous phase	**93%**	**81%**
Lipid/protein % of aqueous phase	**7%**	**19%**
[Na^+] reported by laboratory	**143 mEq/L**	**125 mEq/L**

AJKD

Core Curriculum

Diagnosis and Management of Disorders of Body Tonicity—Hyponatremia and Hypernatremia: Core Curriculum 2020

N. Winn Seay, Ruediger W. Lehrich, and Arthur Greenberg

Overall body fluid concentration is regulated within a narrow range by the concerted action of the hypothalamic-pituitary axis to influence water intake through thirst and water excretion via the effect of vasopressin, or antidiuretic hormone, on renal collecting duct water permeability. Sodium is the principal extracellular cation; abnormalities in overall effective body fluid concentration, or tonicity, manifest as disturbances in serum sodium concentration. Depending on its severity and chronicity, hyponatremia can lead to significant symptoms, primarily related to central nervous system function. Failure to correct hyponatremia can lead to permanent neurologic damage, as can over rapid correction. It is thus essential to stay within specific limits for correction, particularly for chronic hyponatremia. Hypernatremia also leads to central nervous system dysfunction, although goals for its correction rate are less well established. This Core Curriculum article discusses the normal regulation of tonicity and serum sodium concentration and the diagnosis and management of hypo- and hypernatremia.

Complete author and article information appears at end of article text.

Am J Kidney Dis. 75(2): 272-286. Published online October 10, 2019.

doi: 10.1053/j.ajkd.2019.07.014

Case 1: *A 65-year-old woman presents with productive cough, shortness of breath, and fever. She is taking hydrochlorothiazide, 12.5 mg, daily for hypertension. Physical examination reveals temperature of 38.5°C, blood pressure of 90/50 mm Hg, heart rate of 100 beats/min, respiratory rate of 28 breaths/min, and oxygen saturation of 87% while breathing room air, along with dry mucus membranes, left lower-lobe crackles, and absence of edema. Laboratory results include [Na^+] of 128 mEq/L, serum urea nitrogen (SUN) level of 68 mg/dL, serum creatinine level of 3.4 mg/dL, and serum osmolality of 280 mOsm/kg H_2O.*

Question 1: This patient's serum is correctly described as:

a) Hypotonic and hypo-osmolal
b) Hypotonic and iso-osmolal
c) Isotonic and hypo-osmolal
d) Isotonic and iso-osmolal

Tonocity vs Osmolality

- Tonocity means effective osmolality
- Effective osmoles: Na and its anion

$$\text{plasma } [Na^+] = \frac{\text{total body } (Na^+ + K^+)}{\text{total body } H_2O}.$$

Answer: The patient's serum osmolality is within the normal range of 275 to 295 mOsm/kg H_2O. Her effective serum osmolality, or tonicity, is ~256 mOsm/kg H_2O (Effective serum osmolality = S_{Osm} − SUN/2.8 = 280 − 68/2.8 = 256). She is thus iso-osmolal and hypotonic, making (b) the correct answer.

Case 2: *A 70-year-old woman is brought to the emergency department with a day of confusion, nausea, and vomiting. She was started on treatment with chlorthalidone, 25 mg, daily 1 week earlier to treat newly diagnosed hypertension. Physical examination is notable for temperature of 37°C, heart rate of 105 beats/min, blood pressure of 95/60 mm Hg, respiratory rate of 14 breaths/min, and oxygen saturation of 100% while breathing room air. She is acutely ill appearing and not oriented to person, place, or date. Mucous membranes are dry, and no edema is present. Saline solution, 0.9%, is begun with a plan to administer 1 L over the first 2 hours. Laboratory results return, revealing [Na^+] of 104 mmol/L, serum potassium level of 2.8 mmol/L, SUN level of 27 mg/dL, and serum creatinine level of 1.4 mg/dL. She experiences a generalized seizure.*

Question 2: Which of the following is the most appropriate next step in management?

a) Increase rate of normal saline solution
b) Administer tolvaptan
c) Bolus 100 mL of 3% saline solution over 10 minutes
d) Infuse 500 mL of 3% saline solution over 15 minutes

Answer to Question 2: Hypertonic saline solution is indicated for severely symptomatic hyponatremia with a seizure. Acutely increasing the [Na^+] by 4 to 6 mEq/L can prevent further seizure activity, reduce brain swelling, and eliminate the risk for tentorial herniation due to cerebral edema. In a setting in which increasing [Na^+] is a genuine emergency, this can be accomplished by administration of up to three 100-mL boluses of 3% saline solution 10 minutes apart. Tolvaptan and 0.9% saline solution will not increase [Na^+] quickly or reliably enough. Thus, (c) is the correct answer.

- Question 3: After appropriate treatment, no further seizure activity occurs, and repeat [Na+] is 108 mEq/L.

In addition to infusion of isotonic IV fluids and monitoring [Na+] every 2 hours, which of the following is the most appropriate management strategy?

a) Aim for an [Na+] of 120 mEq/L over the first 24 hours

b) Aim for an [Na+] of 114-116 mEq/L over the first 24 hours

c) Aim for an [Na+] of 114-116 mEq/L over the first 24 hours and monitor urine output hourly and UOsm every few hours

d) Aim for an [Na+] of 110-112 mEq/L over the first 24 hours

e) Aim for an [Na+] of 110-112 mEq/L over the first 24 hours and monitor urine output hourly and UOsm every few hours

Answer to Question 3: This patient has multiple risk factors for ODS with over rapid correction, namely presenting serum [Na^+] < 105 mEq/L, hypokalemia, and thiazide diuretic use. A more conservative goal of correcting [Na^+] ideally by 4 to 6 mEq/L and no more than 8 mEq/L in the first 24 hours is appropriate. [Na^+] should be monitored every 2 hours. Because an increase in urine output and decrease in UOsm will precede any increase in [Na^+], hourly urine output should be followed up, which will likely require bladder catheter placement. UOsm should be measured every few hours. Thus, (e) is the correct response.

Table 1. Suggested Treatment Strategies for Management of Hyponatremia According to Chronicity, Symptom Severity, and Risk for ODS

Presentation	Risk for ODS	Goal Increase in [Na^+]	Limit to Increase in [Na^+]	Treatment Strategy
Acute Hypotonic Hyponatremia (duration verified to be <48 h)				
Severe symptoms	Negligible	Rapid increase by 4-6 mEq/L, then gradual increase to normalization	Normalization	Rapidly increase [Na^+] by 4-6 mEq/L with up to three 100-mL boluses of hypertonic saline solution given over 10 min at a time, followed by hypertonic saline solution at 1 mL/kg/h until substantial normalization. If rapid spontaneous correction occurs, it need not be constrained.
Mild or moderate symptoms	Negligible	Normalization	Normalization	Fluid restriction alone if cause rapidly reversible. Otherwise, hypertonic saline solution at 1 mL/kg/h until substantial normalization.
Chronic Hypotonic Hyponatremia (duration known to be >48 h or uncertain)				
Severe, moderate, or mild symptoms	High[1]	4-6 mEq/L in 24 h	8 mEq/L in any 24-h period	Treatment according to cause (volume repletion for hypovolemic hyponatremia, water restriction with SIADH or hypervolemic hyponatremia, etc) and severity of symptoms. Hypertonic saline solution for severely symptomatic hyponatremia with risk for seizures or herniation or a vaptan or urea for mild to moderate refractory euvolemic or hypervolemic hypernatremia. During early phase, closely monitor [Na^+] every 2-4 h and urine output. Re-lower [Na^+] with IV D5W or enteral water ± desmopressin, 1-2 µg, every 6 h if correction over rapid.
Severe, moderate, or mild symptoms	Intermediate	4-8 mEq/L in 24 h	10-12 mEq/L in any 24-h period and no more than 18 mEq/L in any 48-h period	Same strategy as high-risk ODS patients, except with less strict [Na^+] correction limits.
Moderate or mild symptoms	Low (initial [Na^+] > 125 mEq/L)	Normalization	Normalization	Treatment according to cause. Consider vaptan or urea for refractory euvolemic or hypervolemic hypernatremia.

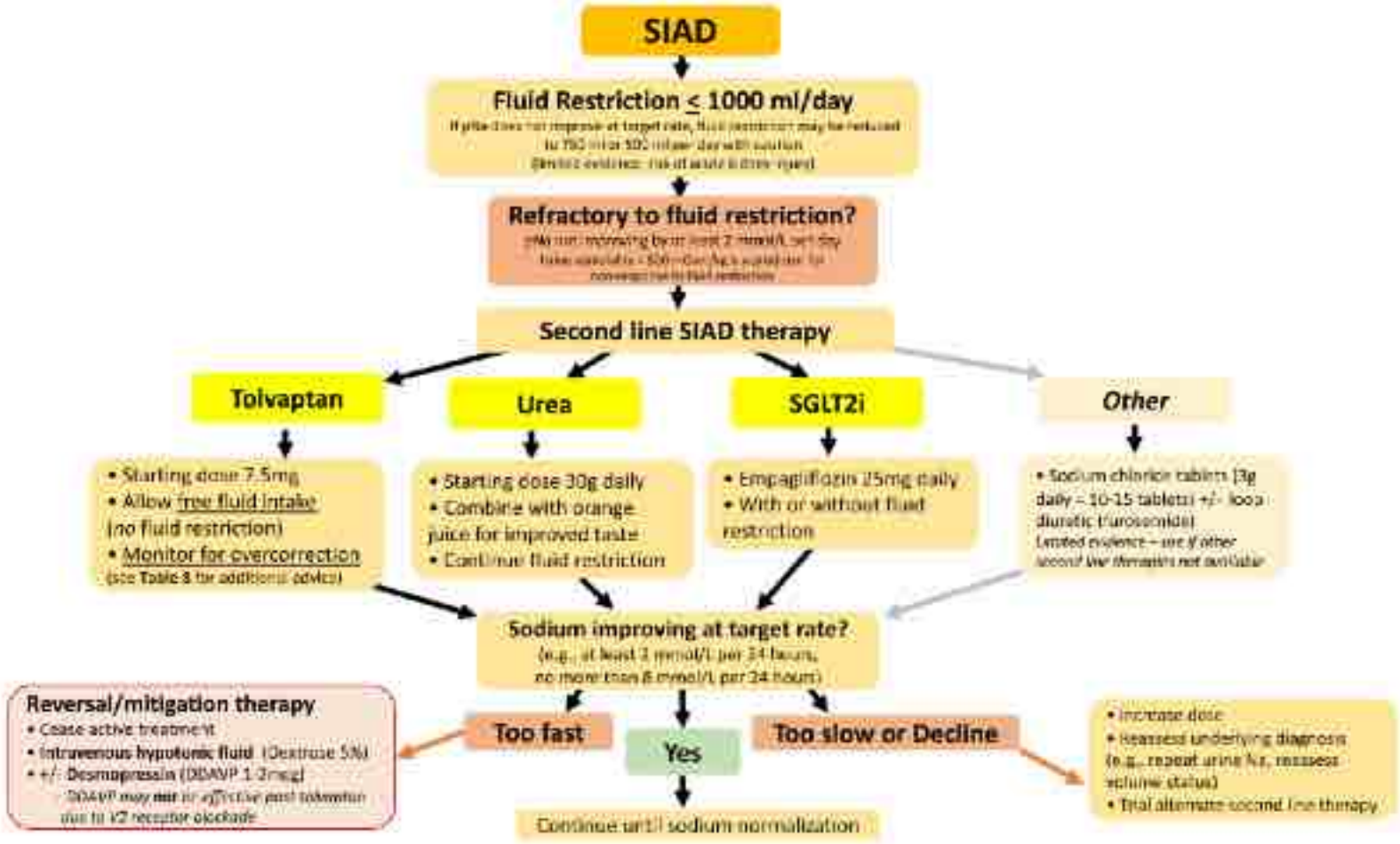


Figure 10. An approach to management of syndrome of inappropriate antidiuresis (SIAD), based on current limited evidence base. pNa, plasma sodium concentration.

Table 4. Formulas for Calculating Initial Saline Infusion Rates.*

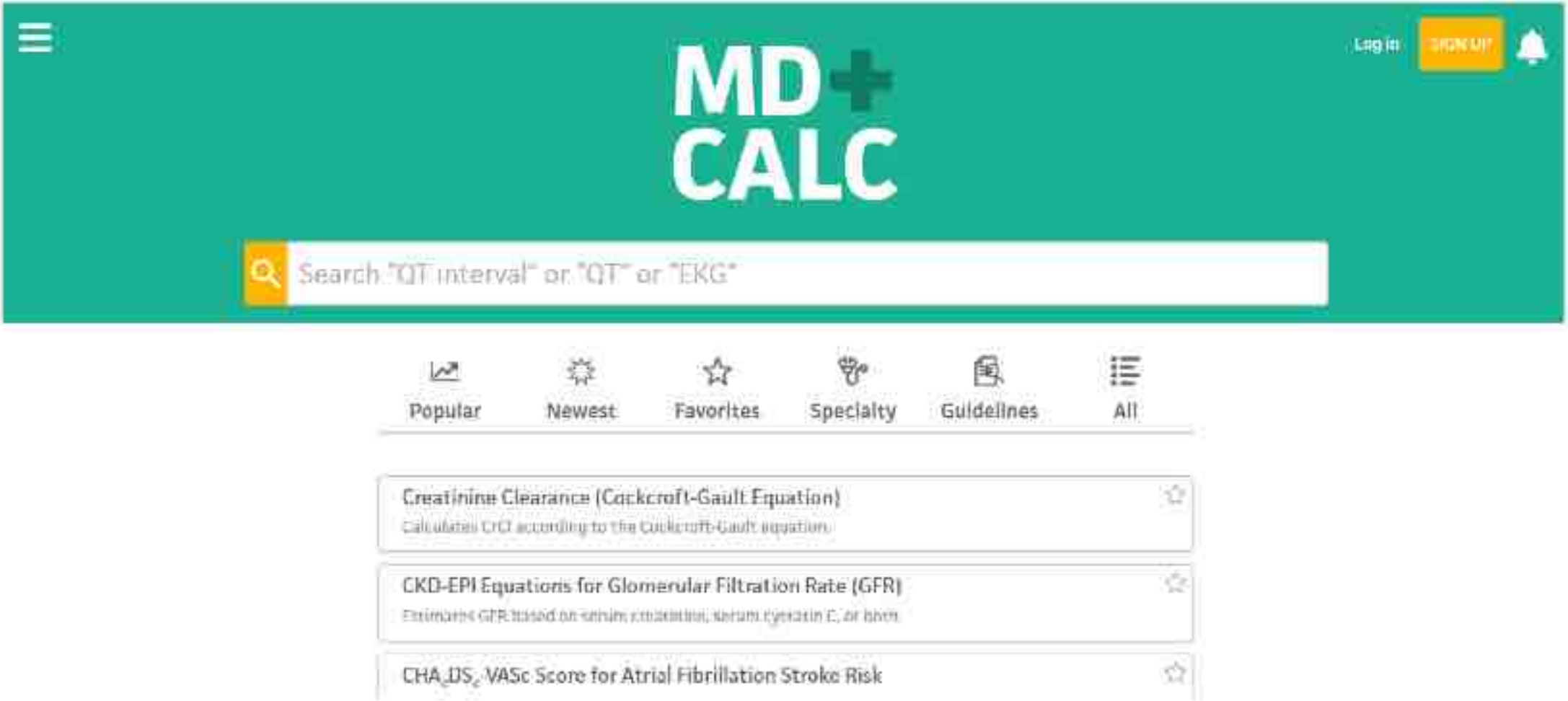
Source	Step 1	Step 2	Example of Rate (ml/hr)
Traditional[1]	$\text{Na required} = \text{TBW} \times ([\text{Na}]_2 - [\text{Na}]_1)$	$\text{Volume (liter)} = \frac{\text{Na required (mmol)}}{513\ \text{mmol/liter}}$	82
Adrogué and Madias[4]	$\Delta[\text{Na}]_1\ \text{(with 1 liter)} = \frac{[\text{Na}]_{\text{inf}} - [\text{Na}]_1}{\text{TBW} + 1}$	$\text{Volume (liter)} = \frac{\text{Desired } \Delta[\text{Na}]_1}{\Delta[\text{Na}]_1\text{(with 1 liter)}}$	107
Barsoum and Levine[39]	$\Delta[\text{Na}]_1 = \frac{(V_{\text{inf}})[\text{Na}]_{\text{inf}} - (V_u)[\text{E}]_{\text{urine}} - (\Delta V)[\text{Na}]_1}{\text{TBW} + \Delta V}$	$\text{Volume (liter)} = \frac{\text{Desired } \Delta[\text{Na}]_1}{\Delta[\text{Na}]_1\ \text{(with 1 liter)}}$	107
Nguyen and Kurtz[40]		$\text{Volume (liter)} = \frac{\text{TBW} \times \left(1 - \frac{[\text{Na}]_1 + 23.8}{[\text{Na}]_2 + 23.8}\right) + V_{\text{input}} - \frac{[\text{E}]_{\text{input}} \times V_{\text{input}}}{[\text{E}]_{\text{urine}}}}{\frac{[\text{E}]_{\text{inf}}}{[\text{E}]_{\text{urine}}} - 1}$	90
Janicic and Verbalis[9]		Rate (ml/hr) is the goal rate of $[\text{Na}]_1$ rise (mmol/liter/hr) per kg of body weight	70

* The examples assume a body weight of 70 kg, current serum sodium ($[\text{Na}]_1$) level of 110 mmol per liter, desired $[\text{Na}]_2$ level of 120 mmol per liter, total body water (TBW) of 42 liters, time of 10 hours, urinary volume of 1 liter, urinary sodium level of 80 mmol per liter, urinary potassium level of 40 mmol per liter, and treatment fluid (infusion) of 513 mmol per liter, where $[\text{Na}]_1$ is the current $[\text{Na}]_1$ and $[\text{Na}]_2$ represents the $[\text{Na}]_1$ level desired after treatment, $\Delta[\text{Na}]_1 = [\text{Na}]_2 - [\text{Na}]_1$, [E] is [Na]+[K]. If the actual rate of correction is different from that predicted, it may be useful to calculate the electrolyte-free water clearance, to help guide treatment. The electrolyte-free water clearance is calculated as

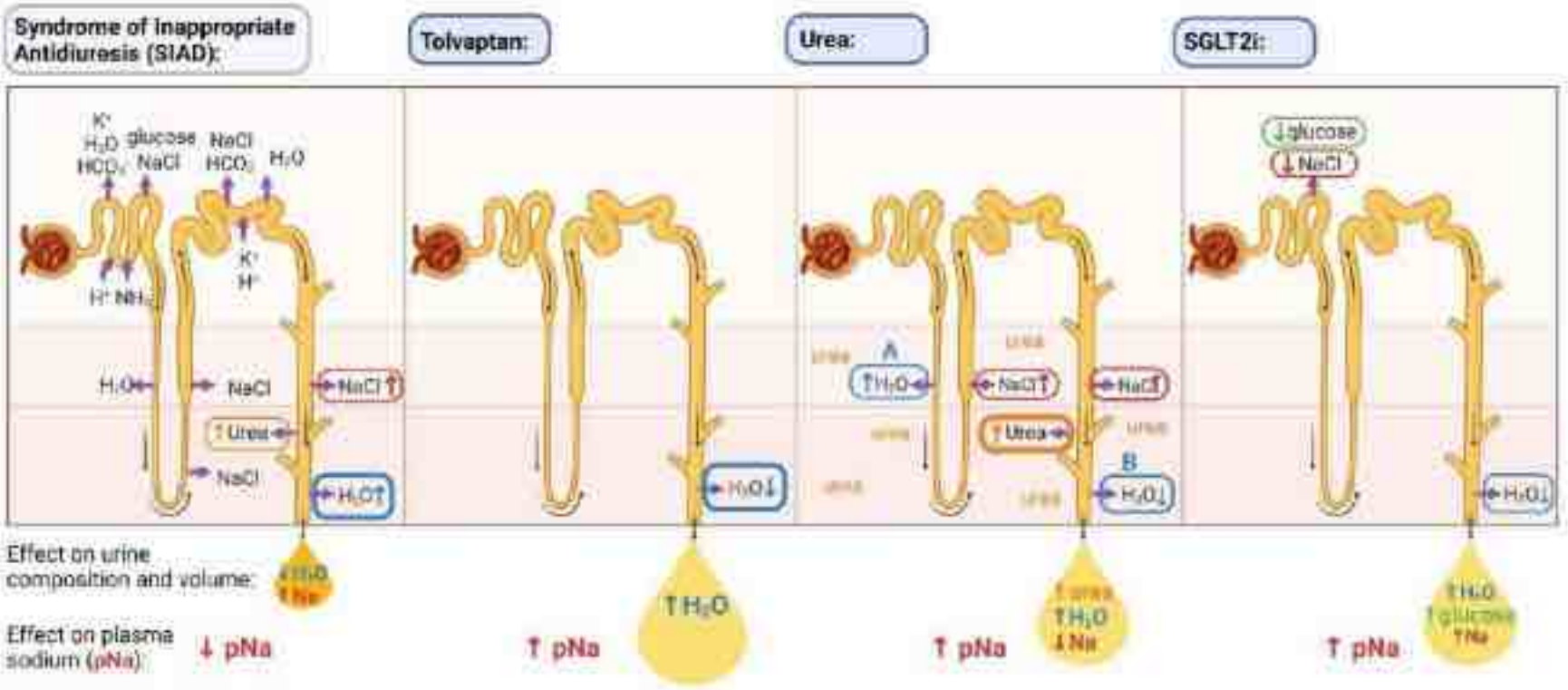
$$C^{e}_{H_2O} = V\left(1 - \frac{U_{Na} + U_k}{P_{Na}}\right),$$

where $C^{e}_{H_2O}$ denotes electrolyte-free water clearance, U_{Na} urinary sodium, U_k urinary potassium, and P_{Na} plasma sodium. If the clearance value is greater than 0, then ongoing losses of free water are contributing to the rise in $[\text{Na}]_1$. In all cases, the formulas are used only to estimate the initial infusion rate; the rate must be adjusted on the basis of the measured rate of the rise in serum sodium. Inf denotes infused fluid.

https://www.mdcalc.com/calc/480/sodium-correction-rate-hyponatremia-hypernatremia




Back
Sodium Correction Rate
CALCULATOR
Weight
80
kg
Serum sodium
120
mEq/L
Fluid type
5% saline (856 mmol/L Na)
3% saline (513 mmol/L Na)
2% saline (342 mmol/L Na)
Normal saline (154 mmol/L Na)
Lactated Ringer's (130 mmol/L Na)
Rate of sodium correction
To avoid central pontine myelinolysis, sodium should not be corrected
0.5
mEq/L/hr
RESULT
62 mL/hr
Fluid rate to increase Na by 0.5 mmol/L/hr


Syndrome of Inappropriate Antidiuresis (SIAD):
Tolvaptan:
Urea:
SGLT2i:
K+
H2O
HCO3-
glucose
NaCl
NaCl
HCO3-
H2O
H+ NH3
K+
H+
H2O
NaCl
NaCl
↑ Urea
NaCl
H2O↑
H2O↓
A
↑H2O
NaCl↑
NaCl
↑ Urea
B
H2O↓
↓glucose
↓NaCl
H2O↓
Effect on urine composition and volume:
↑ H2O
↑ pNa
↑ H2O
↑ urea
↑H2O
↓Na
↑H2O
↑glucose
↑Na
Effect on plasma sodium (pNa):
↓ pNa
↑ pNa
↑ pNa
↑ pNa
Key: Na = Sodium, H2O = Water, urea, glucose

HyperNatremia

Tonocity vs Osmolality

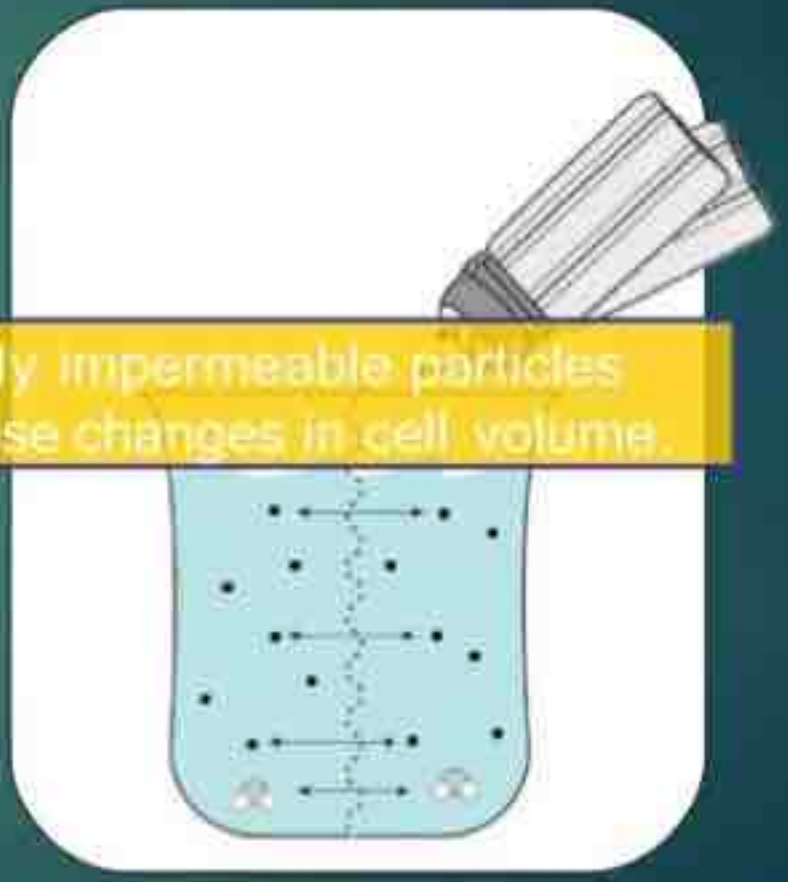
- Tonocity means effective osmolality
- Effective osmoles: Na and its anion

$$\text{plasma } [Na^+] = \frac{\text{total body } (Na^+ + K^+)}{\text{total body } H_2O}.$$

- HyperNa =Na>145 mmol/l

Tonicity versus Osmolality

- Osmolality
  - Total concentration of all particles in solution.
- Tonicity
  - Concentration of only the osmotically active particles.
  - Only impermeable particles contribute to tonicity.



Tonicity versus Osmolality

	OSMOLARITY		
TONICITY	Hyposmotic	Isosmotic	Hyperosmotic
Hypotonic	√	√	√
Isotonic		√	√
Hypertonic			√

Renal Water Excretion

Limitation of the previous equation:

- UREA is included in computing for urine osmolality!
  - ineffective osmole, does not influence serum Na+ concentration or the release of AVP

Electrolyte Free Water clearance [$C_{water(e)}$]

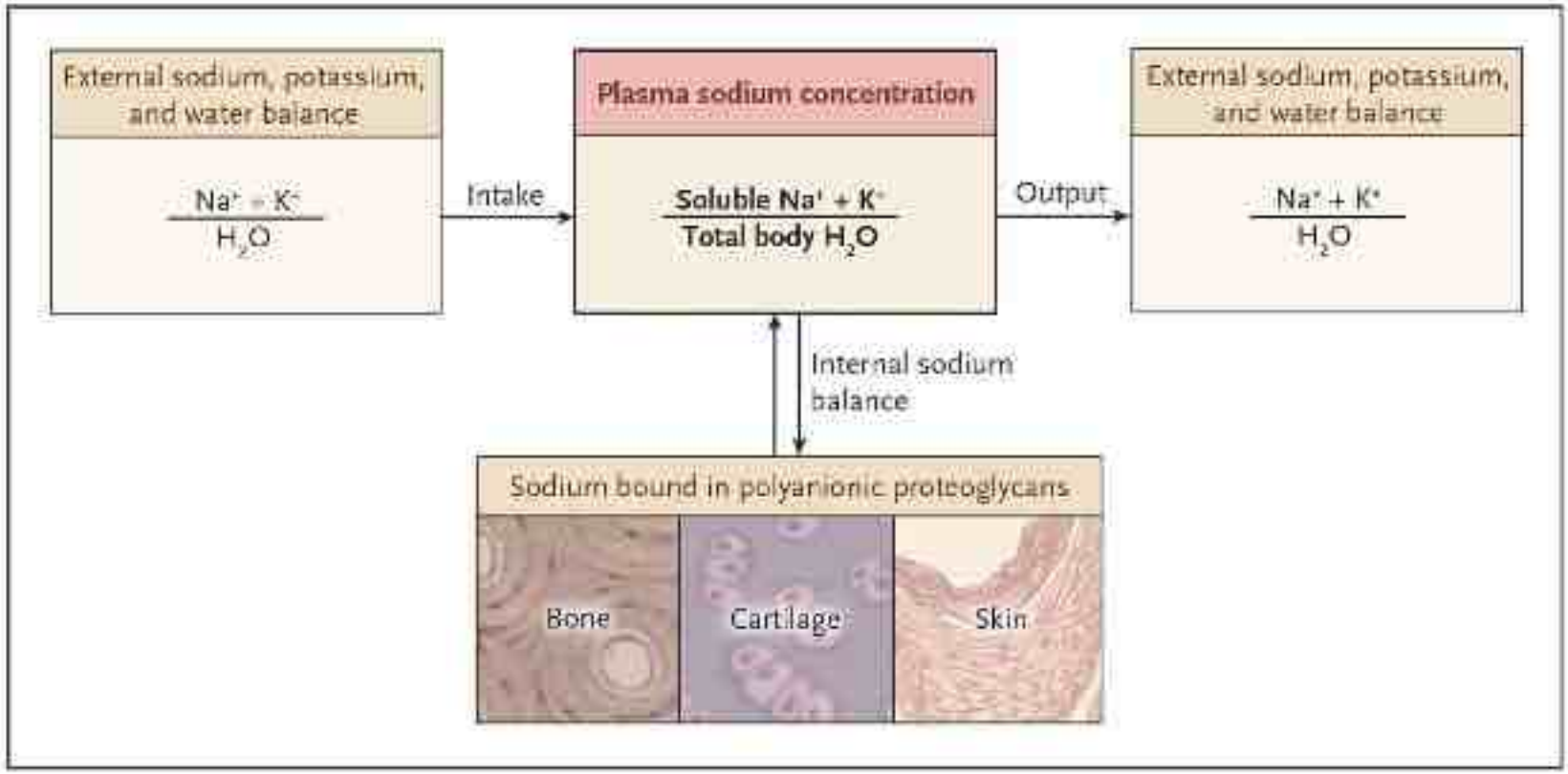
Better predicts changes in serum Na+

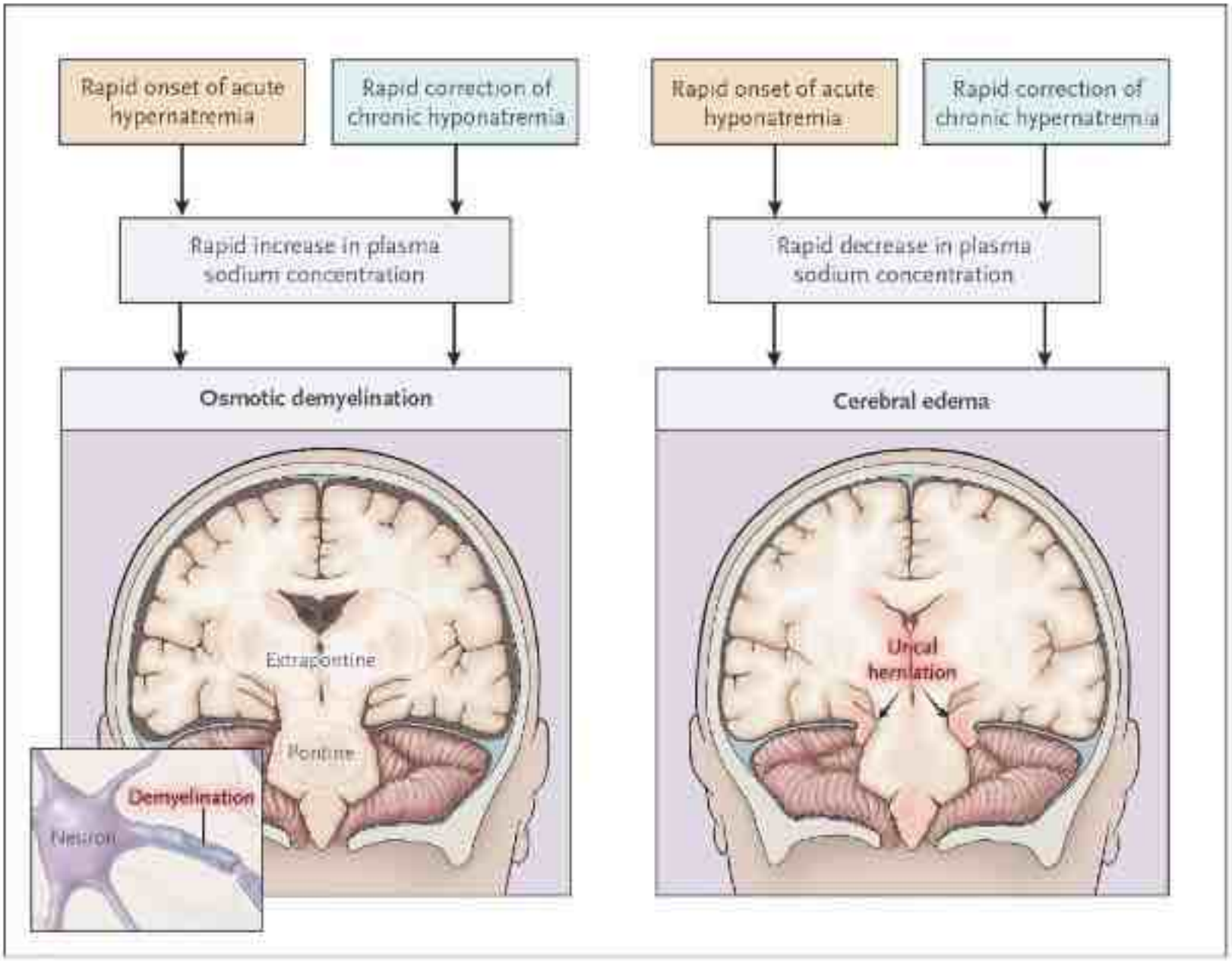
$$C_{water}(e) = V\left(1 - \frac{U_{Na} + U_K}{P_{Na}}\right)$$

1. If **UNa + UK < PNa**, then Cwater(e) is positive and **serum [Na+]** ↑
2. If **UNa + UK > PNa**, then Cwater(e) is negative and **serum [Na+]** ↓

Disorders of water handling = Hyponatremia & Hypernatremia

Disorders of sodium handling = Hypovolemia & Hypervolemia


External sodium, potassium, and water balance
$\frac{Na^+ + K^+}{H_2O}$
Intake
Plasma sodium concentration
$\frac{\text{Soluble } Na^+ + K^+}{\text{Total body } H_2O}$
Output
External sodium, potassium, and water balance
$\frac{Na^+ + K^+}{H_2O}$
Internal sodium balance
Sodium bound in polyanionic proteoglycans
Bone
Cartilage
Skin


Rapid onset of acute hypernatremia
Rapid correction of chronic hyponatremia
Rapid increase in plasma sodium concentration
Osmotic demyelination
Extrapontine
Pontine
Demyelination
Neuron
Rapid onset of acute hyponatremia
Rapid correction of chronic hypernatremia
Rapid decrease in plasma sodium concentration
Cerebral edema
Uncal herniation

Criteria	Classification	Value
Absolute serum sodium concentration	Mild	146–150 mmol/L
	Moderate	151–155 mmol/L
	Severe	> 155 mmol/L [38]
	Extreme	> 190 mmol/L [3]
Time of development (cutoff 48 hours)	Acute vs. Chronic	
Clinical assessment of volume status	Hypovolemic	
	Euvolemic	
	Hypervolemic	

Signs and symptoms

Characteristics of hypernatremia	Symptoms related to the characteristics of hypernatremia
Cognitive dysfunction and symptoms associated with neuronal cell shrinkage	Lethargy Obtundation (depression on sensorium) Confusion Abnormal speech Irritability Seizures (unusual in adults) Nystagmus Myoclonic jerks Muscle spasticity (unusual in adults) Focal neurologic deficits Nausea or vomiting
Dehydration or clinical signs of volume depletion	Orthostatic blood pressure changes Tachycardia Oliguria Dry oral mucosa Abnormal skin turgor Dry axillae Intense thirst
Other clinical findings	Weight loss Generalized weakness Fever Labored respiration

- Severe manifestations of acute hypernatremia are usually seen at serum sodium concentrations above 158 mEq/L

- Hypernatremia is primarily caused by water loss
- Sodium (Na) excess being a less common factor
- 6%-42% of ICU patients and is generally associated with a 50%-60% increase in short-term mortality
- Pre-ICU admission hypernatremia is about 4%
- Even mild hypernatremia (Na <150 mmol/L) is linked to more than a 20% 30-day mortality rate
- Both IAH and PAH independently predict mortality and longer ICU stays

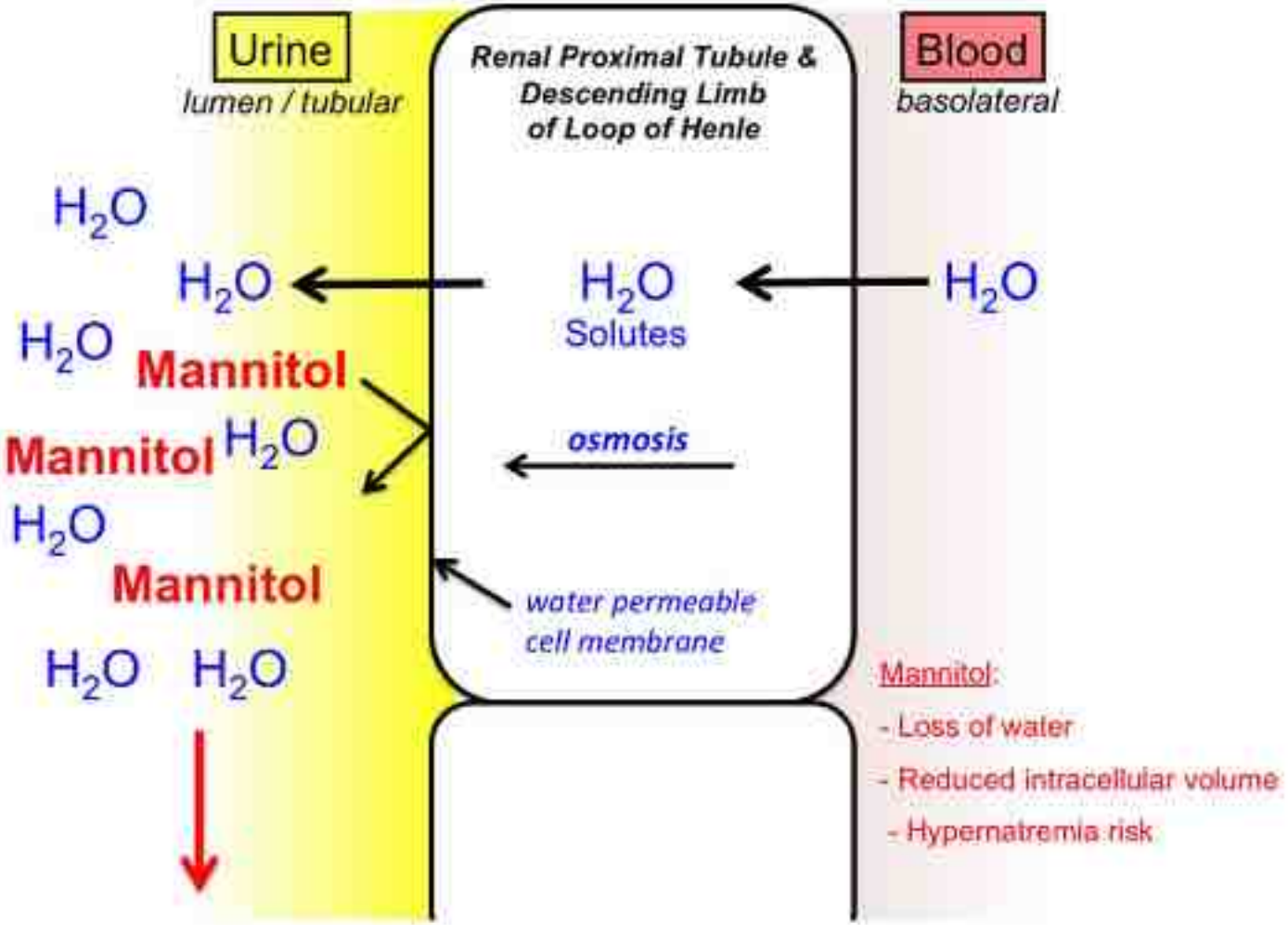
- ↑ plasma tonicity → ↑AVP release and ↑ thirst
- Hypernatremia doesn't occure if the individual can sense and act on thirst
- Infants, individuals with altered sensorium, intubated pts, ill and alone .. are susceptible to HyperNa.
- HyperNa is present on 1/admission or 2/hospitally acquired: the first is geriatric disorder and second is iatrogenic.
- essential hypernatremia: rarely defect in thirst perception caused by hypothalamic lesions leads to reduced water ingestion.

Causes of HyperNatremia

Cause	Proximate Cause	Findings Supporting Diagnosis
Inadequate water intake	Lack of access to water	• Altered sensorium, immobility, endotracheal intubation • Chronic care facility residence • Fluid prescription that does not take into account insensible losses • U_{Osm} > 600 mOsm/kg H_2O
Extrarenal hypotonic fluid loss	GI losses or perspiration	• History of diarrhea, febrile illness, gastric suction, or enteric fistula • U_{Osm} > 600 mOsm/kg H_2O
Renal concentrating defect	Diuretics	• History of loop diuretic use • Isosthenuric urine
	Osmotic diuresis	• Hyperglycemia with glucosuria • Urea-induced osmotic diuresis • Isosthenuric urine (eg, recovery from ATN)
	Central diabetes insipidus	• Presence of brain trauma, surgery, tumor, infiltrative disease, or infection including tuberculosis • Maximally or submaximally dilute urine • Persistently dilute urine during water deprivation test • Low copeptin levels • U_{Osm} increases in response to desmopressin
	Nephrogenic diabetes insipidus	• Treatment with lithium or demeclocycline, hypercalcemia, hypokalemia, renal tubulointerstitial disease, especially sickle cell nephropathy and obstructive uropathy • U_{Osm} < 300 mOsm/kg H_2O • Persistently dilute urine during water deprivation test • High copeptin levels • U_{Osm} fails to increase in response to desmopressin
Excessive salt intake	Hypertonic fluid administration	• Receipt of hypertonic sodium bicarbonate solution during cardiac arrest or hypertonic saline solution • History of dilution error for powdered feeding formulas in infants • Administration of TPN or concentrated enteral tube feeds • U_{Osm} > 600 mOsm/kg H_2O • U_{Na} > 100 mEq/L

Note: Even if not specifically noted, impaired thirst or access to water is typically also present.
Abbreviations: ATN, acute tubular necrosis; GI, gastrointestinal; TPN, total parenteral nutrition; U_{Na}, urine sodium concentration; U_{Osm}, urine osmolality.

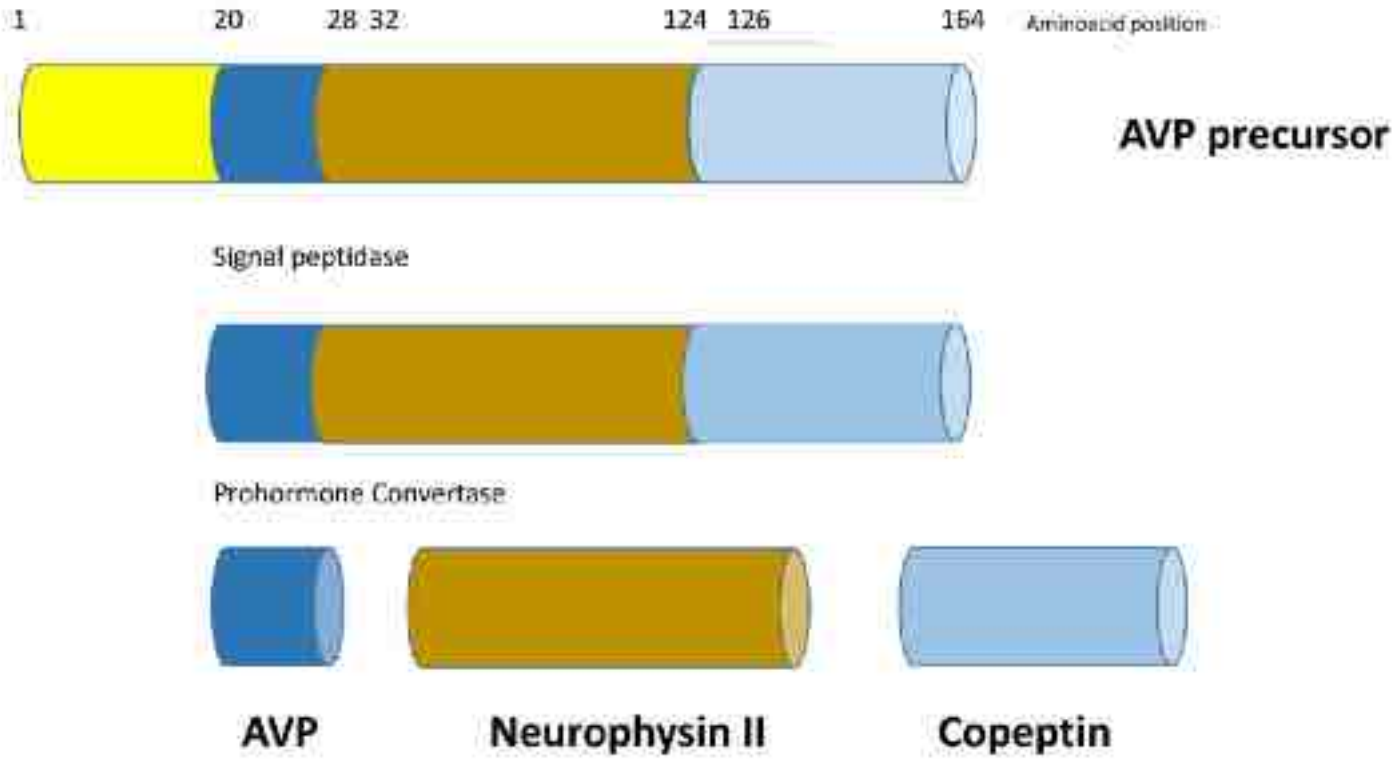
Osmotic diuresis



Measurement of AVP?

Measurements of the more stable vasopressin prohormone carboxy-terminal cleavage peptide, copeptin, have been used to differentiate between primary polydipsia, central DI, andnephrogenic DI.

Copeptin testing may supplant use of the water deprivation test.



PICS

- persistent inflammation, immunosuppression and catabolism syndrome (PICS .
- hypernatremia can lead to inflammation and catabolism via hyperosmolar cell stress.
- profound catabolism can lead to hypernatremia via urea-induced osmotic diuresis.

Treatment

- Chronic HyperNa > 48 hrs
- Each + balance of 3 mL of electrolyte-free water/kg → ↓1mmol/l in Na
- 1.35 ml/kg of D/W 5% up to 150 ml /hr
- Free-water deficit: TBW (L) × (([Na+]/140 mEq/L) − 1)
- In chronic HyperNa correction of 10 mEq/L in 24 hours is safe.

Salt poisoning

- Mortality is up to 50% depends to time of treatment.
- lower the plasma sodium as fast as possible with hypotonic intravenous fluids or emergency hemodialysis.

AVP deficiency or resistance

- D/W 5%, IV , 3 to 6 mL/kg/hour up to a maximum of 666 mL/hour.
- BS and Na motitored q1-3 hr
- When Na reaches to 145 mmol/l, infusion rate ↓ to 1 ml/kg/hr until Na =140.
- Goal is decreasing Na by 2mmol/l/hr and normalizes Na in less than 24 hrs.
- D/W 2.5% in cases of hyperglycemia is recomeneded.
- Risk of hyperglycemia and water loss due to glycosuria in rapid dextrose infusion.
- AVP is also administered.

hypernatremia due to correction of hyperglycemia

- In pts < 40 yrs old rec. slow correction as chronic HyperNa
- In pts ≥ 40 yrs old rec. rapid correction as acute HyperNa.
- Infusion of 0.45% saline at 6 to 12 mL/kg/hr will provide the same amount of electrolyte-free water as 3 to 6 mL/kg/hr of D/W5% .
- serial calculations of the "effective" osmolality (2 x Serum sodium + Serum glucose/18) to monitor the course in plasma tonicity.
- Maximum rate of glucose metabolism is 10 mg/kg/min (+ High doses of insulin) = 600 ml/ hr D/W5%.
- 1/3-2/3 iv fluid: 3.3% dextrose and 0.3% sodium chloride contains only 51 mmol/L of sodium, with osmolarity of 269 mOsmol/L.

$$\text{Water deficit} = \text{Current TBW} \times \left(\frac{\text{Serum [Na]}}{140} - 1\right)$$

Estimate water deficit

- Serves as a guide in **INITIAL** therapy
- May use either of the two formula

1. **Edelman Formula**

   Water deficit* = current TBW x $\left(\frac{\text{serum Na}}{140} - 1\right)$

   *assumes no ongoing fluid/electrolyte losses

   *assumes baseline Na of 140 is the target

Total Body Water (TBW) = 60% of lean body weight

- 60% LBW Young Men (≤65 yrs old)
- 50% LBW Young Women (≤65 yrs old)
- 50% LBW Elderly Men (>65 yrs old)
- 45% LBW Elderly Women (>65 yrs old)

- it is probably reasonable to use values approximately 10 percent lower in hypernatremic patients who are water depleted.

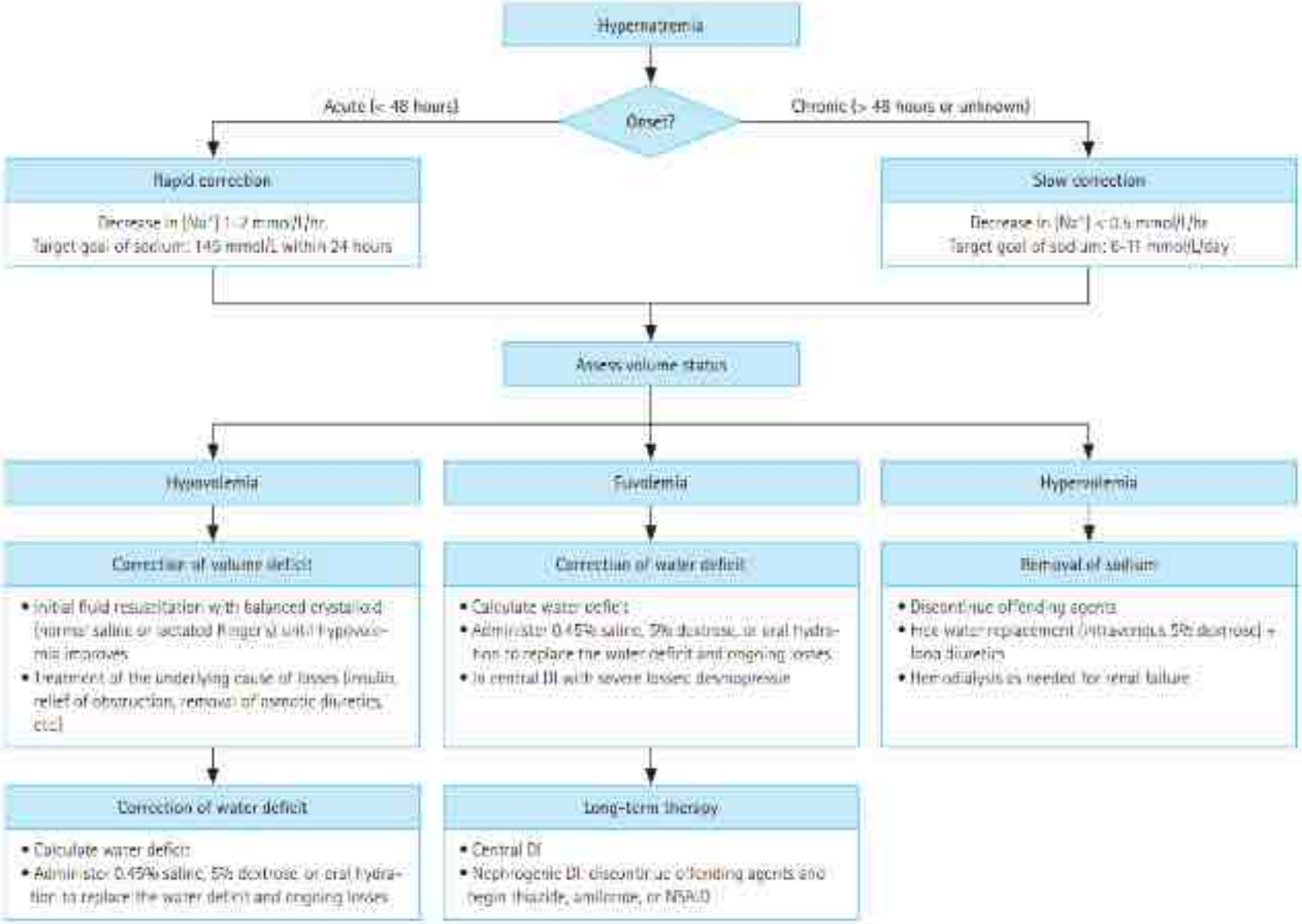

Hypernatremia
Onset?
Acute (< 48 hours)
Chronic (> 48 hours or unknown)
Rapid correction
Decrease in [Na+] 1–2 mmol/L/hr
Target goal of sodium: 145 mmol/L within 24 hours
Slow correction
Decrease in [Na+] < 0.5 mmol/L/hr
Target goal of sodium: 6–11 mmol/L/day
Assess volume status
Hypovolemia
Euvolemia
Hypervolemia
Correction of volume deficit
• Initial fluid resuscitation with balanced crystalloid (normal saline or lactated Ringer's) until hypovolemia improves
• Treatment of the underlying cause of losses (insulin, relief of obstruction, removal of osmotic diuretics, etc.)
Correction of water deficit
• Calculate water deficit
• Administer 0.45% saline, 5% dextrose, or oral hydration to replace the water deficit and ongoing losses
• In central DI with severe losses, desmopressin
Removal of sodium
• Discontinue offending agents
• Free water replacement (intravenous 5% dextrose) + loop diuretics
• Hemodialysis is needed for renal failure
Correction of water deficit
• Calculate water deficit
• Administer 0.45% saline, 5% dextrose, or oral hydration to replace the water deficit and ongoing losses
Long-term therapy
• Central DI
• Nephrogenic DI: discontinue offending agents and begin thiazide, amiloride, or NSAID

Table 2. Treatment and Limits of Correction of Severe Hypernatremia.*

Duration	Related Behavior or Condition	Clinical Features	Initial Therapeutic Goal	Limit of Correction and Management of Overcorrection
Minutes to hours	Acute salt poisoning associated with accidental salt ingestion or salt ingestion in attempted suicide, use of parenteral hypertonic saline, dialysis errors	Seizures, coma, hypertonia, high fever, intracranial hemorrhages, thrombosis of dural sinuses	Rapid infusion of 5% dextrose in water plus emergency hemodialysis to immediately restore normonatremia	Excessive correction not known to be harmful
1–2 days	Unreplaced water from urinary losses associated with glycosuria, neurogenic or nephrogenic diabetes insipidus	Persistent coma, brain demyelination	Decrease plasma sodium concentration by 2 mmol/liter/hr until plasma sodium concentration is 145 mmol/liter; stop or replace water losses	Excessive correction not known to be harmful
Unknown or ≥2 days	In children: diarrhea, inability to breast-feed; in adults: hypodipsia, impaired mental status	Obtundation or coma, rehydration-associated seizures and cerebral edema as a result of rapid correction in children	In children: decrease plasma sodium concentration by 0.3 mmol/liter/hr; in adults: decrease plasma sodium concentration by 10 mmol/liter/day; replace water losses	In children: avoid decreasing plasma sodium concentration by >0.5 mmol/liter/hr; 3% saline for seizures associated with rehydration; in adults: not known

* Severe hypernatremia is defined as a plasma sodium concentration above 150 mmol per liter. In the absence of urinary loss of water, 3 ml of electrolyte-free water per kilogram of body weight will decrease the plasma sodium concentration by approximately 1 mmol per liter.

Is the rate of correction of hypernatremia associated with clinical outcomes?

CJASN
Clinical Journal of American Society of Nephrology

Methods and Cohort

MIMIC

Data from Medical Information Mart for Intensive Care-III (MIMIC-III)

Na >155 mmol/L

On admission
N = 122

Hospital-acquired
N = 327

Rapid correction (>0.5 mmol/L/hr)

VS

Slow correction (≤0.5 mmol/L/hr)

Findings

Rapid Correction		Slow Correction
30 day mortality 25%	NS P=0.80	30 day mortality 28%
30 day mortality 44%	NS P=0.50	30 day mortality 40%

0 cases of cerebral edema, seizures or alteration in consciousness attributable to rapid hypernatremia correction

Conclusions Rapid correction of hypernatremia was not associated with a higher risk for mortality, seizures, alteration of consciousness and/or cerebral edema in critically ill adults with either admission or hospital-acquired hypernatremia.

Kinsuk Chauhan, Pattharawin Pattharanitima, Niralee Patel, Aine Duffy, et al. ***Rate of Correction of Hypernatremia and Health Outcomes in Critically Ill Patients.*** CJASN doi: 10.2215/CJN.10640918. **Visual Abstract by Michelle Lim, MBChB**

MED CALC

https://www.mdcalc.com/calc/480/sodium-correction-rate-hyponatremia-hypernatremia


وجعلنا من الماء كل شيء حي