

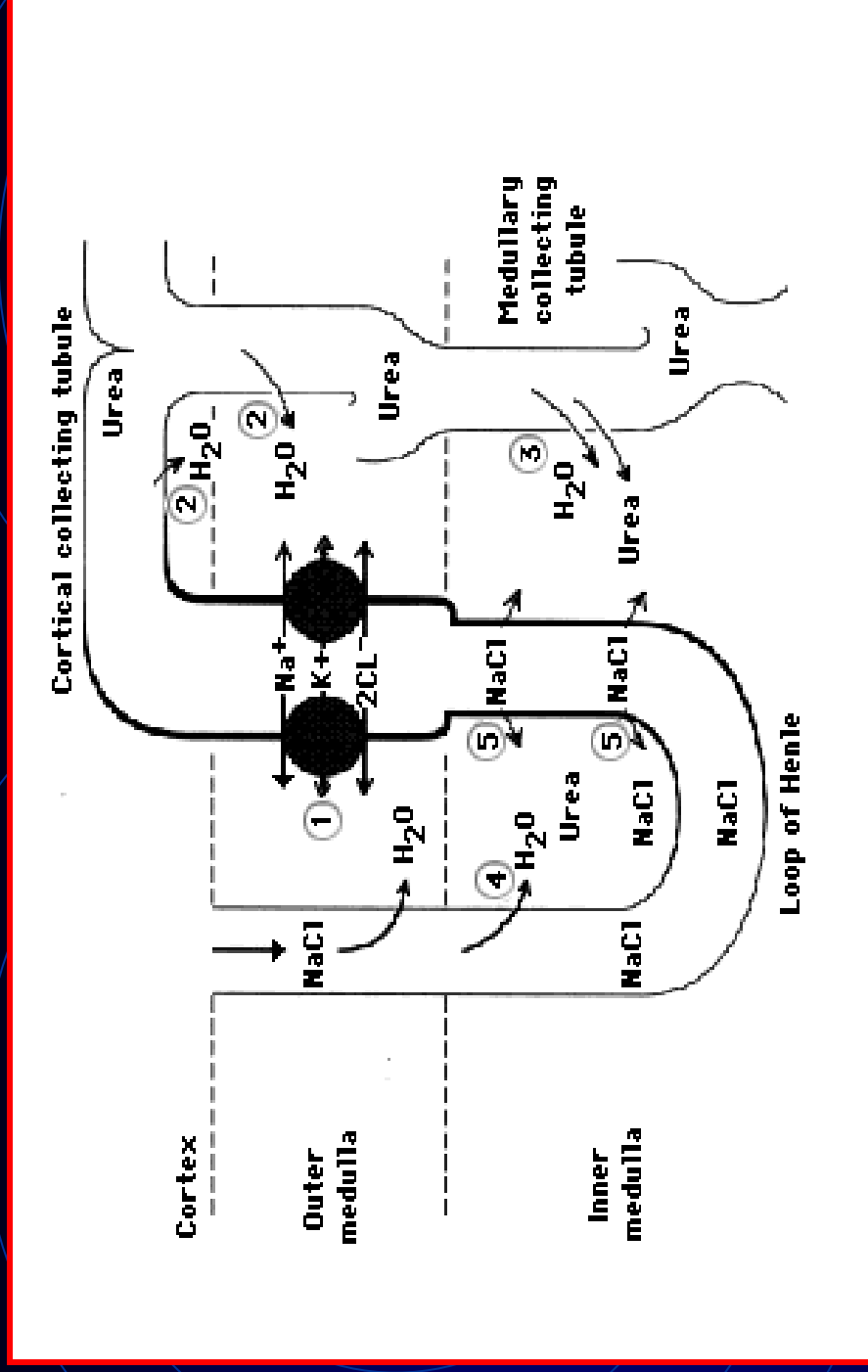
Hyponatremia and Hypernatremia

Disorders of Water Balance

Water Balance

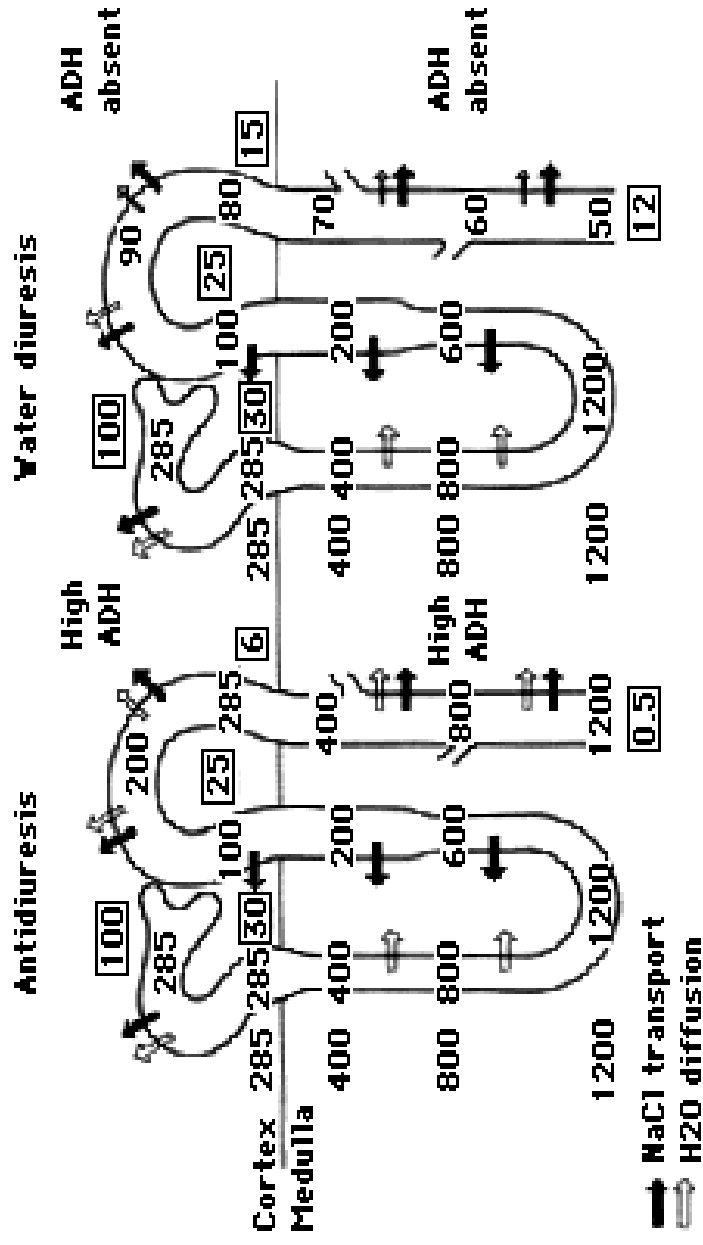
- Water constitutes approximately 55 - 60% of the human body (TBW).
- TBW is divided into:
 - Intracellular – $\frac{2}{3}$
 - Extracellular – $\frac{1}{3}$
 - Plasma – $\frac{1}{4}$
 - Interstitial Fluid – $\frac{3}{4}$

Diagram from Uptodate.



Summary of the steps involved in countercurrent multiplication in which a concentration gradient is established that permits passive NaCl reabsorption in the thin ascending limb in the inner medulla. The thickened lines represent the water impermeability of the ascending limb. See text for details. (From Jamison RL, Maffly RH, N Engl J Med 1976; 295:1059. By permission from the New England Journal of Medicine.)

Diagram from Uptodate

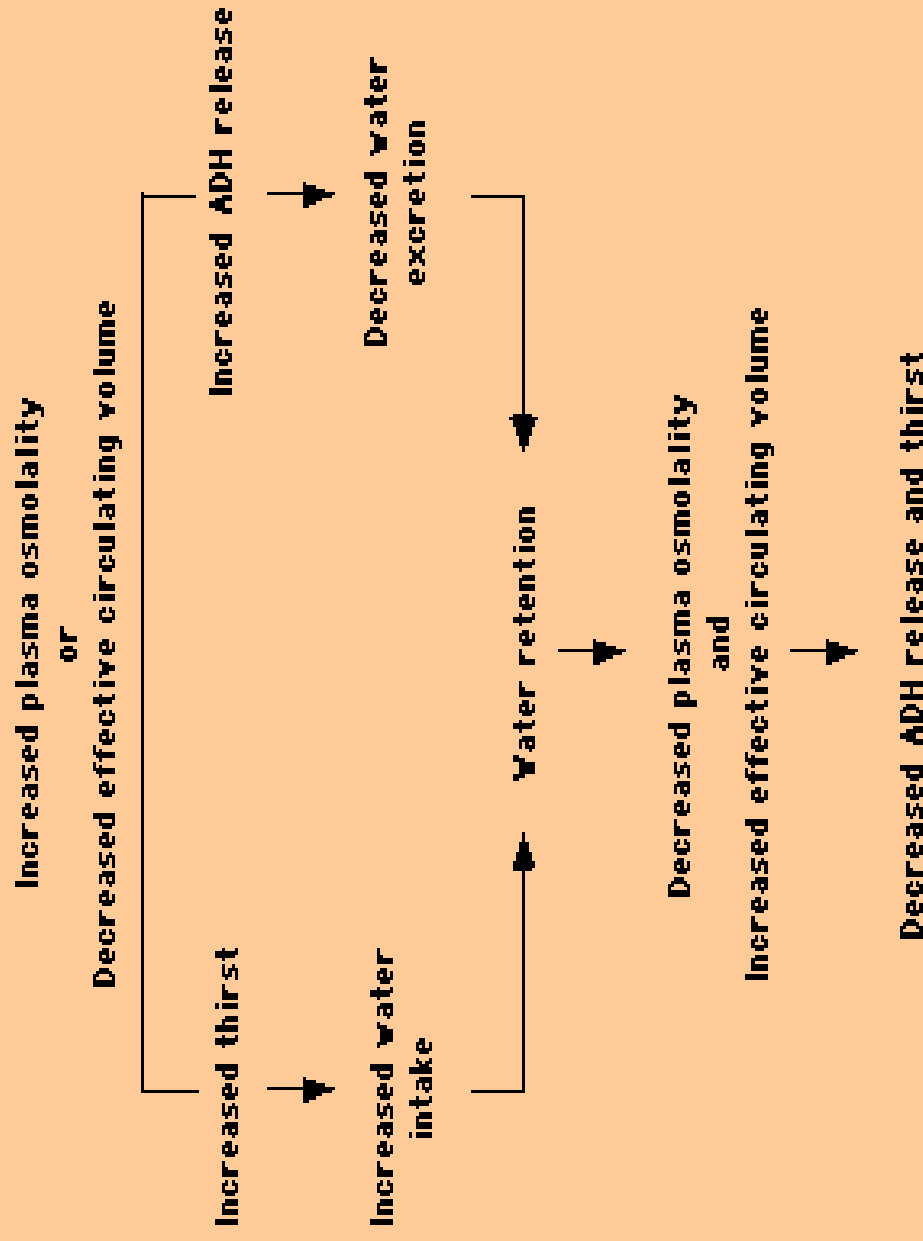


Summary of NaCl and H₂O transport throughout the nephron during an antidiuresis and a water diuresis. The tubular fluid and interstitial concentrations are expressed in milliosmoles per kilogram (mosmol/kg); the large, boxed numbers represent the percentage of the glomerular filtrate remaining in the tubule at each site. Note that the composition and volume of the tubular fluid are essentially the same at the end of the loop of Henle as the excretion of a concentrated or dilute urine is determined primarily in the collecting tubules.

- Plasma osmolality in healthy adults is maintained within a narrow range 275 – 290mOsm/kg.

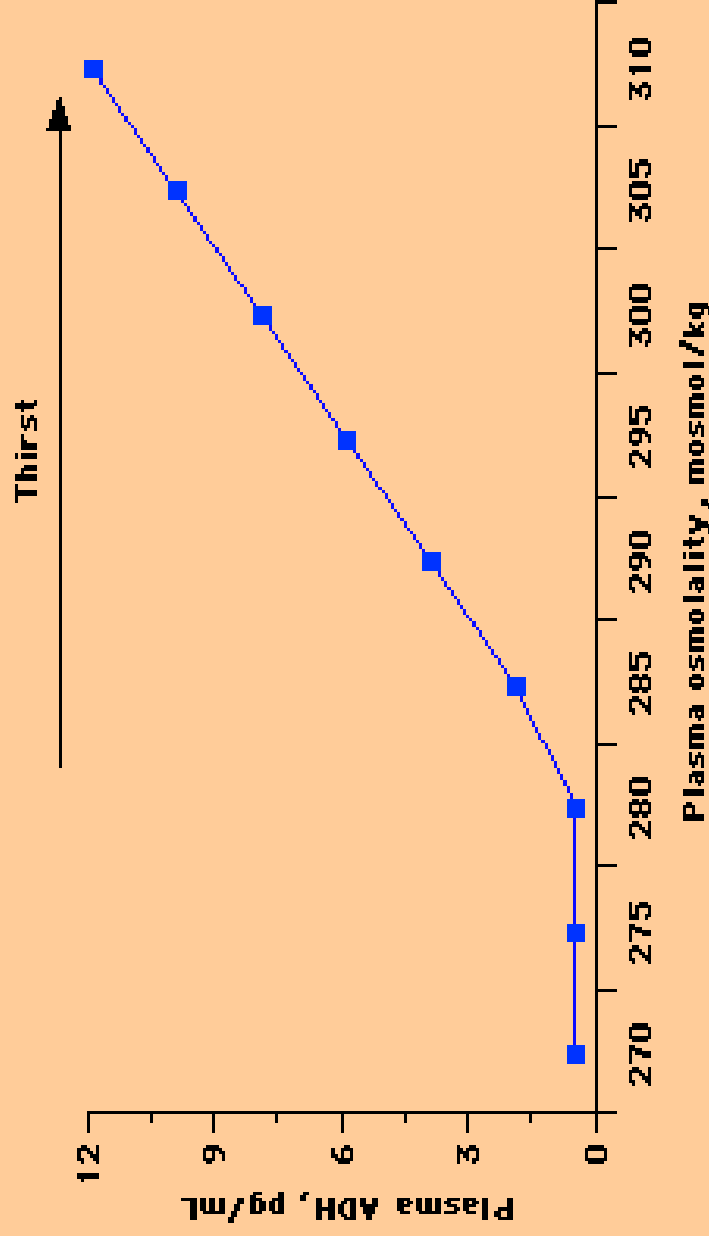
Stimulus for AVP release

Diagram from Uptodate



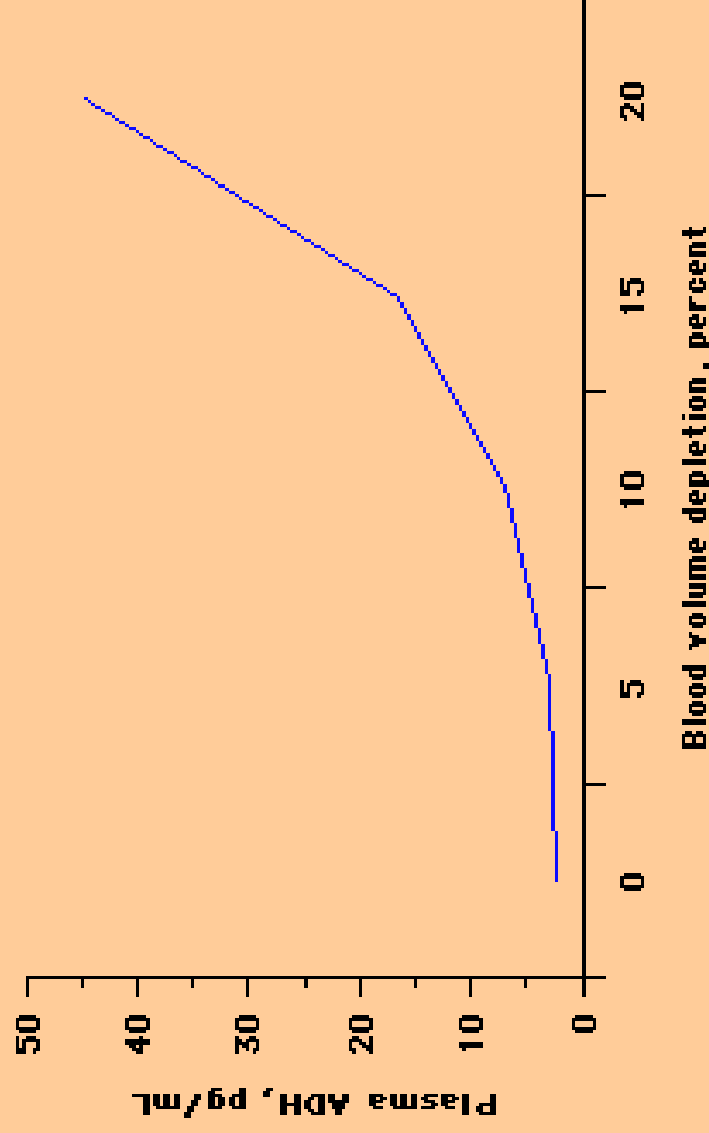
Osmoregulation of ADH release Feedback loop governing the regulation of antidiuretic hormone release and thirst by changes in plasma osmolality or effective circulating volume.

Osmotic Regulation of ADH Release



Osmotic regulation of ADH release and thirst Relation between plasma antidiuretic hormone (ADH) concentration and plasma osmolality in normal humans in whom the plasma osmolality was changed by varying the state of hydration. The osmotic threshold for thirst is a few mosmol/kg higher than that for ADH. (Data from Robertson, GL, Aycinena, P, Zerbe, RL, Am J Med 1982; 72:339.)

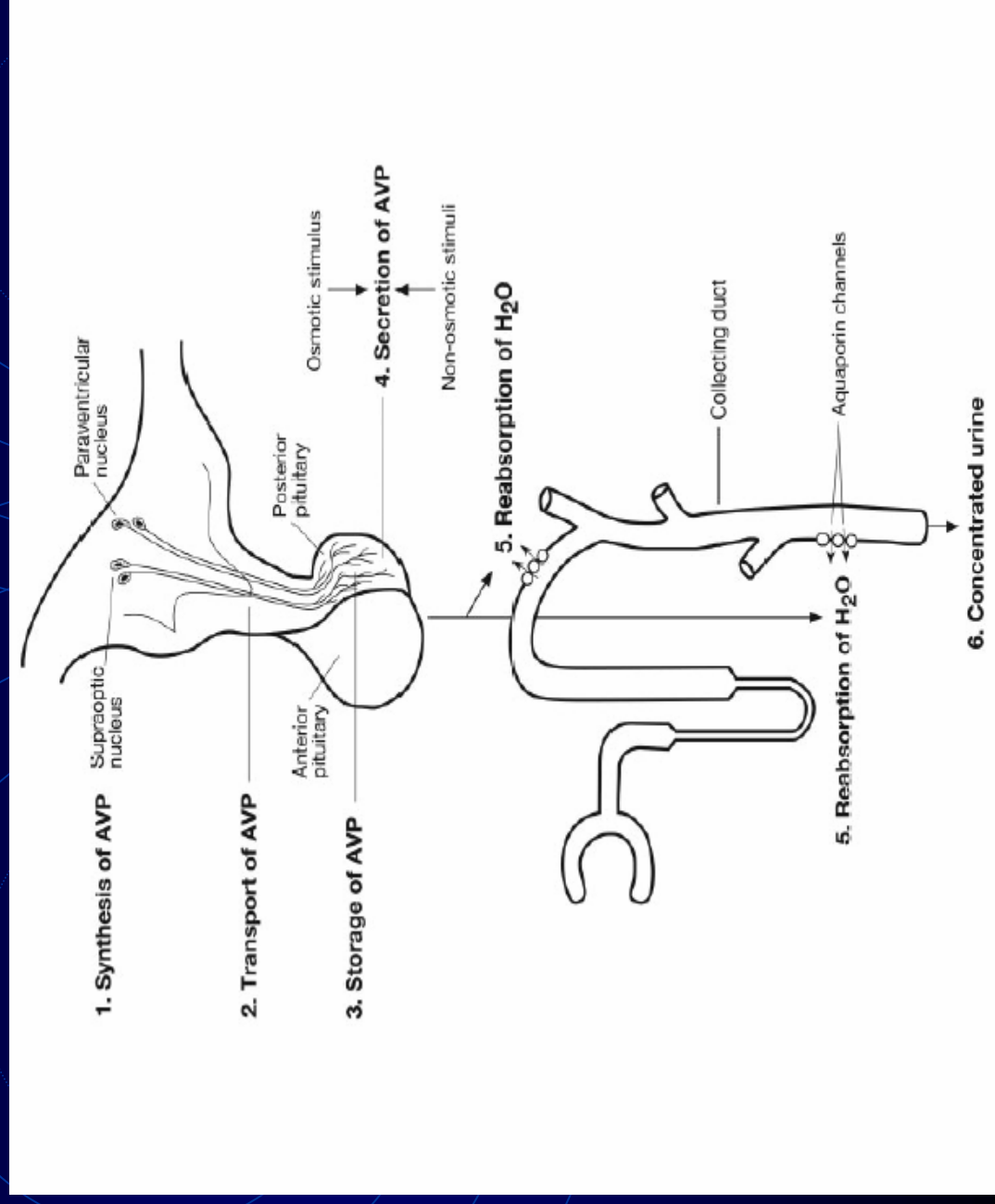
Hypovolemic Stimulus to ADH Release



Hypovolemic stimulus to ADH release Relationship of plasma antidiuretic hormone (ADH) concentrations to isosmotic changes in blood volume in the rat. Much higher ADH levels can occur with hypovolemia than with hyperosmolality, although a relatively large fall in blood volume is required before this response is initiated. (Data from Dunn, FL, Brennan, TJ, Nelson, AE, Robertson, GL, J Clin Invest 1973; 52:3212.)

Anti Diuretic Hormone Arginine Vasopressin (AVP)

Diagram from Uptodate.

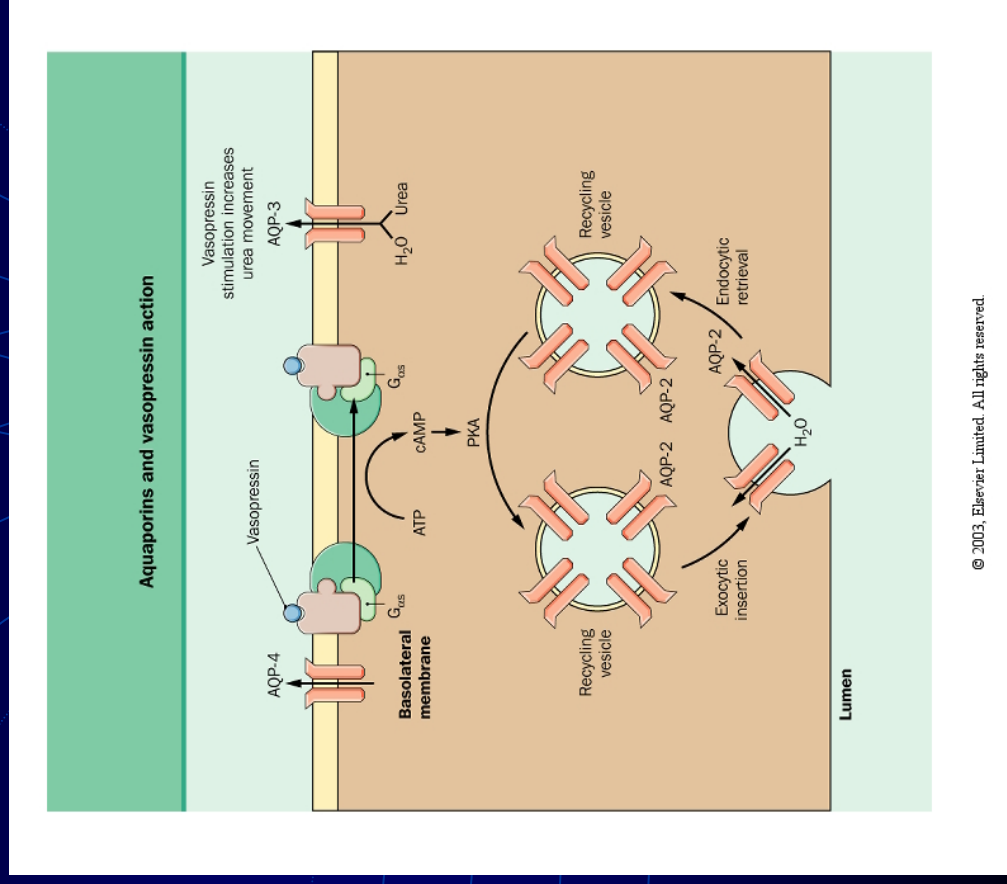


AVP

- There are two major receptors for AVP:
- The V1(V1a and V1b) and V2 receptors.
- Activation of the V1 receptors induces vasoconstriction and enhancement of prostaglandin release.
- Activation of the V2 receptors mediates the antidiuretic response.

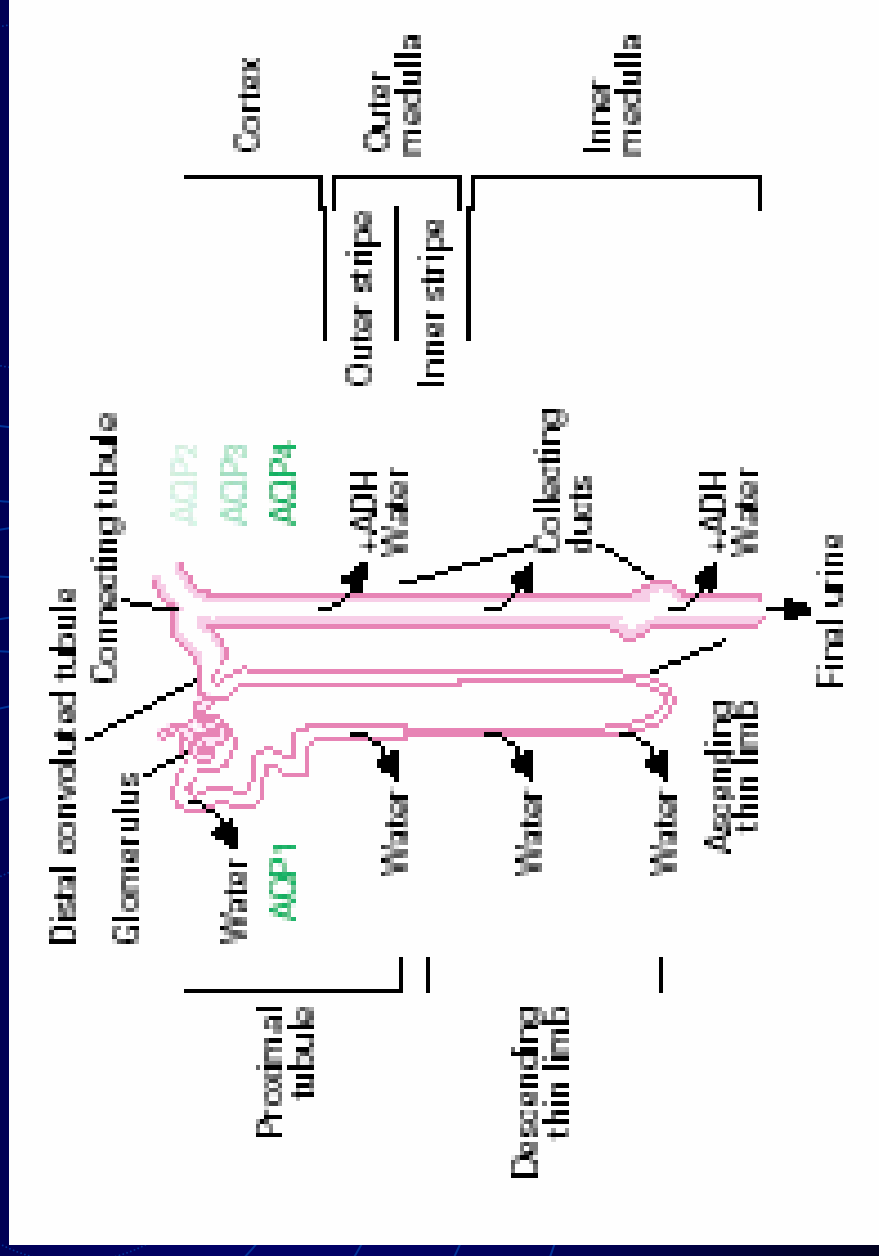
Vasopressin binds to V2 receptor activates adenyly cyclase and promotes cAMP production, which stimulates protein kinase A (PKA) and phosphorylates aquaporin 2. This causes Aquaporin movement to and exocytic-insertion of the vesicle into the apical membranes.

Renal Aquaporins: An overview. Nielsen, S, BJU Int. 2002



Schematic representation of the localization of renal aquaporins and distribution of aquaporin 1,2,3 and 4 in the kidney.

Renal Aquaporins: An overview. Nielsen, S. BJU Int. 2002



Hyponatremia

- Most common electrolyte disorder in hospitalized patients.

Study by Hoorn et al, in Nephrol Dial Transplant 2006, looked at 2,907 hospitalized patients over 3 months the incidence of hyponatremia was 30% and severe hyponatremia (<125 Meq/L) was 3%.

- Generally defined as S. Na level less than 136 mmol/L, though definition of severe hyponatremia varies from 110 to 125mmol/L.

Hyponatremia

- Particularly prevalent in the elderly population due to:
 - Age related decline in renal function.
 - Thirst mechanism diminishes with age, increasing risk of volume depletion.
 - Decreased ability to dilute the urine.
 - Increased secretion of AVP per unit increase in plasma osmolality in older patients.
- In a study of 119 Nursing Home residents over the age of 60, 53% of residents had at least one episode of hyponatremia during a 12 month follow-up. (Miller et al, Journal American Geriatric Society 1995)

Hyponatremia

- Characterized by an excess of extracellular water relative to extracellular sodium.
- Therefore **mainly a problem of water balance**, though the total sodium content in patients with hyponatremia may be normal, decreased or even increased.
- Excretion and absorption of free water by kidneys is under the control of ADH

Evaluation of Hyponatremia

- Initial labs Needed:
 - Serum Osmolality
 - Urine Osmolality – if $>100\text{mmol/kg}$ there is elevated ADH present.
 - Urine spot sodium
- Other helpful labs;
 - Serum Uric acid – low in SIADH and salt wasting nephropathy
 - TSH, Cortisol, Creatinine

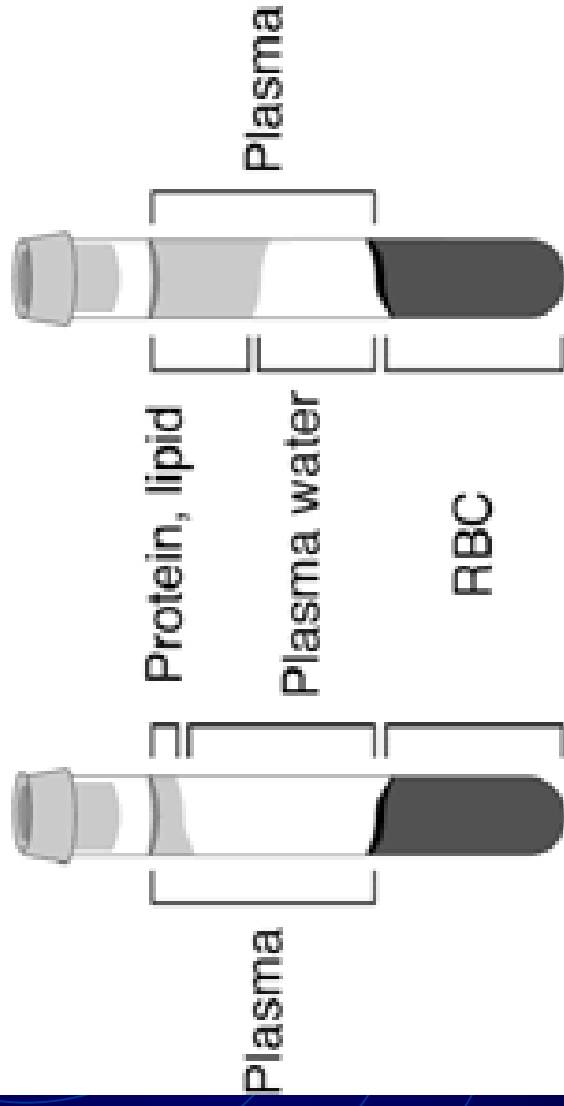
Evaluation of Hyponatremia

Divided into:

- Elevated S. Osmolality:
 - Hyperglycemia or mannitol infusion
- Normal S. Osmolality:
 - Hyperproteinemia or hyperlipidemia (pseudohyponatremia)
- Decreased S. Osmolality: Wide differential.

Pseudohyponatremia

Normal Pseudohyponatremia

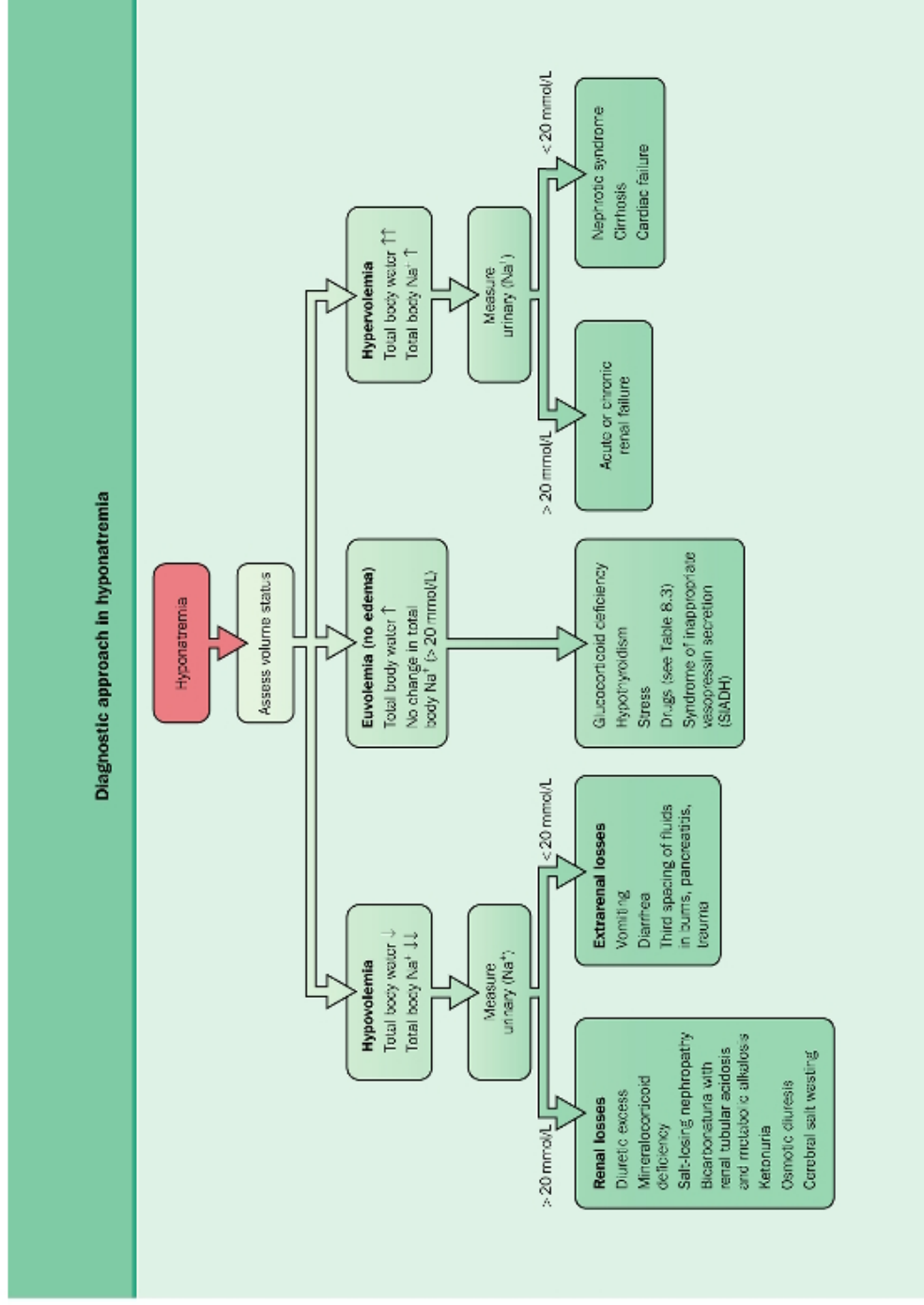


Source: Hall JB, Schmidt GA, Wood LDH: *Principles of Critical Care*, 3rd Edition: <http://www.accessmedicine.com>

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Clinical Diagnostic Algorithm for Hyponatremia

Johnson and Feehally (textbook)



Hypovolemia associated with decreased total body sodium

- GI losses and Third Space Sequestered Losses:
 - Urine Na will be low, usually $<10\text{mmol/L}$ and the urine is hyperosmolar.
 - In patients with vomiting and metabolic alkalosis, bicarbonaturia occurs and HCO_3 is lost with Na, so the urine Na may be greater than 20mmol/L , the Cl however will still be $<10\text{mmol/L}$
- Diuretics
 - Associated with high urine Na $>20\text{mmol/L}$.
 - Hyponatremia occurs almost exclusively with the use of thiazide diuretics.
 - Underweight women and elderly patients more prone to it.
 - Hyponatremia usually occurs within 14 days of initiation of therapy.

- **Salt Losing Nephropathy**
 - Occurs in patients with advanced CKD, and disorders such as Bartters and Gitlemans syndrome among others, and is characterized by hyponatremia and hypovolemia.
- **Mineralocorticoid deficiency**
 - Urine Na > 20mmol/L.
 - Decreased ECF volume provides the stimulus for vasopressin release.
- **Osmotic diuresis**
 - Diabetic patient with severe hyperglycemia, mannitol diuresis or urea diuresis after relief of urinary tract obstruction
 - Urinary Na typically >20mmol/L. Na wasting in diabetic is accentuated by ketonuria.
- **Cerebral salt wasting**
 - Usually occurs with subarachnoid hemorrhage. Mechanism postulated to be release of BNP from brain with resultant increase in Na excretion and hypovolemia

Hypervolemia associated with increased total body sodium

- Congestive Heart Failure
 - Decreased intravascular circulating volume.
 - Urine Na < 20mmol/L
- Hepatic Failure
 - Share same pathophysiologic mechanisms with patients with heart failure.
- Nephrotic Syndrome
 - Some patients have intravascular volume depletion resulting from hypoalbuminemia and lowered plasma oncotic pressure.
- Advanced CKD
 - Increased in fractional excretion of Na and narrow range of water handling leads to urine Na >20mmol/L and water retention.

Hyponatremia associated with normal total body sodium

- Glucocorticoid deficiency
- Hypothyroidism
- Psychosis
- Postoperative hyponatremia
- Drugs
- SIAD

Syndrome of Inappropriate Antidiuresis SIAD

- Newer terminology since not all patients have elevated circulating levels of AVP. It is divided into:
 - SIADH – Secretion of AVP is independent of serum osmolality.
 - Reset Osmostat – AVP does become fully suppressed, resulting in dilute urine, but at a S. Na lower than normal
 - Mutations in the water channel regulating vasopressin receptor, resulting in concentrated urine in the absence of AVP.

Diagnostic Criteria for SIAD

- Essential features:
 - S. Osmo < 275mOsm/Kg of water
 - U. Osmo > 100mOsm/Kg of water
 - Clinical Euvolemia
 - Urinary sodium >40 mmol/L (with normal dietary salt intake).
 - Normal thyroid, adrenal and renal function.
 - No recent use of antidiuretics
- Supplemental features:
 - Plasma uric acid <4 mg/dl
 - BUN < 10mg/dl
 - FeNa >1%: Feurea >55%
 - Failure to correct hyponatemia after 0.9% saline.

Drugs associated with hyponatremia

Johnson and Feehally (Textbook)

Drugs associated with hyponatremia*	
Vasopressin analogs	Drugs that potentiate renal action of vasopressin
Desmopressin (DDAVP) Oxytocin	Chlorpropamide Cyclophosphamide Nonsteroidal anti-inflammatory agents Acetaminophen (paracetamol)
Drugs that enhance vasopressin release	
Chlorpropamide Clofibrate <i>Carbamazepine–oxycarbazepine</i> Vincristine Nicotine Narcotics <i>Antipsychotics/antidepressants</i> Ifosfamide	Drugs that cause hyponatremia by unknown mechanisms <i>Haloperidol</i> Fluphenazine Amitriptyline Thioridazine Fluoxetine <i>Metamphetamine (MDMA or Ecstasy)</i> Sertraline
<p>*Not including diuretics Modified with permission from Veis and Berl¹⁹ Italics: The common causes</p>	

Hyponatremia not related to increased ADH secretion

- If initial urine osmolality is $< 100\text{mosmol/kg}$:
 - Psychogenic Polydipsia
 - Beer Potomania
- If initial urine osmolality is $> 100\text{mosmol/kg}$:
 - Reset osmostat
 - Salt losing nephropathy (renal sodium excretion from the excessive release of natriuretic factor in the brain)

Low Dietary Solute Intake

- Most people take in and excrete 600 – 1000mosmol/kg. Urinary osmoles are mainly salt and urea (glucose usually gets metabolized).
- Example: Person is taking in and excreting 600mosmol/kg. If you can dilute your urine down to 60mosmol/kg – you can excrete upto 10L urine/day.
- If someone only takes in 240mosmol/kg, then at the lowest urine osmolality (60 mosmol/kg), they can only excrete about 4L of urine/day. Therefore, if that person drinks any more than 4L/day, the extra water stays behind and causes hyponatremia.

Psychogenic Polydipsia

- Same concept applies:
 - If a person is taking in 600 mosmol/kg , at maximum urine dilution (60 mosmol/kg), they can only get rid of 10L of water. If they drink more than that they will retain water and become hyponatremic.

Range of Symptoms of Hyponatremia

- Non-specific Neurological Symptoms:

- Confusion
- Headache
- Nausea and vomiting
- Muscle cramps

- Severe Neurological Complications:

- Seizures
- Brainstem herniation
- Coma
- Death

Brain Adaptation to Hyponatremia

- Osmotic cerebral oedema that occurs with plasma hypo-osmolality and hyponatremia affects both intracellular and extracellular compartments in the gray and white matter.
- Cerebral oedema is counteracted by an adaptive process known as regulatory volume decrease (RVD) that normalizes cell volume.

Brain Adaptation to Hyponatremia

- RVD (Regulatory Volume Decrease):
 - 1- Displacement of fluid from the interstitial to the cerebrospinal fluid and systemic circulation (driven by hydrostatic pressure).
 - 2- Extrusion from the brain cells of inorganic, osmotically active solutes including sodium chloride (lost within minutes), potassium (more gradually – complete in about 3 hrs).
 - 3- Extrusion from the brain of organic osmolytes, primarily aminoacids (myoinositol is the most prevalent organic osmolyte in the human brain) – occurs over next 48 hrs.
- In animal studies we have seen these adaptive responses limit the increase in brain water to 4% higher than normonatremic animal. Without the extrusion of the organic osmolytes, the increase in brain water would be >10% - which is incompatible with survival.

Brain Adaptation to Hyponatremia

- Acute hyponatremia (over < 24 hr) can overwhelm this protective mechanism.
- If the decline in serum Na is slow and gradual (> 48hrs), cerebral swelling and the neurological symptoms are minimized.

Correction of Hyponatremia

- The plasma sodium concentration can be raised in hyponatremic patients either by:
 - Restricting water intake.
 - By giving salt.
 - By giving vasopressin receptor antagonist.
- The choice of therapy is primarily governed by the cause and severity of the hyponatremia.

Correction of Hyponatremia

- Symptomatic/Acute Hyponatremia - correct by 1.5 – 2.0 Meq/l per hr. in first 4 hrs, but total correction for 24hr. should still be about 12 MEQ/L per day.
- Asymptomatic/Chronic Hyponatremia – correct by 0.5Meq/L per hr., or 10 – 12 Meq/L per day.

Calculating the rate of correction for severe symptomatic hyponatremia with 3% saline based on Na deficit

Example: 70kg patient with S. Na of 110.

- $(0.6 \times 70 \text{ kg}) \times (120 - 110) = 420 \text{ MEQ deficit of Na.}$
- Correct at rate of 1.5meq/L/hr you would require to give 420meq over 6.6hr. - 64 meq/hr.
- 3% NS has 513 MEQ/L of Na – therefore roughly every 2cc of 3% saline will have 1meq of Na. You would have to give 128cc/hr.
- This should be the initial correction rate for the first 4 hrs, checking the labs q 2hr. Remember you want to correct 10 -12 MEQ total over 24 hrs.

Why not use 0.9% NS alone to correct S. Na in SIADH

- Urine osmolality is 600mosmols/kg and we give NS which has approximately 150meq or both Na and Cl (total 300mosmol).
- NaCl excretion is intact in SIADH.
- Then the 300mosmol will be excreted in 500cc of urine, leaving behind 500 free water and therefore worsening underlying hyponatremia.
- In SIADH, you need to have intake which is more concentrated than the urine (eg water restriction, salt tablets, 3% NS or saline plus lasix).

Treatment of Chronic Hyponatremia due to SIAD

- Restrict fluid intake
- Encourage dietary intake of salt and protein
- Demeclocycline 300 – 600mg bid or urea 15-60gm daily
- Vasopressin receptor antagonist (when available orally).

Treatment of chronic asymptomatic hyponatremia

Johnson and Feehally (Textbook)

Treatment of chronic asymptomatic hyponatremia					
Treatment	Mechanism of action	Dose	Advantages	Limitations	
Fluid restriction	Decreases availability of free water	Variable	Effective and inexpensive Not complicated	Non-compliance	
Pharmacologic inhibition of vasopressin action					
Lithium	Inhibits the kidney's response to vasopressin	900–1200 mg daily	Unrestricted water intake	Polyuria, narrow therapeutic range, neurotoxicity	
Demeclocycline	Inhibits the kidney's response to vasopressin	300–600 mg twice daily	Effective; unrestricted water intake	Neurotoxicity, polyuria, photosensitivity, nephrotoxicity	
V ₂ receptor antagonist	Antagonizes vasopressin action	–	Ongoing trials	–	
Increased solute (salt) intake					
with furosemide (furosemide)	Increases free water clearance	Titrate to optimal dose; coadministration of 2–3 g NaCl	Effective	Ototoxicity, K ⁺ depletion	
with urea	Osmotic diuresis	30–60 g daily	Effective; unrestricted water intake	Polyuria, unpalatable, gastrointestinal symptoms	

Vaptans

- AVP (Arginine Vasopressin) receptor antagonist.
- Conivaptan – IV agent works on both V2 and V1 receptors. Approved by FDA for treatment of euvolemic hyponatremia in hospitalized patients.
- Lixivaptan and Tolvaptan – oral agent, acts on V2 receptors.
- Main side effects seem to be thirst.

Osmotic Demyelination Syndrome

- Overly rapid correction of S.Na results in dehydration of neurons and glia which leads to ODS.
- Correction of hyponatremia causes efflux of water from the brain, triggering a “de-adaptation process”
- The inorganic and organic osmolytes which were lost during RVD (regulatory volume decrease) re-enter the brain and re-establish osmotic equilibrium.
- The reuptake of organic osmolytes after correction of hyponatremia is slower than the initial loss during the adaptation to hyponatremia.
- People with malnutrition, Chronic ETOH abuse and hypokalemia are more at risk of ODS.

Osmotic Demyelination Syndrome

- Includes both central pontine and extrapontine myelinolysis.
- Begins with lethargy and affective changes, followed by mutism or dysarthria, spastic quadriparesis and pseudobulbar palsy.

Patients at risk for neurologic complications

Johnson and Feehally (textbook)

Hyponatremic patients at risk for neurologic complications	
Acute cerebral edema	Osmotic demyelination syndrome
Postoperative menstruant females	Alcoholics
Elderly women taking thiazides	Malnourished patients
Children	Hypokalemic patients
Psychiatric polydipsic patients	Burn victims
Hypoxemic patients	Elderly women on thiazide diuretics
Hypoxemia	
With permission from Lauriat and Berl ^{2,4}	

Hypernatremia

Pathogenesis of Hypernatremia

- Decreased free water supply.
 - Poor access to free water.
 - Hypothalamic lesions affecting thirst.
- Water loss
 - Renal: Osmotic diuresis, Central or Nephrogenic DI.
 - GI: Osmotic diarrhea
 - Insensible losses: Fever, Exercise and exposure to heat.
- Solute load
 - Administration of hypertonic sodium containing solutions.

Workup of Hypernatremia

- Why is the patient not drinking?
- Is there increased free water loss:
 - ?Polyuria
 - Uosm: if < 250 – DI
 - Uosm: if > 300 – Solute diuresis
 - ?GI (Osmotic diarrhea)
- Is the patient getting too much solute?

Treatment of Hypernatremia

- Provide free water.
- Calculate the free water deficit:
 - 0.5 x body weight x (PNa/140 – 1) for men
 - 0.4 x body weight c (PNa/140 – 1) for women
- Rate of correction for Na 0.5meq/hr.

Example of Hypernatremia

- 60 year old female with ARDS on ventilator support on pressors and TPN. Hemodynamically stable.
 - PNa = 150. Urine output 150ml/hr
 - U osm = 504 U Na = 40meq
 - Urine dipstick = 2+ S glucose = 400
- What is the cause of hypernatremia?
- How would you treat him?

Calculation of water deficit

- Calculate amount of water:
 - $0.4 \times \text{body weight} \times (\text{PNa}/140 - 1)$
 - $0.4 \times 50 \times (150/140 - 1) = 1.4 \text{ liters}$
 - Insensible losses = 1.0 liters
 - Total volume = 2.4 liters
- Rate (0.5meq/hour)
 - For Na to go from 150 to 140 = 20hrs.
 - Prescription: $2400/20 = 120\text{ml/hr}$ free water

TABLE 2. FORMULAS FOR USE IN MANAGING HYPERNATREMIA AND CHARACTERISTICS OF INFUSATES.

FORMULA ^a	CLINICAL USE
1. Change in serum Na ⁺ = $\frac{\text{infusate Na}^+ - \text{serum Na}^+}{\text{total body water} + 1}$	Estimate the effect of 1 liter of any infusate on serum Na ⁺
2. Change in serum Na ⁺ = $\frac{(\text{infusate Na}^+ + \text{infusate K}^+) - \text{serum Na}^+}{\text{total body water} + 1}$	Estimate the effect of 1 liter of any infusate containing Na ⁺ and K ⁺ on serum Na ⁺
INFUSATE	EXTRACELLULAR-FLUID DISTRIBUTION
	mmol per liter
5% Dextrose in water	0
0.2% Sodium chloride in 5% dextrose in water	34
0.45% Sodium chloride in water	77
Binger's lactate	130
0.9% Sodium chloride in water	154
	%
	40
	55
	73
	97
	100



• End