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جان و خرد
کز این برتر
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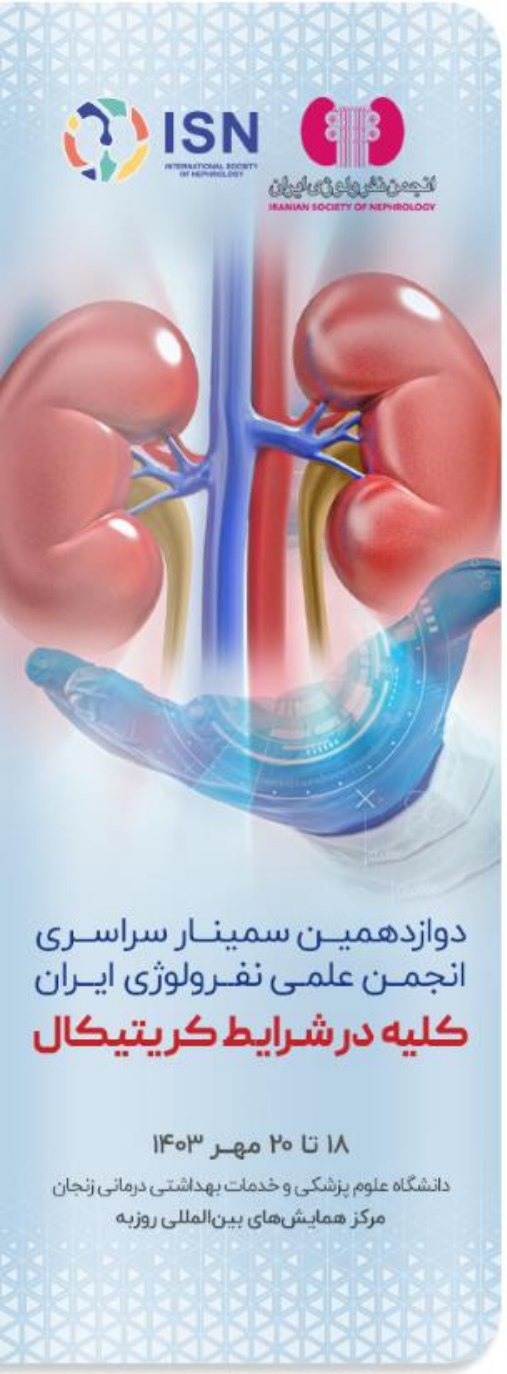
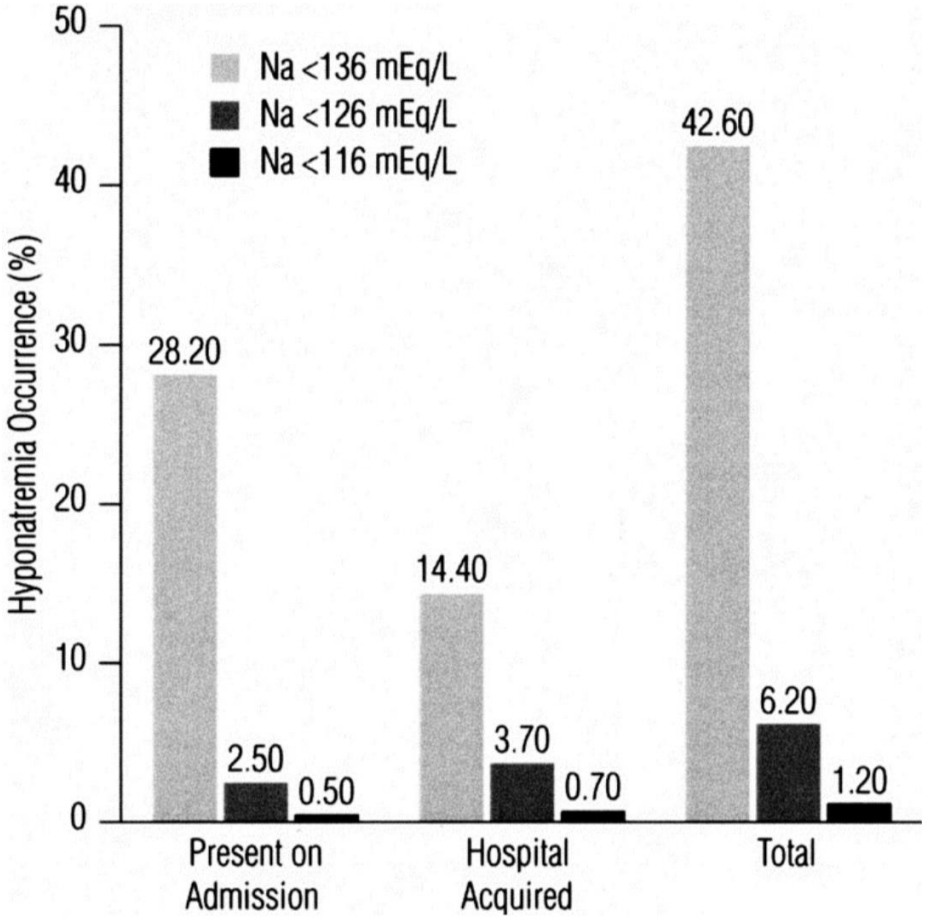
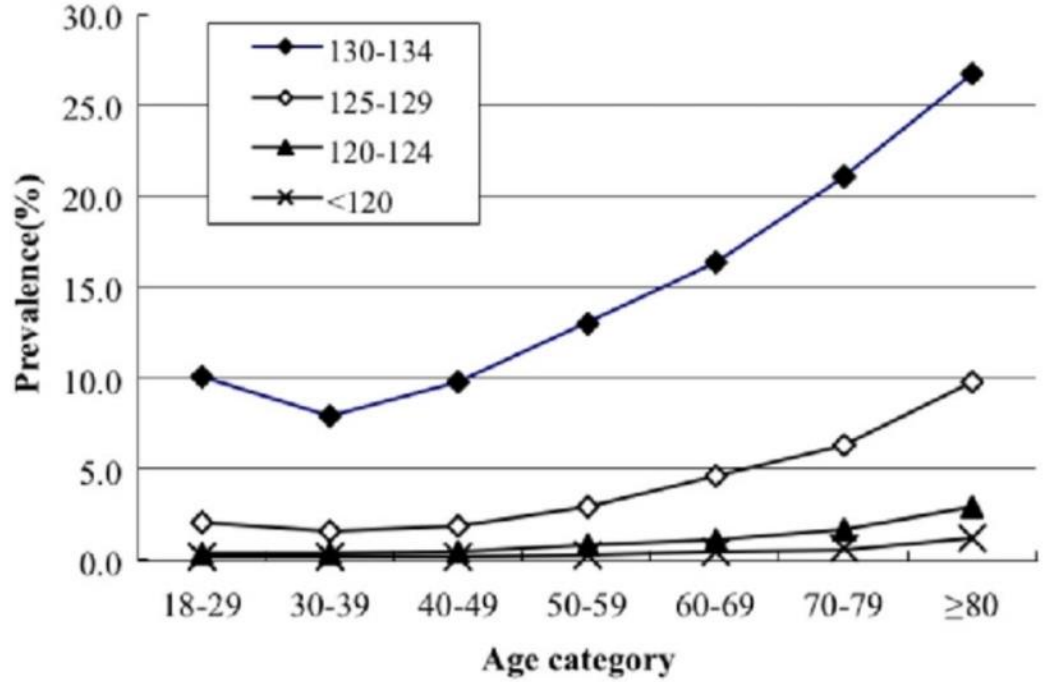


دکتر علی صدوق

استادیار گروه نفرولوژی
دانشگاه علوم پزشکی اراک

Dysnatremia in Critically ill Patients


Na <136 mEq/L
Na <126 mEq/L
Na <116 mEq/L
Hyponatremia Occurrence (%)
50
40
30
20
10
0
28.20
2.50
0.50
14.40
3.70
0.70
42.60
6.20
1.20
Present on Admission
Hospital Acquired
Total


130-134
125-129
120-124
<120
Prevalence(%)
30.0
25.0
20.0
15.0
10.0
5.0
0.0
18-29
30-39
40-49
50-59
60-69
70-79
≥80
Age category

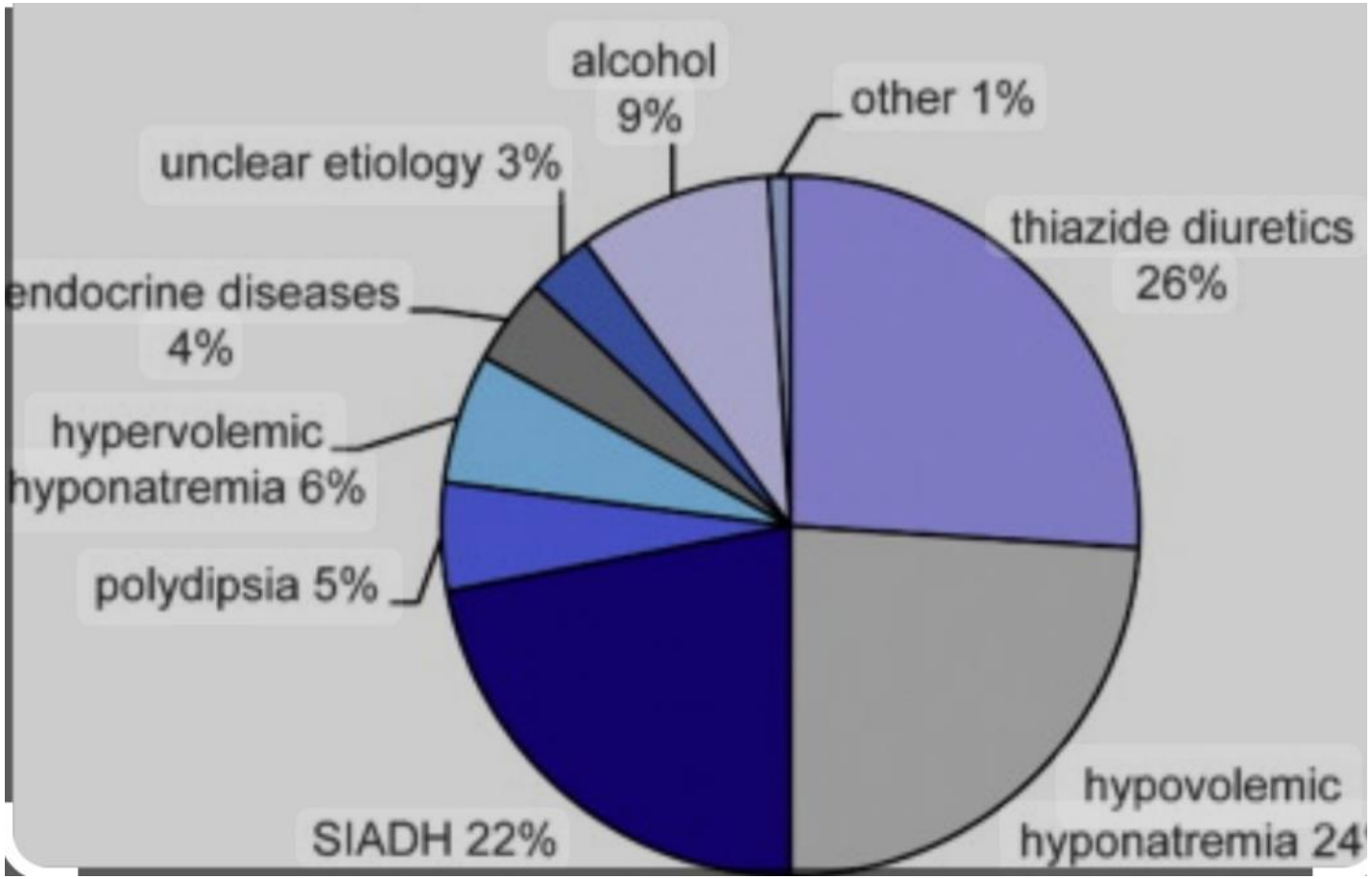

alcohol
9%
other 1%
unclear etiology 3%
thiazide diuretics
26%
endocrine diseases
4%
hypervolemic
hyponatremia 6%
polydipsia 5%
SIADH 22%
hypovolemic
hyponatremia 24

Table 23-1 Pathophysiologic factors that diminish renal water excretion

Diminished generation of free water in the loop of Henle and distal tubule
- A. Decreased fluid delivery to these segments
  1. Effective circulating volume depletion
  2. Renal failure
- B. Inhibition of NaCl reabsorption by diuretics

Enhanced water permeability of the collecting tubules due to the presence of ADH
- A. Syndrome of inappropriate ADH secretion
- B. Effective circulating volume depletion
- C. Adrenal insufficiency
- D. Hypothyroidism

Table 23-2 Etiology of hyponatremia and hypoosmolality

Disorders in which renal water excretion is impaired
- A. Effective circulating volume depletion
  1. Gastrointestinal losses: vomiting, diarrhea, tube drainage, bleeding, intestinal obstruction
  2. Renal losses: diuretics, hypoaldosteronism, Na^+-wasting nephropathy
  3. Skin losses: ultramarathon runners, burns, cystic fibrosis
  4. Edematous states: heart failure, hepatic cirrhosis, nephrotic syndrome with marked hypoalbuminemia
  5. K^+ depletion
- B. Diuretics
  1. Thiazides in almost all cases
  2. Loop diuretics
- C. Renal failure
- D. Nonhypovolemic states of ADH excess
  1. Syndrome of inappropriate ADH secretion
  2. Cortisol deficiency
  3. Hypothyroidism
- E. Decreased solute intake
- F. Cerebral salt wasting

Disorders in which renal water excretion is normal
- A. Primary polydipsia
- B. Reset osmostat: effective volume depletion, pregnancy, psychosis, quadriplegia, malnutrition

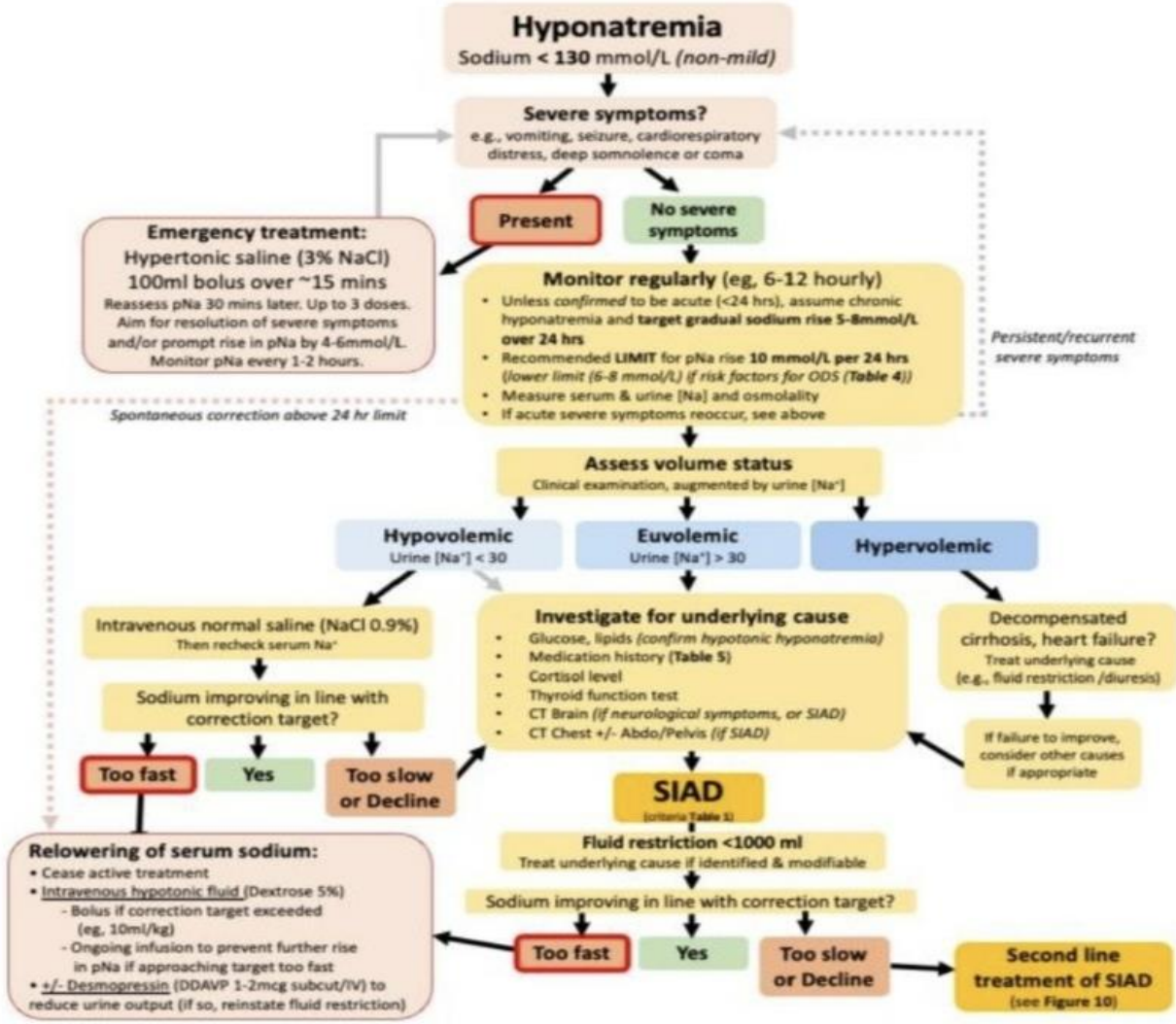
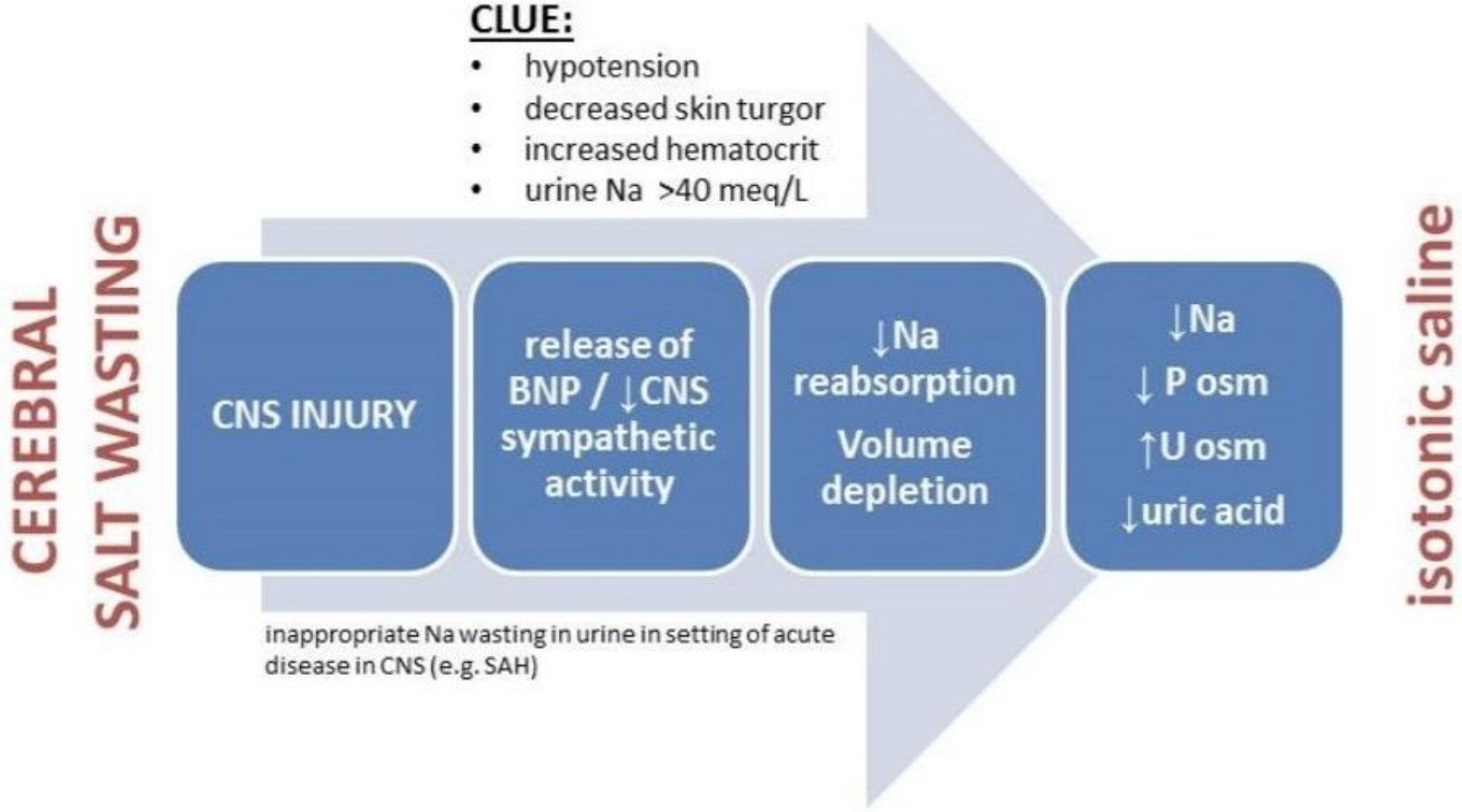


Figure 8. Diagnosis and initial management of nonmild hyponatremia while confirming a diagnosis of SIAD. CT, computed tomography; IV, intravenous; Na^+, sodium; NaCl, sodium chloride; ODS, osmotic demyelination syndrome; pNa, plasma sodium concentration; SIAD, syndrome of inappropriate antidiuresis; subcut, subcutaneous. Original figure, with reference to guidelines by Spasovski 2014 and Verbalis 2013 (3, 15).


CLUE:
• hypotension
• decreased skin turgor
• increased hematocrit
• urine Na >40 meq/L
CEREBRAL SALT WASTING
CNS INJURY
release of BNP / ↓CNS sympathetic activity
↓Na reabsorption
Volume depletion
↓Na
↓ P osm
↑U osm
↓uric acid
isotonic saline
inappropriate Na wasting in urine in setting of acute disease in CNS (e.g. SAH)

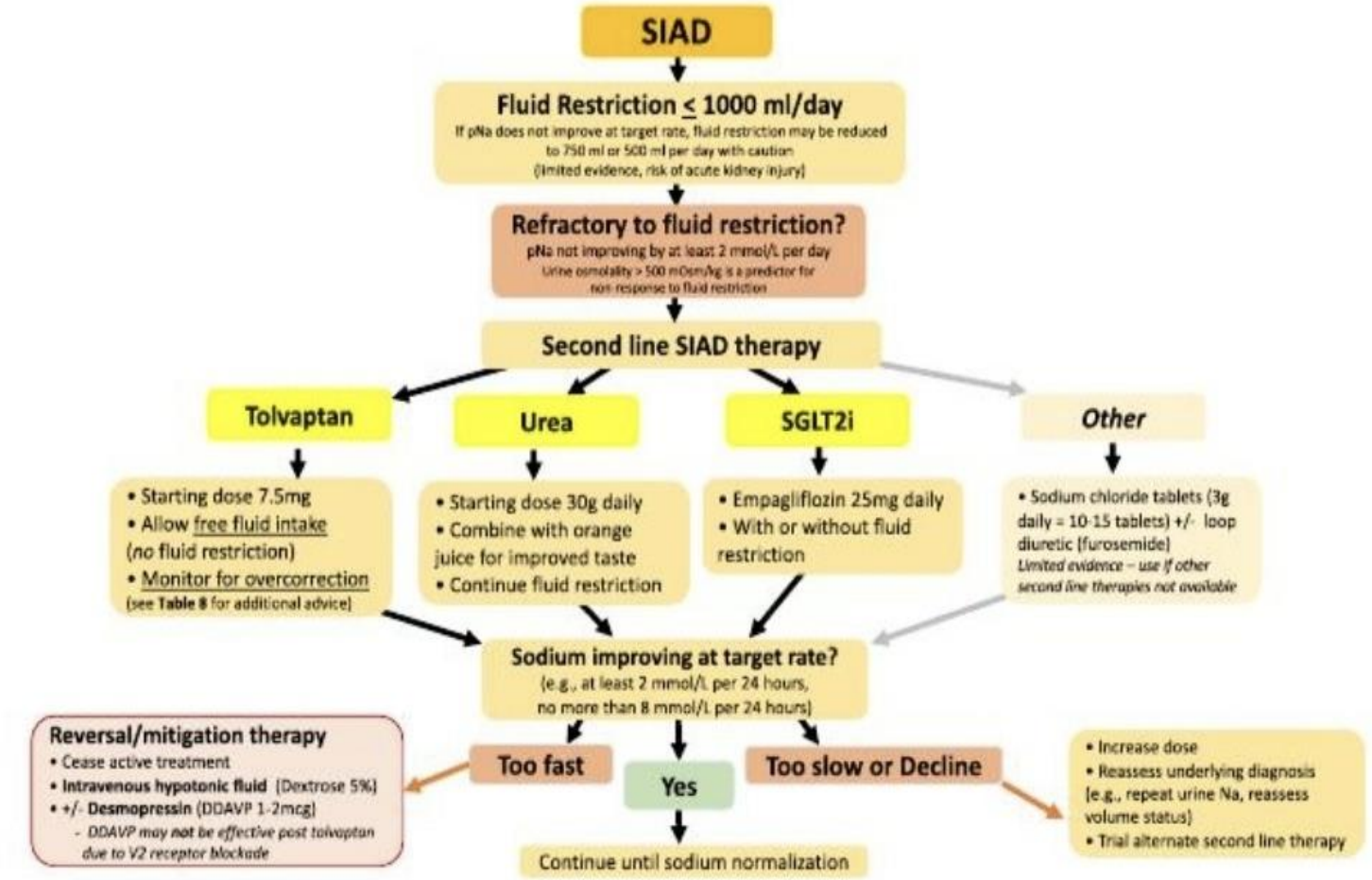


Figure 10. An approach to management of syndrome of inappropriate antidiuresis (SIAD), based on current limited evidence base. pNa, plasma sodium concentration.

Box 3. Diagnostic Criteria and Clinical Data Consistent With SIADH

Bartter & Schwartz Criteria for SIADH

- Hypotonic hyponatremia (effective S_{Osm} < 275 mOsm/kg H_2O)
- Euvolemia
- Less than maximally dilute urine (U_{Osm} > 100 mOsm/kg H_2O)
- Elevated urine sodium excretion commensurate with lack of avid sodium retention during normal intake of sodium and water (U_{Na} > 30 mEq/L)
- Absence of advanced kidney disease, cirrhosis, or heart failure
- Absence of alternative causes of euvolemic hypotonic hyponatremia with less than maximally dilute urine including but not limited to hypothyroidism, glucocorticoid insufficiency, or diuretic use

Additional Data Supporting Diagnosis of SIADH

- Serum uric acid < 4 mg/dL
- Fractional excretion of uric acid > 10%
- Worsening of hyponatremia with IV normal saline solution infusion
- Plasma vasopressin or copeptin level inappropriately elevated relative to serum osmolality
- Abnormal response to water load (excretion of < 80% of 20 mL/kg load in 4 h with failure to dilute urine to <100 mOsm/kg H_2O)

Abbreviations: IV, intravenous; S_{Osm}, serum osmolality; U_{Na}, urine sodium concentration; U_{Osm}, urine osmolality; SIADH, syndrome of inappropriate antidiuretic hormone secretion.

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Table 2 | Diagnostic criteria for the syndrome of inappropriate antidiuresis

Essential criteria

- Plasma sodium <135 mEq/l
- Plasma osmolality <275 mOsm/kg
- Clinical euvolemia
- Urine osmolality >100 mOsm/kg
- Urine sodium >30 mEq/l with normal dietary sodium intake
- Normal kidney, adrenal, and thyroid function
- No recent diuretic use

Supplemental criteria

- Plasma uric acid <4 mg/dl
- Blood urea nitrogen <10 mg/dl
- Fractional excretion of sodium >1%
- Fractional excretion of urea >55%
- Hyponatremia improves with fluid restriction
- Hyponatremia fails to correct with administration of NaCl 0.9%
- Abnormal water loading test (<80% excretion of a water load of 20 ml/kg over 4 h)
- Elevated plasma vasopressin levels despite plasma hypotonicity and clinical euvolemia

Kidney International (2020) **98,** 870–882

Table 5. Medications that can cause hypotonic hyponatremia

- AVP release stimulants or potentiators
  - Antidepressants
    - SSRIs and SNRIs (on initiation (78))
    - Tricyclics (eg, amitriptyline)
    - MAOI
  - Antiepileptics
    - Carbamazepine, oxcarbazine, sodium valproate, lamotrigine
  - Antipsychotics
    - Phenothiazines (eg, chlorpromazine, thiridazine)
    - Butyropenones (eg, haloperidol)
  - Cancer therapy
    - Vinca alkaloids (eg, vincristine)
    - Alkalating agents (cyclophosphamide, melphalan, ifosfamide)
    - Methotrexate, pentostatin
  - Miscellaneous
    - Tramadol (79), MDMA ("ecstasy"), interferon, NSAIDs, ACEI (rarely), nicotine, amiodarone, proton pump inhibitors, nicotine, clofibrate, monoclonal antibodies, levamisole, first-generation sulphonylureas (chlorpropramide, tolbutamine), ginkgo biloba (80)
- AVP receptor activation
  - AVP analogues: desmopressin, vasopressin, terlipressin (terlipressin a rare cause due to selective V1 receptor activity)
  - Receptor crosstalk: oxytocin
- Reset osmostat
  - Carbamazepine
  - Venlafaxine
- Natriuretic agents that may mimic SIAD (ie, due to increased urine sodium concentration)
  - Thiazides, indapamide, amiloride, loop diuretics
  - Platinum compounds (eg, cisplatin)
  - Trimethoprim (including co-trimoxazole)

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; AVP, arginine vasopressin; MAOI, monoamine oxidase inhibitors; MDMA, 3,4-methylenedioxymethamphetamine; NSAID, nonsteroidal anti-inflammatory drug; SIAD, syndrome of inappropriate diuresis; SNRI, serotonin and norepinephrine (noradrenaline) reuptake inhibitors; SSRI, selective serotonin reuptake inhibitors. Adapted from Liamis Am J Kid Dis 2008 (81) with permission, with additional reference to Spasovski 2014 (15).

Table 1. Causes of the Syndrome of Inappropriate Antidiuresis (SIAD).*

Categories	Causes	Comments
Cancer	Pulmonary and mediastinal, nasopharyngeal, gastrointestinal, genitourinary	Most commonly observed in small-cell lung cancer (approximately 25% of the cases of SIAD that are caused by cancer), followed by head and neck cancer and olfactory neuroblastoma; ectopic production of AVP by some cancers has been documented (e.g., small-cell lung cancer and its metastases and olfactory neuroblastoma); tumor regression can reverse SIAD
Pulmonary conditions	Infections, asthma, acute respiratory failure	Most commonly seen in pneumonia of all causes; observed with positive-pressure ventilation
Central nervous system disorders	Mass lesions, infections, cerebrovascular accident, head trauma, pituitary surgery, acute psychosis	Develops in up to 56% of patients with subarachnoid hemorrhage and up to 35% of those with transsphenoidal pituitary surgery; a rare but treatable cause of rapidly progressive dementia, anti-LGI1 limbic encephalitis, leads to SIAD in 60 to 90% of patients
Drug-related	Stimulants of AVP release (e.g., opiates, ifosfamide, MDMA [also known as "ecstasy"], vincristine, and platinum compounds), enhancers of AVP effects (e.g., NSAIDs), AVP analogues (e.g., desmopressin and oxytocin), and stimulants of V2R (e.g., SSRIs, haloperidol, carbamazepine, cyclophosphamide, and chlorpropamide)	MDMA intoxication can result in severe hyponatremia because AVP stimulation is coupled with excessive ingestion of fluids on the users' belief that they can avoid the characteristic hyperthermia; desmopressin, prescribed for enuresis (nocturnal polyuria), can cause severe hyponatremia and occasionally osmotic demyelination syndrome; antidepressants are among the most common causes, especially in underweight older women (risk is highest with SSRIs and lowest with mirtazapine); high-dose intravenous cyclophosphamide can result in severe hyponatremia if large amounts of fluid are prescribed for prevention of hemorrhagic cystitis
Other	Exercise-associated, pain, stress, severe nausea, general anesthesia, postoperative state, gain-of-function variants in V2R gene (nephrogenic SIAD)	Prevention of exercise-associated hyponatremia requires that athletes drink only in response to thirst and avoid weight gain during exercise; in postoperative state, hyponatremia reflects combined effects of pain, stress, nausea, anesthesia, opiates, and hypotonic fluids; most cases of hereditary SIAD feature persistent activation of V2R (gene located on the X chromosome) that is unresponsive to vaptans
Idiopathic		Widely variable prevalence (17 to 60% of cases), most commonly reported in older patients; occasionally, an apparent idiopathic case has later been found to have been caused by occult tumor

* AVP denotes arginine vasopressin, LGI1 leucine-rich, glioma-inactivated 1 antibodies, MDMA 3,4-methylene-dioxymethamphetamine, NSAIDs nonsteroidal antiinflammatory drugs, SSRIs selective serotonin-reuptake inhibitors, and V2R vasopressin 2 receptor.

	CSW	SIADH
Body weight	same or ↓	↑
Extracellular volume	↓	↑
Signs or symptoms of dehydration	present	absent
Central venous pressure	↓	same or ↑
Plasma sodium	↓	↓
Urine sodium	↑	↑
Net sodium loss	↑	normal
Urine output	normal or ↑	↓
Serum osmolality	↓	↓
Urine osmolality	↑	↑
Blood urea nitrogen	normal or ↑	↓
Plasma AVP	↓	↑
Haematocrit	normal or ↑	↓
Plasma aldosterone	↓	normal or ↑
Plasma renin	normal, ↑ or ↓	↓
Treatment	Salt supplementation and fluid replacement	Fluid restriction

Biochemical marker	SIADH	CSWS
Intravascular volume status	Normal to high	Low
Serum sodium	Low	Low
Urinary sodium level	High	Very high
Vasopressin level	High	Low
Urine output	Normal or low	High
Serum uric acid level	Low	Low
Initial fractional excretion of urate	High	High
Fractional excretion of urate after correction of hyponatremia	Normal	High
Urinary osmolality	High	High
Serum osmolality	Low	Low
Blood urea nitrogen/creatinine level	Low to normal	High
Serum potassium level	Normal	Normal to high
Central venous pressure	Normal to high	Low
Pulmonary capillary wedge pressure	Normal to high	Low
Brain natriuretic peptide level	Normal	High
Treatment	Water restriction	Fluids and/or mineralocorticoid

CSWS = Cerebral salt wasting syndrome; SIADH = Syndrome of inappropriate antidiuretic hormone

Table 23-5 Major steps in the initial evaluation of hyponatremia

Plasma osmolality
- A. Low: true hyponatremia
- B. Normal or elevated: pseudohyponatremia or renal failure

Urine osmolality
- A. Less than 100 mosmol/kg: primary polydipsia or reset osmostat
- B. Greater than 100 mosmol/kg: other causes of true hyponatremia in which water excretion is impaired

Urine sodium concentration
- A. Less than 25 meq/L: effective circulating volume depletion (including heart failure and hepatic cirrhosis), by dilution in primary polydipsia if the urine output is very high
- B. Greater than 40 meq/L: SIADH, renal failure, reset osmostat, diuretics (when drug still acting), adrenal insufficiency, some patients with vomiting (in whom there is obligatory $NaHCO_3$ loss in the urine; see page 565), osmotic diuretics (with pseudohyponatremia due to glucose or mannitol)

Table 23-6 Acid-base and potassium disturbances in hyponatremia

Metabolic acidosis	Normal pH	Metabolic alkalosis
Plasma K^+ concentration may be normal or elevated	Plasma K^+ concentration usually normal	Plasma K^+ concentration may be normal or reduced
Renal failure	SIADH	Vomiting
Adrenal insufficiency	Primary polydipsia (may see hypokalemia)	Nasogastric suction
	Edematous states (no diuretics)	Diuretics
	Pure cortisol deficiency	
Plasma K^+ concentration may be normal or reduced	Hypothyroidism	
Diarrhea or drainage of intestinal secretions		

Table 23-7 Basic therapeutic regimen in the different causes of hyponatremia

NaCl	H_2O restriction
True volume depletion	SIADH
Diuretics	Edematous states
Adrenal insufficiency	Renal failure
	Primary polydipsia

Hillier Formula
Correction of serum sodium concentration in the presence of hyperglycemia

$$\text{Corrected } (Na^+) = \text{Measured } (Na^+) + 2.4 \times \frac{(\text{glucose (mmol/L)}) - 5.5}{5.5}$$

Simplified 'rule of thumb': Corrected Na = Measured Na + 1/3 (glucose)

Adrogué-Madias Formula
Estimation of the effect of 1000 mL of intravenous fluid on the serum sodium concentration.
Total body water is calculated as 60% of the weight in kilograms for women, and 50% of the weight in kilograms for men.

$$\text{Change in serum } Na^+ \text{after 1L fluid} = \frac{(\text{Infusate } Na^+ + \text{Infusate } K^+) - \text{serum } Na^+}{\text{Total body water} + 1}$$

Fractional excretion of uric acid (FE-UA)
An alternative measure to urine sodium concentration to identify SIAD in patients despite the use of diuretics. Uric acid is excreted in the proximal tubule and its urinary concentration is not affected by common diuretics, unlike urine sodium concentration.
Raised FE-UA (>12%) has a high positive predictive value for SIAD regardless of recent diuretic use (6).

$$\text{FEUA} = \frac{\text{Urine } UA \times \text{Serum } Cr}{\text{Urine } Cr \times \text{Serum } UA} \times 100$$

Fürst Ratio (Fürst Equation)
Calculation of a Urine:Serum electrolyte ratio, which can predict response to fluid restriction.
The Fürst equation ratio has been used to assist dosing of fluid restriction:

- Fürst ratio <0.5 → fluid restriction 1000 ml/day recommended
- Fürst ratio 0.5-1 → fluid restriction 500 ml/day recommended

A Fürst ratio >1 is said to predict non-response to fluid restriction. However, one study found the Fürst ratio does not perform as well as urine osmolality >500 mOsm/kg/H_2O or urinary sodium concentration >130 mmol/L in predicting non-response (8).

$$\text{Fürst ratio} = \frac{\text{Urine } Na^+ + \text{Urine } K^+}{\text{Serum } Na^+}$$

Figure 2. Useful formulae in the management of hyponatremia. Cr, creatinine; FEUA, fractional excretion of uric acid; mOsm, milliosmoles; Na UA, uric acid.

References (in order): Hiller 1999 (9), Adrogué 1997 (344), Maesaka 1998 (207), and Fürst 2000 (276).

Table 4. Recommended plasma sodium concentration daily correction targets and limits in current hyponatremia guidelines

	General hyponatremia	Hyponatremia with risk factors for ODS
US expert opinion (3)	Target: 4-8 mmol/24 h Limit: 10-12 mmol/24 h	Target: 4-6 mmol/L/24 h Limit: 6-8 mmol/L/24 h
EU guidelines (15)	Target: 5 mmol/L/24 h Limit: 10 mmol/L/24 h in first 24 h, 8 mmol/L/24 h subsequent days	Same as general

Abbreviations: EU, European Union; ODS, osmotic demyelination syndrome.

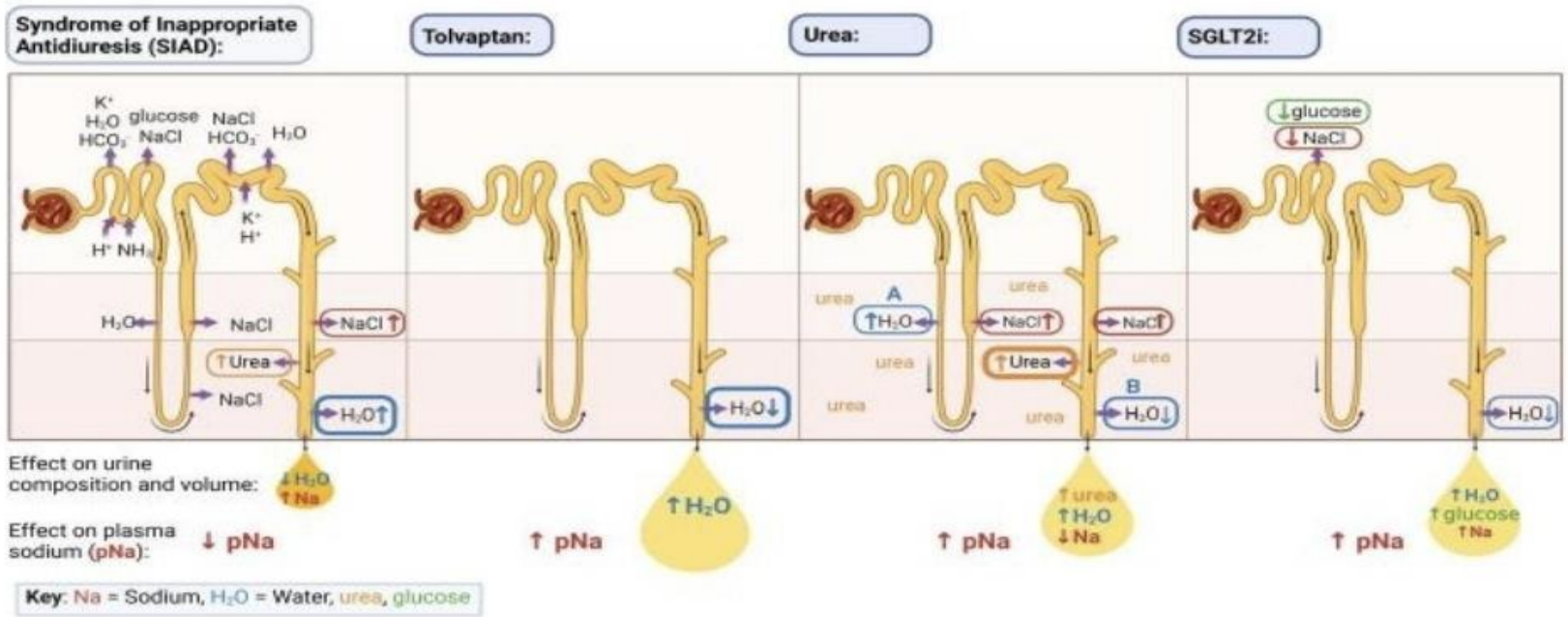


Figure 11. Renal physiology in SIAD, and mechanisms of action of tolvaptan, urea, and SGLT2i at the nephron. **SIAD**: Nonosmotic increase in circulating AVP leads to increased water resorption in the collecting duct via aquaporins, plus reduced sodium resorption in the proximal convoluted tubule, ascending limb, and distal convoluted tubule, resulting in concentrated urine production and decreased serum sodium concentration (see Fig. 5). AVP also promotes water retention by upregulating expression of UT-A1s to increase reabsorption of urea, augmenting medullary interstitial osmolality and hence urinary concentrating ability. **Tolvaptan**: blockade of AVP V2 receptor leads to reduced water resorption in the context of reduced aquaporins, resulting in a free water diuresis leading to a rise in serum sodium. **Urea**: Administration of urea leads to increased concentration of urea both in the filtrate and the renal interstitium. This leads to A, increased water resorption in the descending limb due to the osmotic effect of urea, initially leading to an elevated sodium concentration in the filtrate in the descending limb. This leads to increased sodium resorption by passive diffusion in the ascending limb, reducing sodium loss. Later, the osmotic draw of urea in the filtrate leads to B, reduced water resorption in the collecting duct, resulting in an osmotic diuresis and rise in serum sodium. **SGLT2i**: SGLT2i inhibitors act at the sodium-glucose cotransporter in the proximal tubule to reduce resorption of glucose and sodium. The primary effect is glycosuria (even in those without diabetes mellitus), accompanied by increased water excretion due to an osmotic diuresis. There is a transient increase in sodium excretion as well; however, the net effect on plasma sodium level is to increment when used in hyponatremia. AVP, arginine vasopressin; SIAD, syndrome of inappropriate diuresis; SGLT2i, sodium-glucose cotransporter 2 inhibitor. Original figure created with biorender.com, with reference to Decaux 1980 regarding urea physiology (306).

Table 9. Expected efficacy of urea (ure-Na) vs oral sodium chloride (600-mg NaCl tablets) for an illustrative 70-kg woman (total body water 35 L) with hyponatremia due to syndrome of inappropriate antidiuresis (pNa 125, UOsm 500)

	Urea	Sodium chloride
Formulation	21-g sachet of powder	Tablet
Contents	Urea 15 g = 249.5 mmol	600 mg NaCl = 10.3 mmol Na + 10.3 mmol Cl
Renal solute load	250 mOsm	21 mOsm
Water loss [a]	500 mL (1 sachet)	42 mL (1 tablet) *420 mL (10 tablets)*
Net water balance if taken with 140 mL water	−360 mL (1 sachet)	+98 mL (1 tablet) *−280 mL (10 tablets)*
Anticipated change in pNa [b]	+1.3 mmol/L (1 sachet)	*+ 1.0 mmol/L (10 tablets)*

Italic refers to calculations for 10 x 600 mg sodium chloride tablets.
Abbreviation: pNa, plasma sodium concentration.
[a] Assuming urine osmolality of 500 mOsm/L
[b] Using the Adrogué-Madias formula (184) and assuming total body water of 35 L and pNa 125 mmol/L.

BOX 15.4

From Verbalis JG, Goldsmith SR, Greenberg A, et al: Diagnosis, evaluation, and treatment of hyponatremia: expert panel recommendations. *Am J Med.* 2013;126(Suppl 1):S1–S42.

General Recommendations for Using Fluid Restriction and Predictors of Its Increased Likelihood of Failure

General Recommendations

- Restrict all intake that is consumed by drinking, not just water.
- Aim for a fluid restriction that is 500 mL/day below the 24-hour urine volume.
- Do not restrict sodium or protein intake unless indicated.

Predictors of Likely Failure of Fluid Restriction

- High urine osmolality (>500 mOsm/kg H_2O)
- Sum of urine Na^+ and K^+ concentrations exceeds serum Na^+ concentration
- 24-hour urine volume $<$ 1500 mL/day
- Increase in serum Na^+ sodium concentration $<$ 2 mmol/L/day in 24 hours on fluid restriction $\leq$ 1 L/day

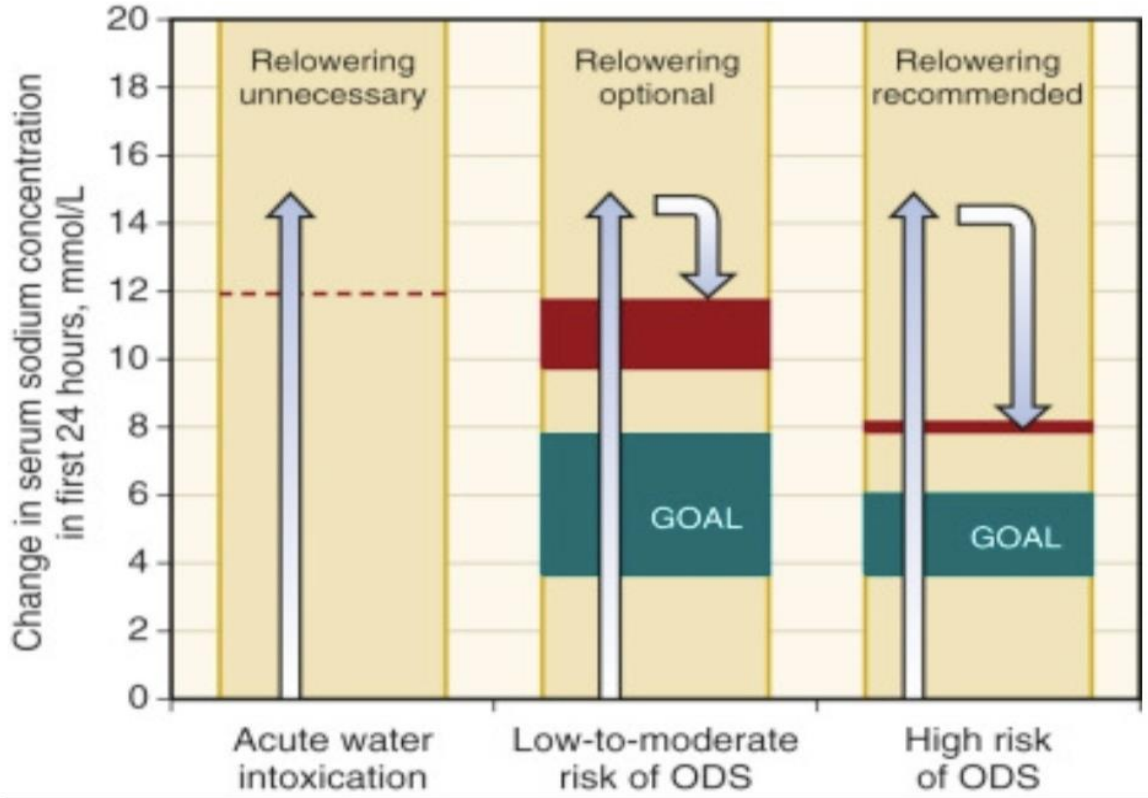


Fig. 15.20

Recommended goals *(green)* and limits *(red)* for correction of hyponatremia based on the risk of producing osmotic demyelination syndrome (ODS). Also shown are recommendations for relowering of the serum [Na^+] to goals for patients presenting with serum [Na^+] < 120 mmol/L who exceed the recommended limits of correction in the first 24 hours.

(From Verbalis JG, Goldsmith SR, Greenberg A, et al: Diagnosis, evaluation, and treatment of hyponatremia: expert panel recommendations. *Am J Med.* 2013;126(Suppl 1):S1 – S42.)

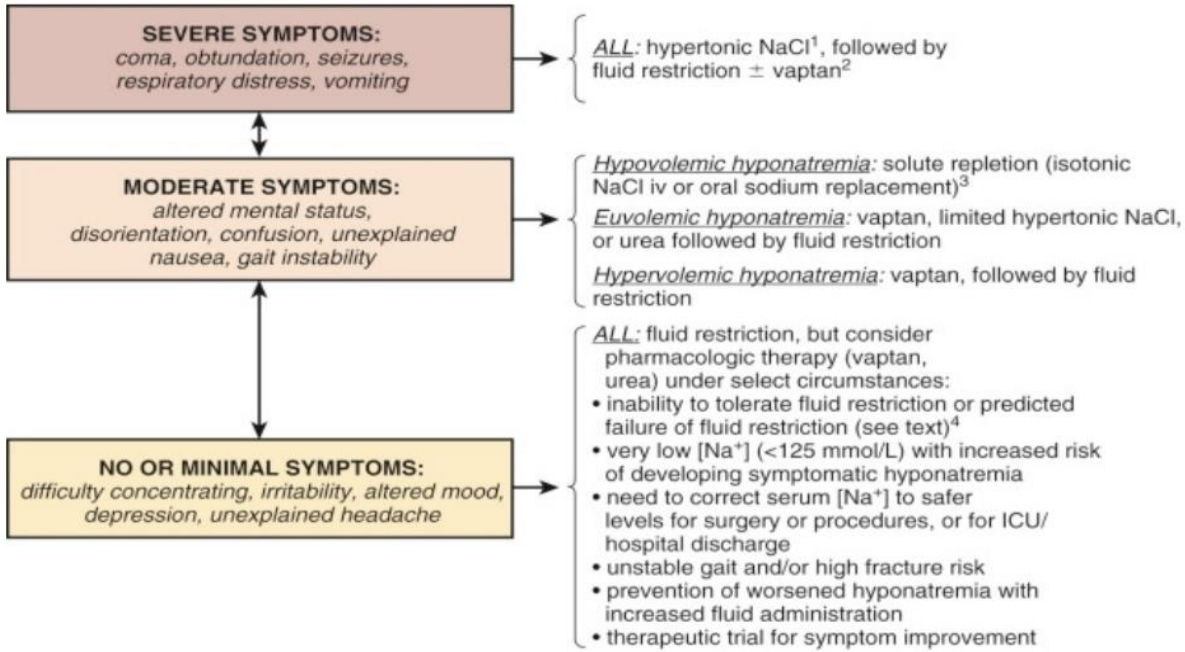
BOX 15.5

From Verbalis JG, Goldsmith SR, Greenberg A, et al: Diagnosis, evaluation, and treatment of hyponatremia: expert panel recommendations. *Am J Med.* 2013;126(Suppl 1):S1–S42.

Factors Increasing Risk of Osmotic Demyelination Syndrome [a]

a Requiring slower correction of chronic hyponatremia.

- Serum sodium concentration $\leq$ 105 mmol/L
- Hypokalemia [b] b Unlike the rate of increase in serum [Na^+], neither the precise level of the serum potassium concentration nor the degree of alcoholism, malnutrition, or liver disease that alters the brain's tolerance to an acute osmotic stress have been rigorously defined.
- Alcoholism [b]
- Malnutrition [b]
- Advanced liver disease [b]



1. Some authors recommend simultaneous treatment with desmopressin to limit speed of correction.
2. No active therapy should be started within 24 hours of hypertonic saline to decrease the risk of overly rapid correction of [Na+] and risk of ODS.
3. With isotonic NaCl infusion, serum [Na+] must be followed closely to prevent overly rapid correction and risk of ODS due to secondary water diuresis.

Fig. 15.21

Algorithm for the treatment of patients with euvolemic hyponatremia based on their presenting symptoms. The *arrows* between the symptom boxes indicate movement of patients between different symptom levels. *ALL,* All types of hypotonic hyponatremia; *ICU,* intensive care unit; *iv,* intravenous; *ODS,* osmotic demyelination syndrome.

(Modified from Verbalis JG: Emergency management of acute and chronic hyponatremia. In Matfin G, ed. *Endocrine and Metabolic Emergencies.* Washington, DC: Endocrine Press; 2014:359.)

Etiology of SIADH	Likely duration of SIADH*	Relative risk of chronic SIADH
Tumors producing vasopressin ectopically (small-cell lung carcinoma, head and neck carcinoma)	Indefinite	High
Drug-induced, with continuation of offending agent (carbamazepine, SSRI)	Duration of drug therapy	
Brain tumors	Indefinite	
Idiopathic (senile)	Indefinite	
Subarachnoid hemorrhage	1–4 weeks	
Stroke	1–2 weeks	
Inflammatory brain lesions	Dependent on response to therapy	Medium
Respiratory failure (chronic obstructive lung disease)	Dependent on response to therapy	
HIV infection	Dependent on response to therapy	
Traumatic brain injury	2–7 days to indefinite	
Drug-induced, with cessation of offending agent	Duration of drug therapy	
Pneumonia	2–5 days	
Nausea, pain, prolonged exercise	Variable, depending on cause	
Postoperative hyponatremia	2–3 days postoperatively	Low
*Time frames are based on clinical experience.		

Fig. 15.22

Estimated probability of need for long-term treatment of SIADH, depending on underlying cause.

Box 1. Selected Formulas Useful for the Classification and Management of Dysnatremias

Plasma osmolality, mOsm/kg H_2O: (2 × [Na^+] (mEq/L)) + SUN (mg/dL)/2.8 + glucose (mg/dL)/18

Plasma tonicity, mOsm/kg H_2O: Measured plasma osmolality (mOsm/kg H_2O) − SUN (mg/dL)/2.8 or (2 × [Na^+] (mEq/L)) + glucose (mg/dL)/18

Edelman formula, simplified: [Na^+] = (eNa^+ + eK^+)/TBW

Urine to serum electrolyte ratio: (U_{Na} + U_K)/[Na^+][a]

Electrolyte-free water excretion: Urine Volume × (1 − (U_{Na} + U_K)/[Na^+])

Infusion rate, hypertonic saline solution: 1 mL/kg/h can be expected to increase [Na^+] 1 mEq/L/h

Infusion rate, D5W, to relower [Na^+]: 3 mL/kg/h

Free-water deficit: TBW (L) × (([Na^+]/140 mEq/L) − 1)[b]

Note: The formula for calculated plasma osmolality does not reflect the contribution of ethanol, methanol, or other toxic ingestions. Measured plasma osmolality should not be used for decision making in hyponatremia if an ingestion is suspected. A difference between plasma osmolality calculated with this formula and measured plasma osmolality can be used to infer the presence of a foreign substance. Infusion rates are approximations and do not take into account ongoing losses of water or solute; [Na^+] should be monitored frequently during infusion.

Abbreviations: D5W, 5% dextrose in water; eK^+, exchangeable potassium content; eNa^+, exchangeable sodium content; [Na^+], serum sodium concentration; SUN, serum urea nitrogen; TBW, total-body water; U_{Na}, urine sodium concentration; U_K, urine potassium concentration.

[a]Ratio > 1 predicts treatment failure with fluid restriction alone and worsening of hyponatremia in response to normal saline solution.

[b]TBW = 0.6 × body weight (kg).

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[a]	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.

Note: In patients with substantial risk for ODS (especially those with starting [Na^+] < 120 mEq/L) who experience an increase in [Na^+] exceeding the recommended limit, consider re-lowering [Na^+] to a value below target by administration of electrolyte-free water. Urine output and/or osmolality should also be followed to detect onset of a spontaneous water diuresis (especially with volume depletion or thiazide-associated hyponatremia) that can lead to over rapid correction. Desmopressin may be useful in this setting to limit ongoing urinary water loss.

Abbreviations: D5W, 5% dextrose in water; IV, intravenous; [Na^+], serum sodium concentration; ODS, osmotic demyelination syndrome; SIADH, syndrome of inappropriate antidiuretic hormone secretion.

Based on recommendations from Verbalis et al (Diagnosis, evaluation, and treatment of hyponatremia: expert panel recommendations. *Am J Med.* 2013;126(10)(suppl 1):S1-S42).

[a][Na^+] ≤ 105 mEq/L, hypokalemia, alcoholism, malnutrition, and advanced liver disease.

Table 2. Treatment Approaches.

Treatment	Mechanism	Amount or Dose	Efficacy	Adverse Effects	Comments
Fluid restriction	Reduces electrolyte-free water intake and total body water; should include all fluids, not just water	Moderate, <1.5 liters per day; severe, <1 liter per day	First-line treatment; difficult to adhere to and thus often ineffective	Increases thirst; may result in low caloric intake	Inexpensive and safe; predictors of failure at baseline include urine output of <1.5 liters per day, urine osmolality >500 mOsm per kg of water, and the sum of urine sodium and urine potassium levels exceeding the serum sodium level; contraindicated in subarachnoid hemorrhage and other intracranial processes
Sodium chloride supplement	Increases body sodium content, reduces electrolyte-free water intake, and increases water excretion	2–5 g per day (500 mg per tablet); frequently combined with furosemide 20 mg twice daily or equivalent loop diuretic to increase aquaresis	Limited long-term efficacy	Increases body sodium content, risking sodium and fluid excess; combining with furosemide can cause potassium depletion	Inexpensive; addition of sodium chloride plus furosemide to severe fluid restriction has no persistent benefit with respect to correction of serum sodium levels; contraindicated in hypertension, heart failure, and other sodium-retentive states
Urea	Increases electrolyte-free water excretion (by means of osmotic diuresis); decreases sodium excretion	15–60 g per day orally or enterally combined with moderate fluid restriction; 30 g of urea (500 mOsm) increases water excretion by 1 liter (for urine osmolality of 500 mOsm per kg of water)	Short- and long-term efficacy reported in observational studies	Nausea, diarrhea, and bitter taste; rare overly rapid correction of serum sodium, but osmotic demyelination not reported	Palatability is improved by dissolving in fruit juice or syrup (European guideline provides a recipe); citrus-flavored U.S. formulation (ure-Na) is available; initially used in Europe but more recently prescribed worldwide; contraindicated in volume depletion, kidney failure, and liver failure
Tolvaptan	Sole therapy that addresses underlying pathophysiology; competitive vasopressin receptor 2 blocker	15–60 mg per day orally combined with moderate fluid restriction; initiated in hospital to allow close monitoring of serum sodium (every 6–8 hr or more frequently depending on risk of osmotic demyelination syndrome) and dose adjustment; fluid restriction should not be used during the initial dose-finding phase to decrease risk of overly rapid correction of serum sodium; 7.5 mg per day appears as effective as 15 mg per day as a starting dose	Highly effective both in short- and long-term use; aquaretic response and increase in serum sodium correlate directly with severity of hyponatremia	Polyuria and increased thirst; overly rapid correction of serum sodium occurs in 13 to 25% of patients in real-life experience (appears to be exclusive to baseline serum sodium of <125 mmol per liter); sporadic cases of osmotic demyelination syndrome; 7.5-mg dose not associated with overly rapid correction in chronic SIAD	Food and Drug Administration warns against use for >30 days (on the basis of duration of pivotal trials) and in patients with liver disease; not recommended by the European guideline owing to risks of overly rapid correction of serum sodium level and hepatotoxicity; hepatotoxicity not observed in tolvaptan trials for hyponatremia, but reversible hepatotoxicity was reported in trials that used high doses of tolvaptan to alter course of polycystic kidney disease; cost is a barrier to use in some countries

- case: a 49-year-old man with SCLC develops severe vomiting after the institution of chemotherapy.on admission,the estimated JVP is below 5 cmH2o,the skin turgor is reduced and the following lab. tests are obtained:

plasma-Na:114 meq/L,Plasma Osm.:243 mosmol/Kg,Urine-Na:6 meq/L,Urine Osm.:498 mosmol/Kg

What is the most probable diagnosis?

- The clinical and laboratory findings are consistent with true volume depletion,it is also possible,however,that the patient has underlying SIADH due to his malignancy.the patient is initially treated with isotonic saline and the next morning the plasma Na concentration has increased to 122 meq/L.at this time,the urine-Na concentration and osmolality can be used to distinguish among three possibilities:

1-hypovolemia alone was responsible for the hyponatremia,and the patient is still volume-depleted.as a result,the urine-Na will still be low and the urine-Osm. still elevated because of the nonosmotic release of ADH.

2-hypovolemia alone was responsible for the hyponatremia,and the patient is now euvolemic.in this setting,the urine-Osm. will be below 100 mosmol/Kg,since there is no longer any stimulus to ADH secretion.urinary Na excretion will be elevated,but the urine-Na may,by dilution,still be less than 25 meq/L.

3-both hypovolemia and SIADH contributed to the hyponatremia,and the patient is now euvolemic.this will be manifested by a urine-Na above 40 meq/L and a persistently elevated urine-Osm,since there is continued ADH release.

- A 60-year-old man weighing 70 Kg has an oat-cell carcinoma of the lung and is admitted the hospital with a 2-week history of progressive lethargy and obtundation.the PH/EX is within normal limits except for the obtundation.the following laboratory studies are obtained:

Plasma-Na:105 meq/L,plasma-K:4 meq/L,plasma-Cl:72 meq/L,plasma-Hco3:21 meq/L,Posm:222 mosmol/Kg,Uosm:604 mosmol/Kg,urine-Na:78 meq/L

What is the most likely diagnosis?

How and at what initial rate would you raise the plasma-Na concentration?

- The most likely diagnosis is SIADH due to the oat-cell carcinoma.
- Hypertonic saline should be given initially in view of the marked hyponatremia and neurologic symptoms.the approximate Na deficit that must be corrected to raise the plasma-Na concentration to a safe value of 120 meq/L can be estimated from :

$$\text{Na deficit} = 0.6 * 70 * (120-105) = 630 \text{ meq}$$

This reqires approximately 1200 ml of 3% saline,which should be given at the rate of 40 ml/hr over 30 hr to raise the plasma-Na concentration by 0.5 meq/L/hr.furosemide will enhance the efficacy of this regimen by lowering Uosm,thereby increasing free-water-excretion.

- A 72-year-old woman with HTN and CKD-G4(baseline Cr:2.5-2.8 mg/dl) is admitted to the hospital with malaise and confusion.approximately 10 days before,her primary care practitioner had increased enalapril to 20 mg twice daily (from 10 mg twice daily) and added furosemide 20 mg twice daily (from 10 mg twice daily) to get better control of BP.at that visit,her serum Na was 124 meq/L and serum Cr was 3 mg/dl.over the next week,she has become lethargic with decreased urine output and confused.at the urging of her daughter,she has been drinking excessive amount of fluid(>2 lit/day) over the past week.on presentation,she was not oriented to person or place,and her vital signs were notable for an elevated respiratory rate and an O2sat of 80% on room air but otherwise normal.

PH/EX: ↑ JVP,bibasilar rales,and an S4 on cardiac examination.

Lab. Tests: Na:112 meq/l ,K: 6.8 meq/l , BUN: 93 mg/dl, Cr:3.6 mg/dl, Hco3: 15 meq/l.

Which of the following would be your next step in management of this patient?

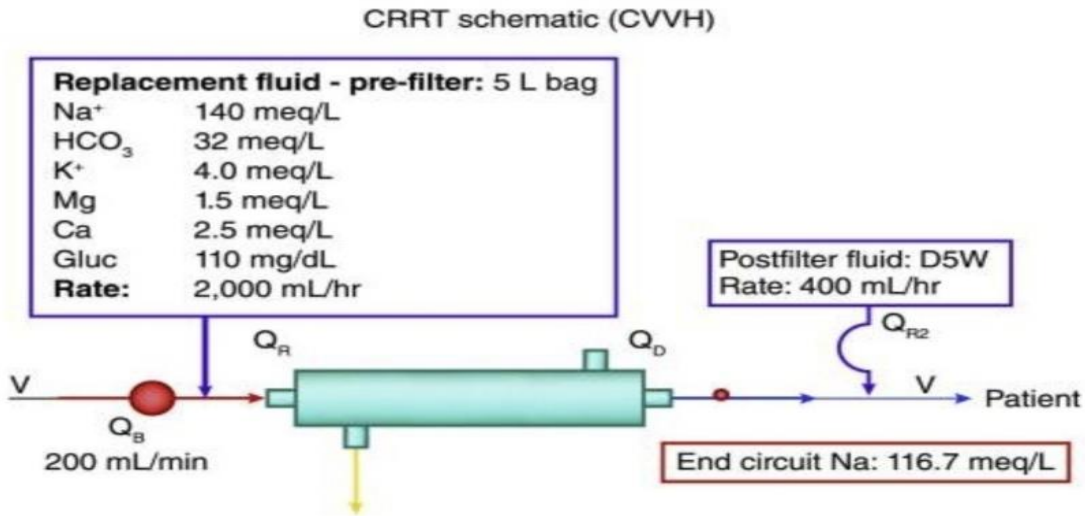
A-0.9% saline infused at 125 ml/hr.

B-hemodialysis with a custom sodium dialysate of 130 meq/l.

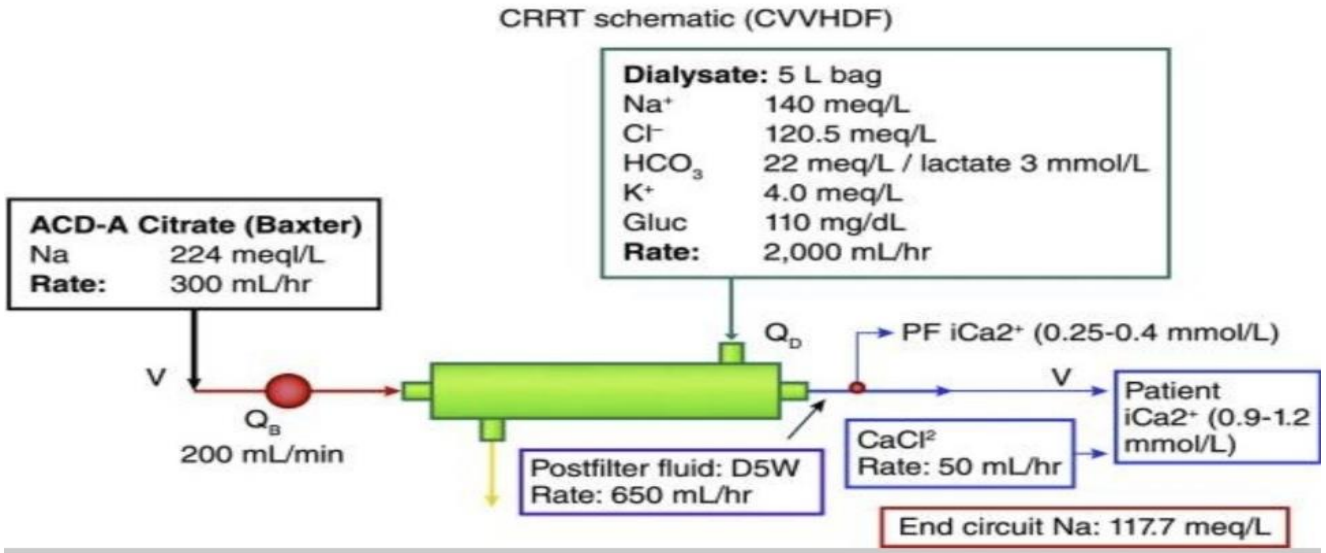
C-CVVH with a custom replacement solution.

D-tolvaptan 30 mg/day.

A **Continuous venovenous hemofiltration (CVVH)**



B **Continuous venovenous hemodiafiltration (CVVHDF)**



Thanks for your attention