Clinical approach to dysnatremias

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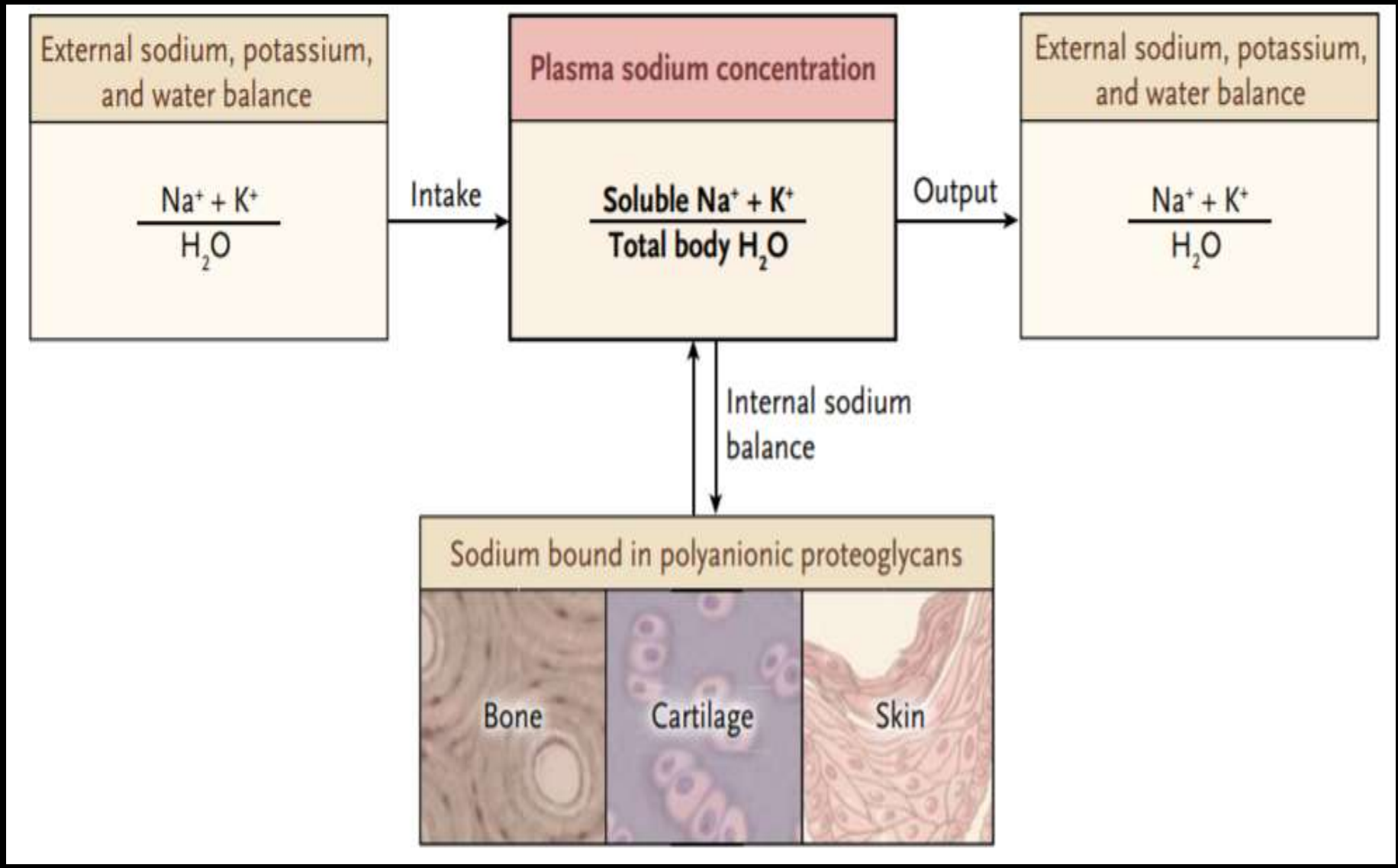
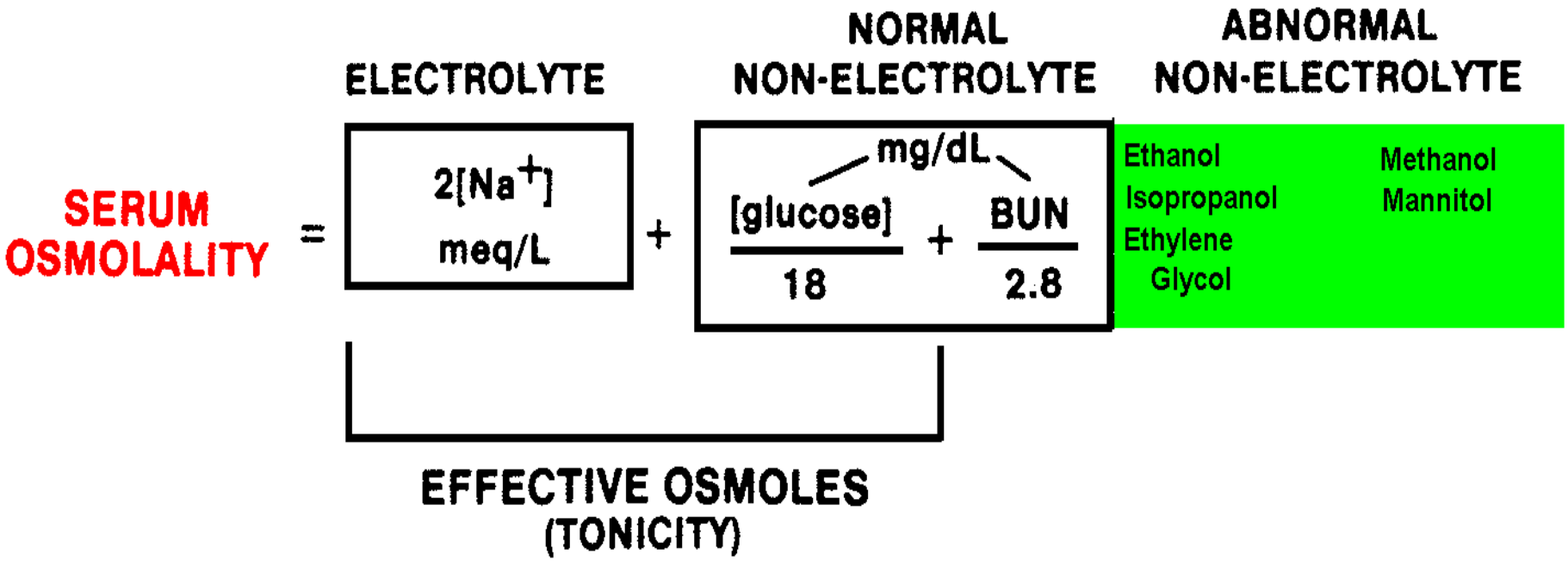
Internal and external solute and water balance and the plasma sodium concentration



Sterns R N Engl J Med 2015;372:55-65

Serum osmolality,calculated and measured, tonicity



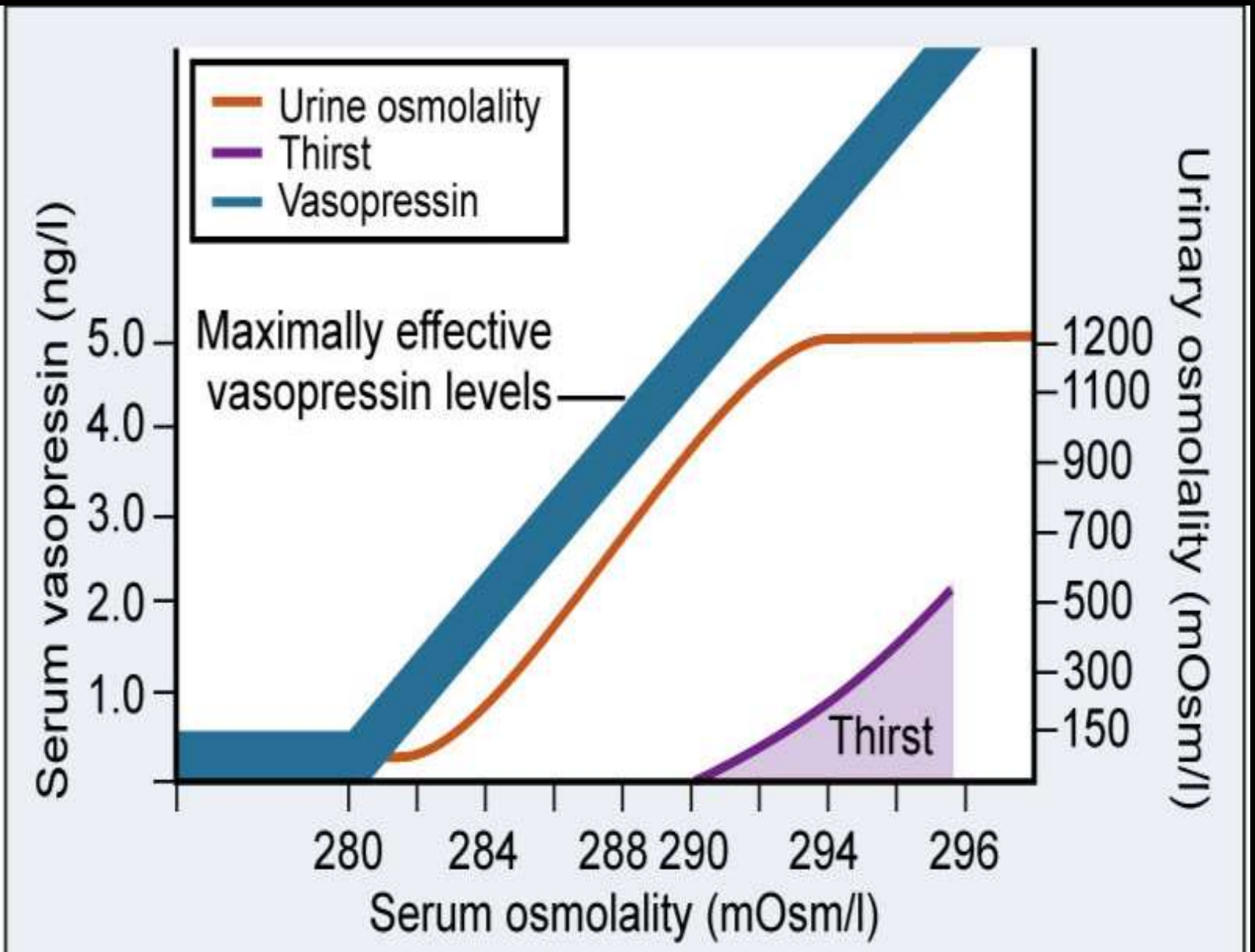
NORMAL:

CALCULATED OSM ± 10 mOsm/L = MEASURED OSM
(Na, Glucose, BUN)

OSMOLAL GAP:

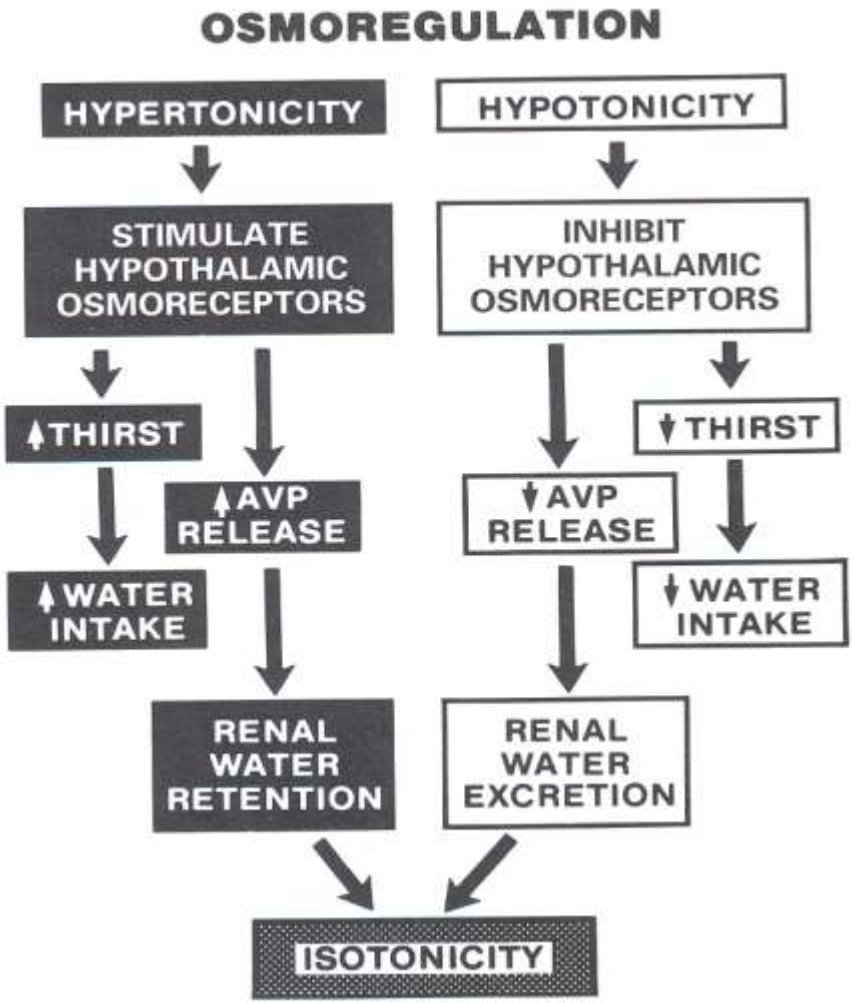
CALCULATED OSM << MEASURED OSM
(NON-ELECTROLYTE solute other than glucose or urea;or pseudohyponatremia)

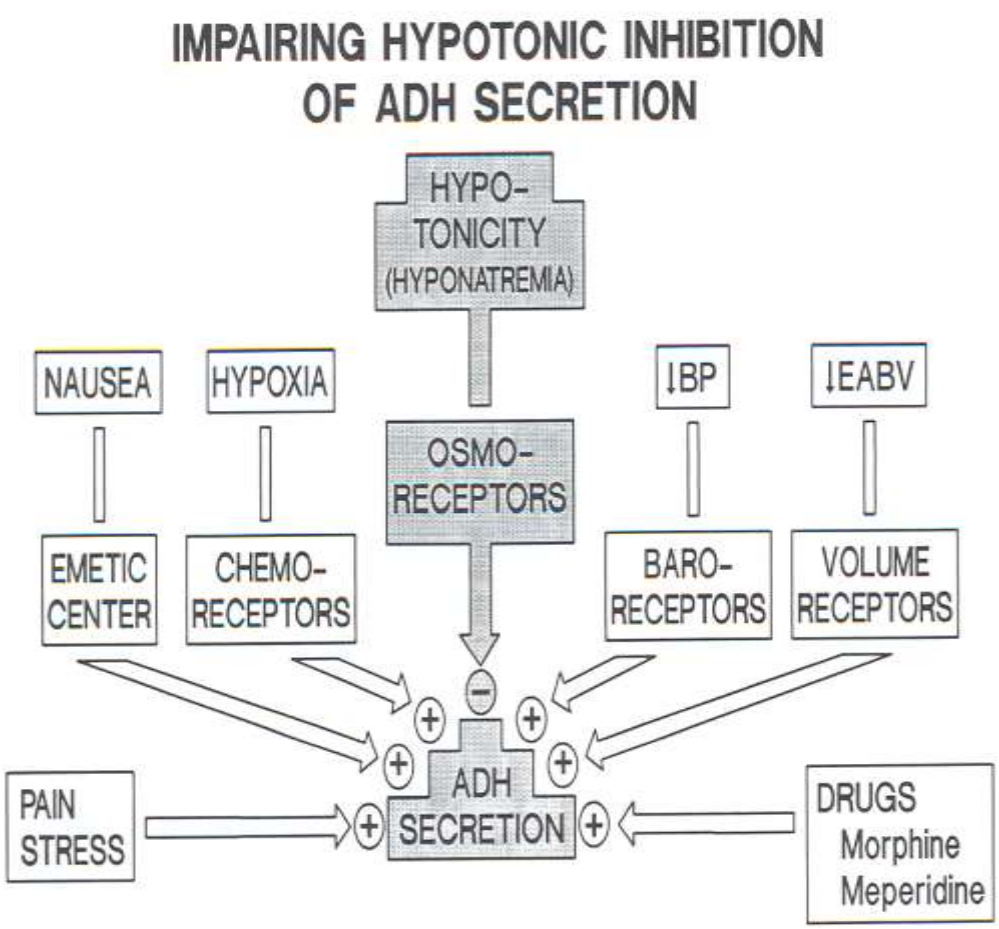
Vasopressin and thirst response to changes in serum osmolality



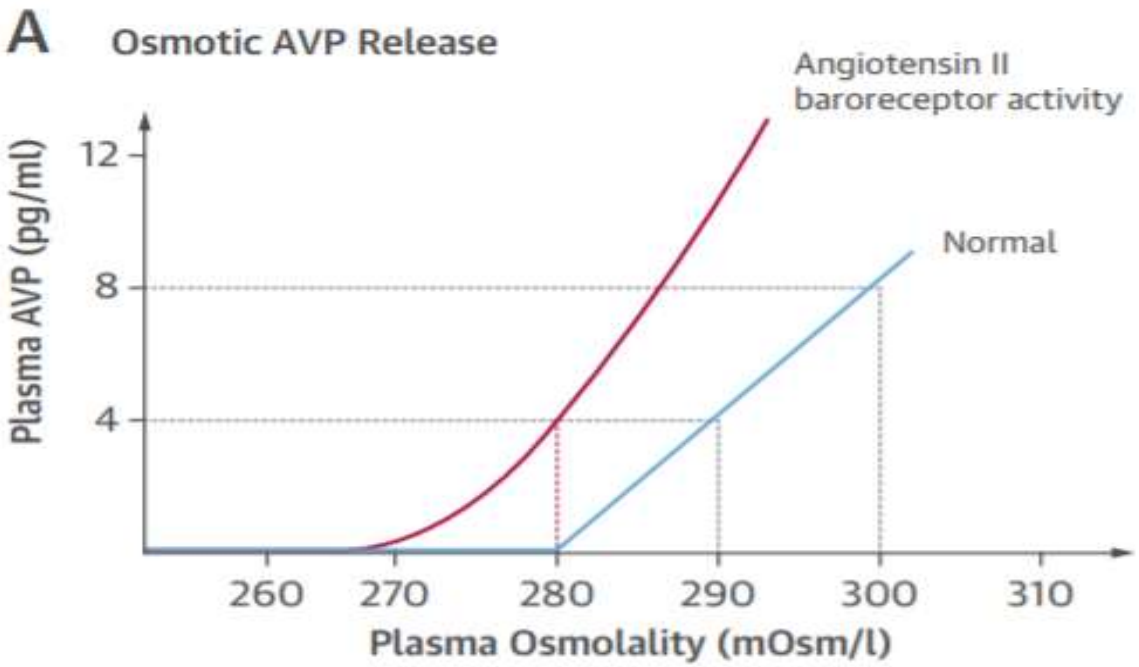
Comprehensive Clin Nephrology Eds Floege et al, 2010

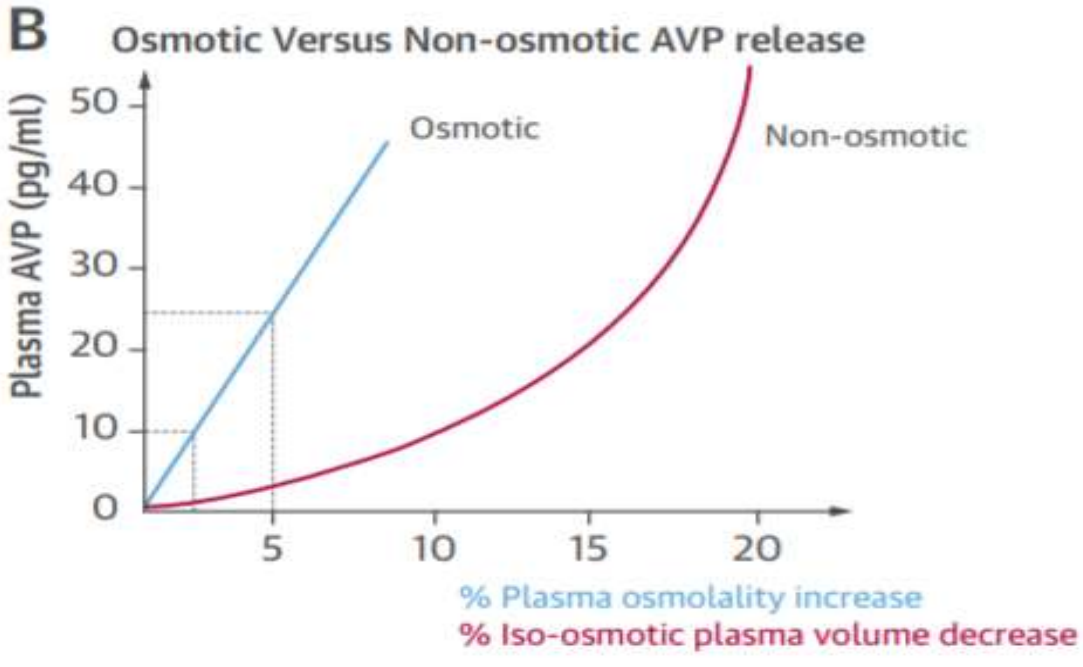
Tonic and non-tonic regulation of water balance





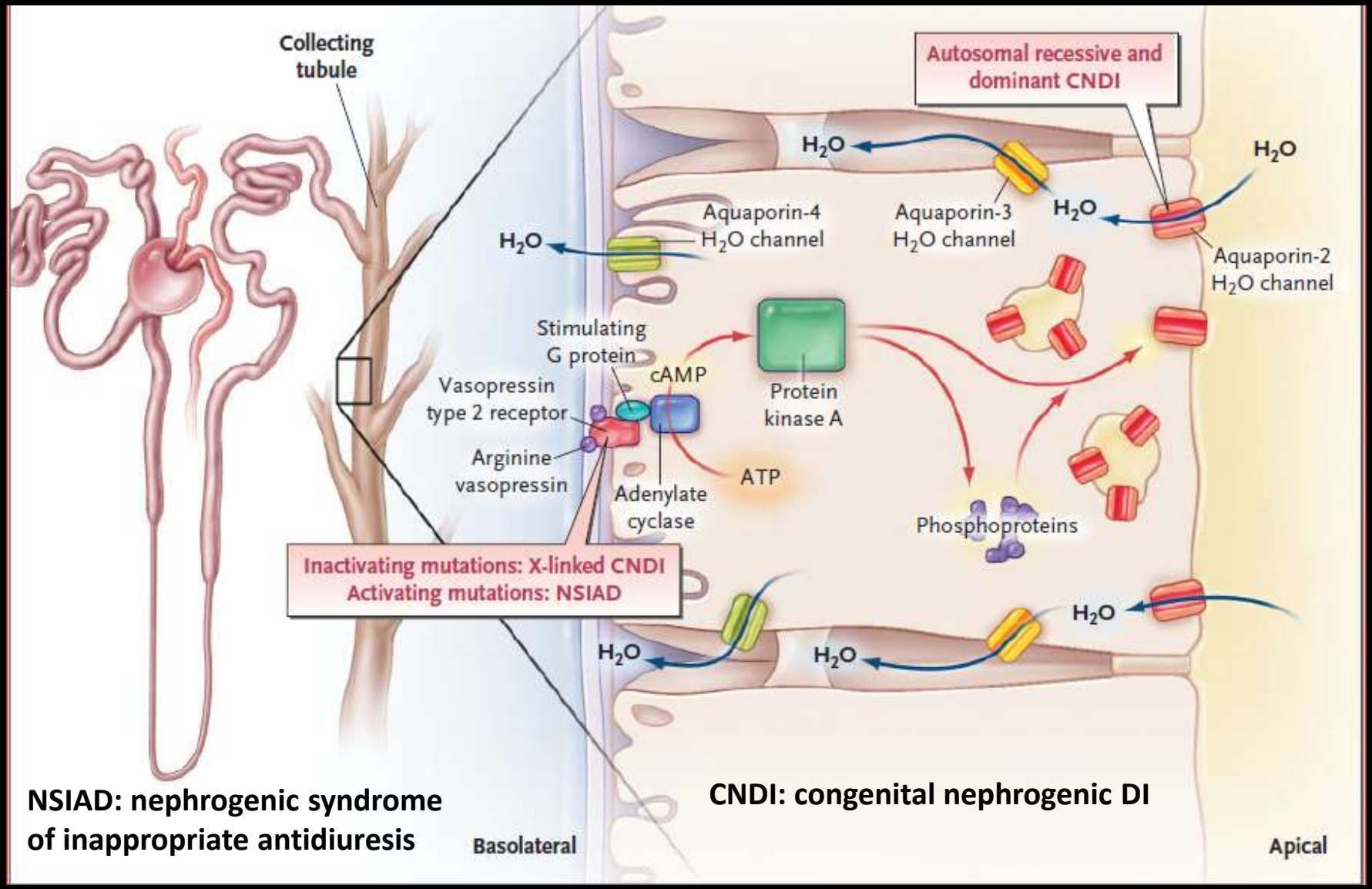
Determinants of AVP plasma levels





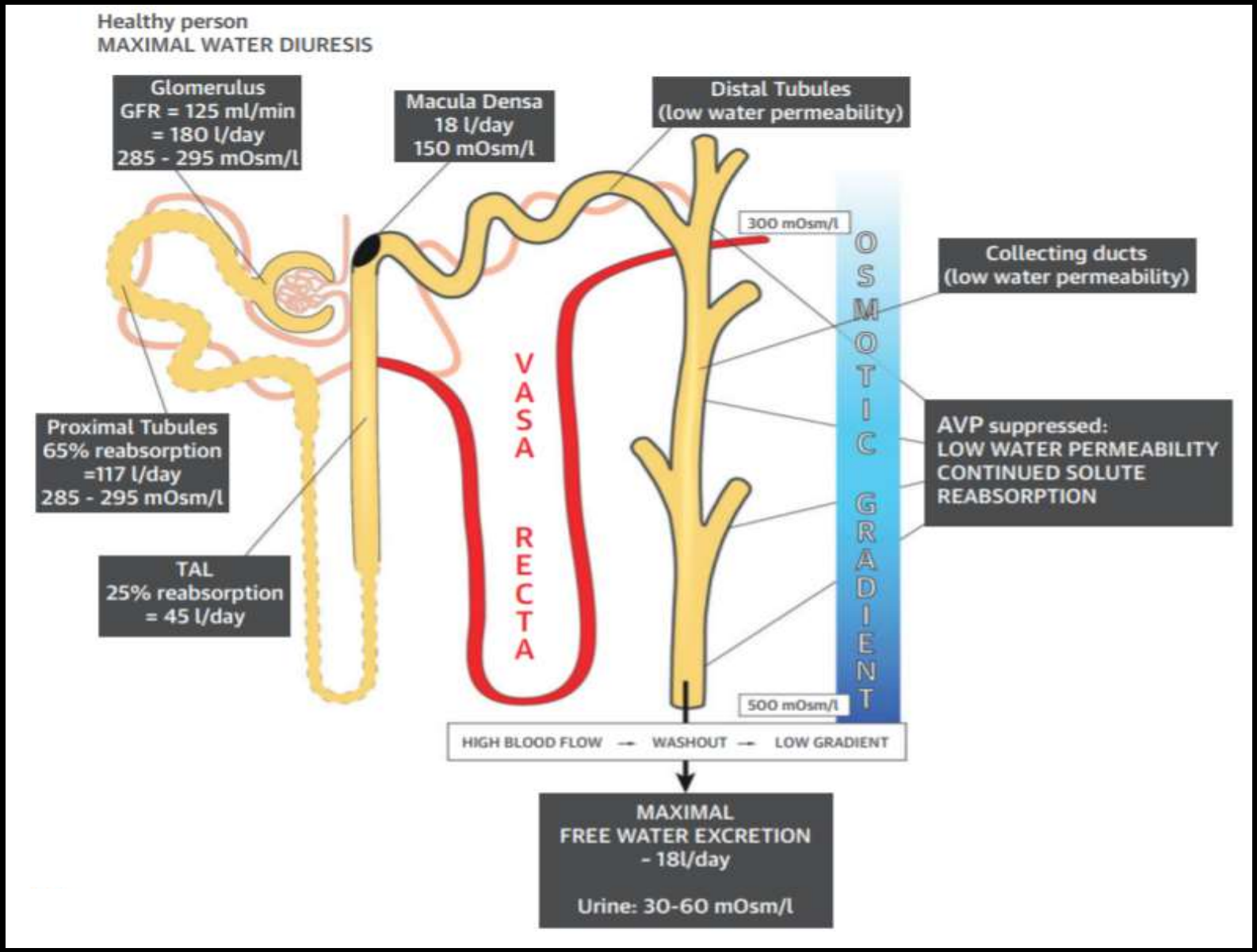
Verbrugge et al, J Am Coll Cardiol 2015;65:480–492

Pathway of AVP signaling in collecting duct cells involved in water excretion



Knoers N, N Engl J Med; **352;** 1847-1850**, 2005**

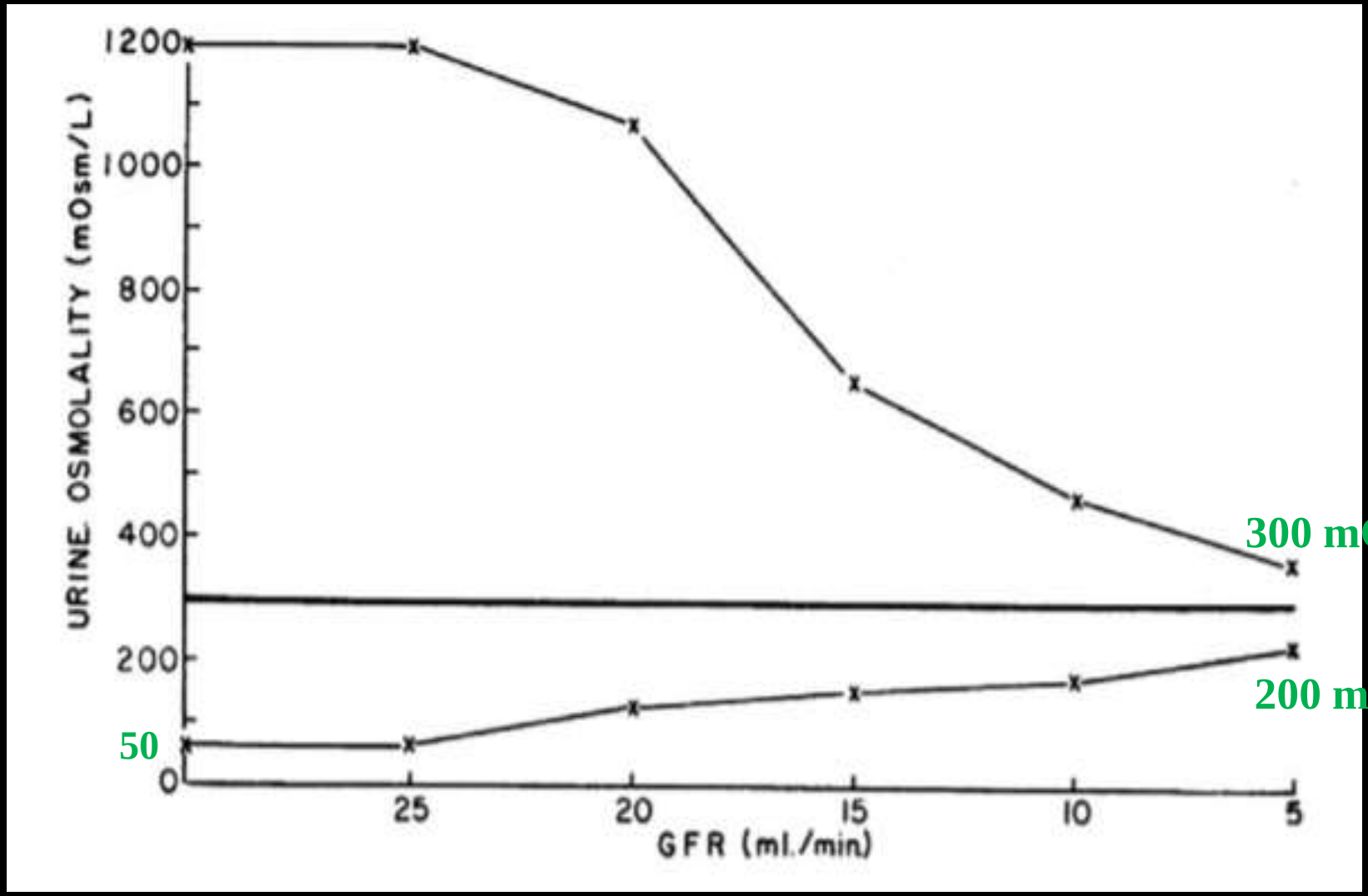
Maximal free water excretion in healthy subjects



Verbrugge et al, J Am Coll Cardiol 2015;65:480–492

Theoretical maximal and minimal urinary osmolalities in progressive kidney disease

(assuming solute excretion of 600 mOsm/24 h)



Bricker et al , J Clin Invest. 1959;38(3):516- 523

	Urine concentration	Osmolality, mOsm/kg[1]
Na	50 mEq/l	100
K	20 mEq/l	40
Urea	168 mg/dl	60
Osmolality		200
Effective osmolality (tonicity)		140

Total osmolar load needing to be excreted, mOsm/day	Obligate urine output, l/day[1]	Electrolyte-free water clearance, l/day[1]
600	3	1.5
300	1.5	0.75
150	0.75	0.375

[1] Assumes that the urine osmolality is 200 mOsm/kg and the tonicity is 140 mOsm/kg or approximately half of the serum tonicity.

A hypothetical patient with mild urinary diluting capacity

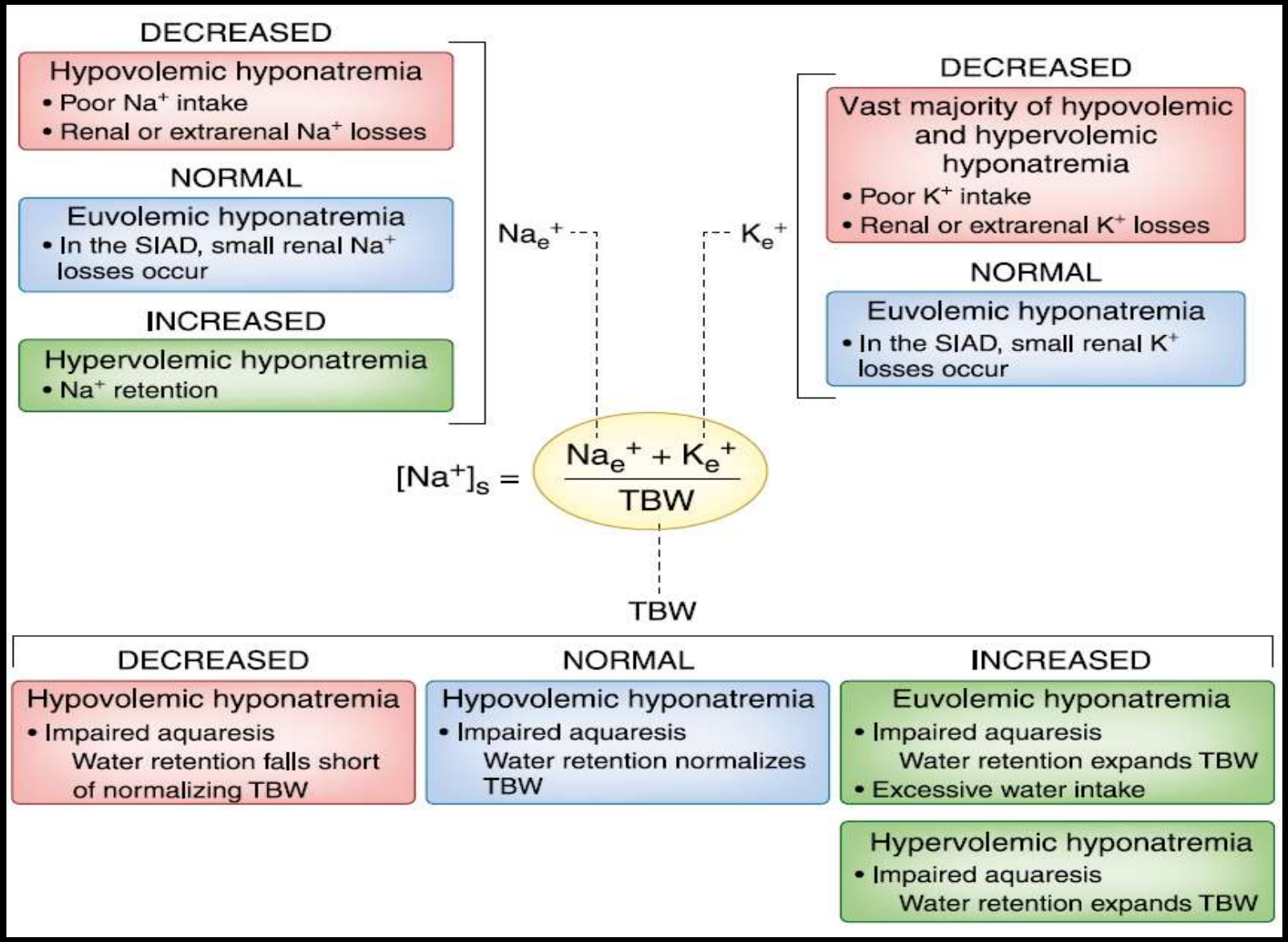
Osmolar contribution of electrolytes= Na+ K (mmol/l) x 2
Osmolar contibution of urea = concentration in mg/dl divided by 2.8

Obligate urine volume (l/day) and electrolyte-free water clearance l/day in function of total osmolar load to be excreted (mOsm/day)

McGreal et al, Kidney Dis 2016;2:56–63

	Potomania	Potomania + protein and NaCl restricion
GFR L/24 hour	160 L	160 L
Max distal delivery	30 L	30 L
Osmotic load	750 mOsm	300 mOsm
Max diuresis	15 L	6 L
Uosm	50 mOsm /L	50 mOsm/L
Fluid intake	15 L	15 L
Plasma sodium (mmol/L)	140	110

Pathogenesis of hypotonic hyponatremia as derived from the Edelman equation



Adrogué, Madias, JASN 23: 1140–1148, 2012

Hyponatremia- General Concepts

(1) **Plasma osmolality** ~ $\frac{\text{Extracellular + Intracellular solutes}}{\text{TBW}}$

(2) **Plasma osmolality** ~ $\frac{[(2 \times Na_e + 2 \times K_e)]}{\text{TBW}}$

(3) **Plasma Na** ~ $\frac{[(Na_e + K_e)]}{\text{TBW}}$

Clinical significance of hyponatremia

- Hyponatraemia is the most common electrolyte disorder in hospitalised patients
  - In a prospective study between 2002 and 2003, hyponatraemia was present on admission in 14.5% of 98,411 hospitalised patients[1]
- Hyponatraemia is associated with:
  - Increased morbidity
    - Gait and attention impairments, which may lead to falls and fractures and subsequent increased hospitalisation[2,3]
  - Increased length of hospital stay[4-6]
  - Increased risk of death (in hospital and 1 year and 5 years post discharge), even in mild hyponatraemia[1]
    - Mortality is 60 x greater in severe hyponatraemia (< 120 mmol/l), even in the absence of symptoms, compared with normonatraemic patients[7]

1. Waikar SS, et al. *Am J Med*. 2009;122:857–865.
2. Renneboog B, et al. *Am J Med*. 2006;119:71.e1–8.
3. Kenge FG, et al. *Q J Med*. 2008;101:583–588.
4. Sherlock M, et al. *Clin Endocrinol*. 2006;64:250–254.
5. Sherlock M, et al. *PMJ*. 2009;85:171–175.
6. Gill G, et al. *Clin Endocrinol*. 2006;64:246–249.
7. Anderson RJ, et al. *Ann Intern Med*. 1985;102:164-168.

Relation of dysnatremia with mortality in critically ill patients

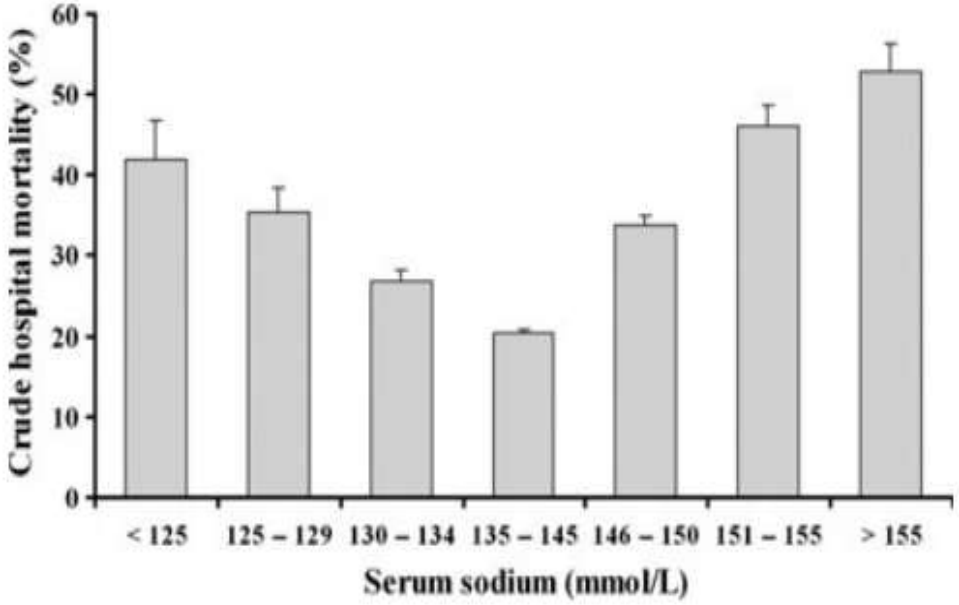
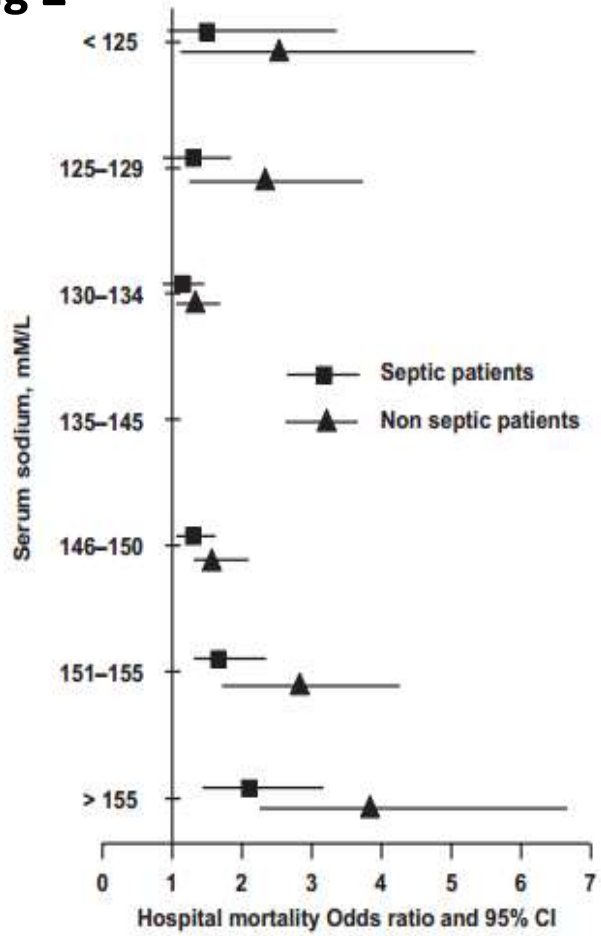


Figure 1 Crude hospital mortality in the different categories of natraemia.

Fig 2: odds for mortality in septic vs non septic ptients

Fig 2



Vandergheynst et al, Eur J Clin Invest 2013; 43 (9): 933–948

Hyponatremia: classification by neurological symptoms

	Serum sodium	Neurological symptoms	Typical duration of hyponatremia
Severe	< 125 mmol/L	Vomiting, seizures, obtundation, respiratory distress, coma	Acute (< 24-48 hrs)
Moderate	< 130 mmol/L	Nausea, confusion, disorientation, altered mental status, unstable gait/falls	Intermediate or chronic (> 24-48 hrs)
Mild	< 135 mmol/L	Headache, irritability, difficulty concentrating, altered mood, depression	Chronic (several days, to many weeks-months)

The severity of neurological symptoms is more dependent on the degree of brain volume regulation than on the serum (Na+]

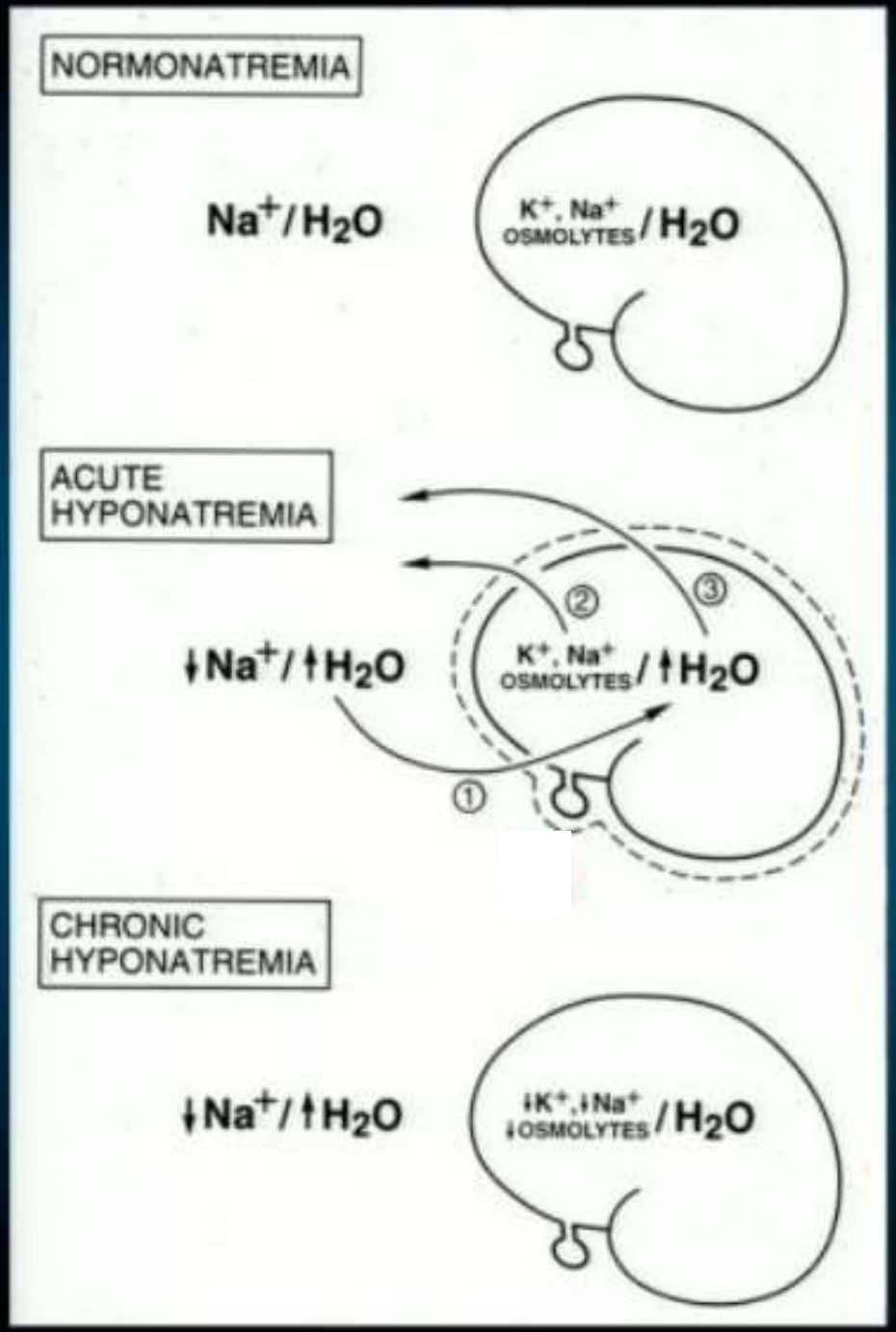
Chronic hyponatremia is associated with much less severe symptomatology

	acute	chronic
patients	14	52
duration	< 12 hrs	3 days
serum [Na^+]	112 ± 2	118 ± 1
stupor or coma	100%	6%
seizures	29%	4%
mortality	50%	6%
low [Na^+] deaths	36%	0%

Arieff et al. *Medicine* 56:121, 1976 (hospital consults in one year; [Na^+]<128 mmol/L)

brain volume regulation

1. true loss of brain solute
2. can reduce or eliminate brain edema despite severe hypoosmolality
3. time dependent process



Gullans & Verbalis
Ann Rev Med
44:289-301, 1993

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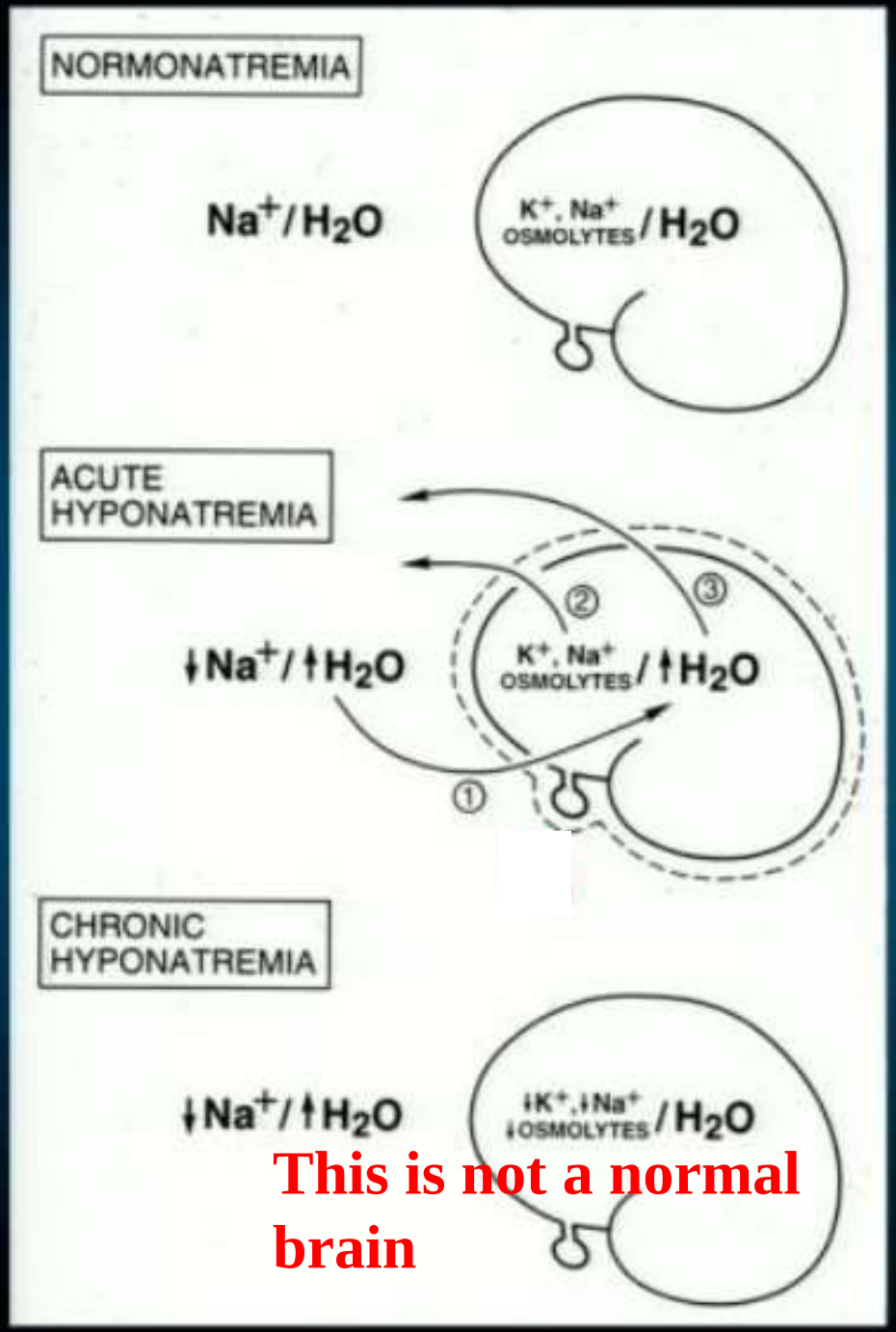
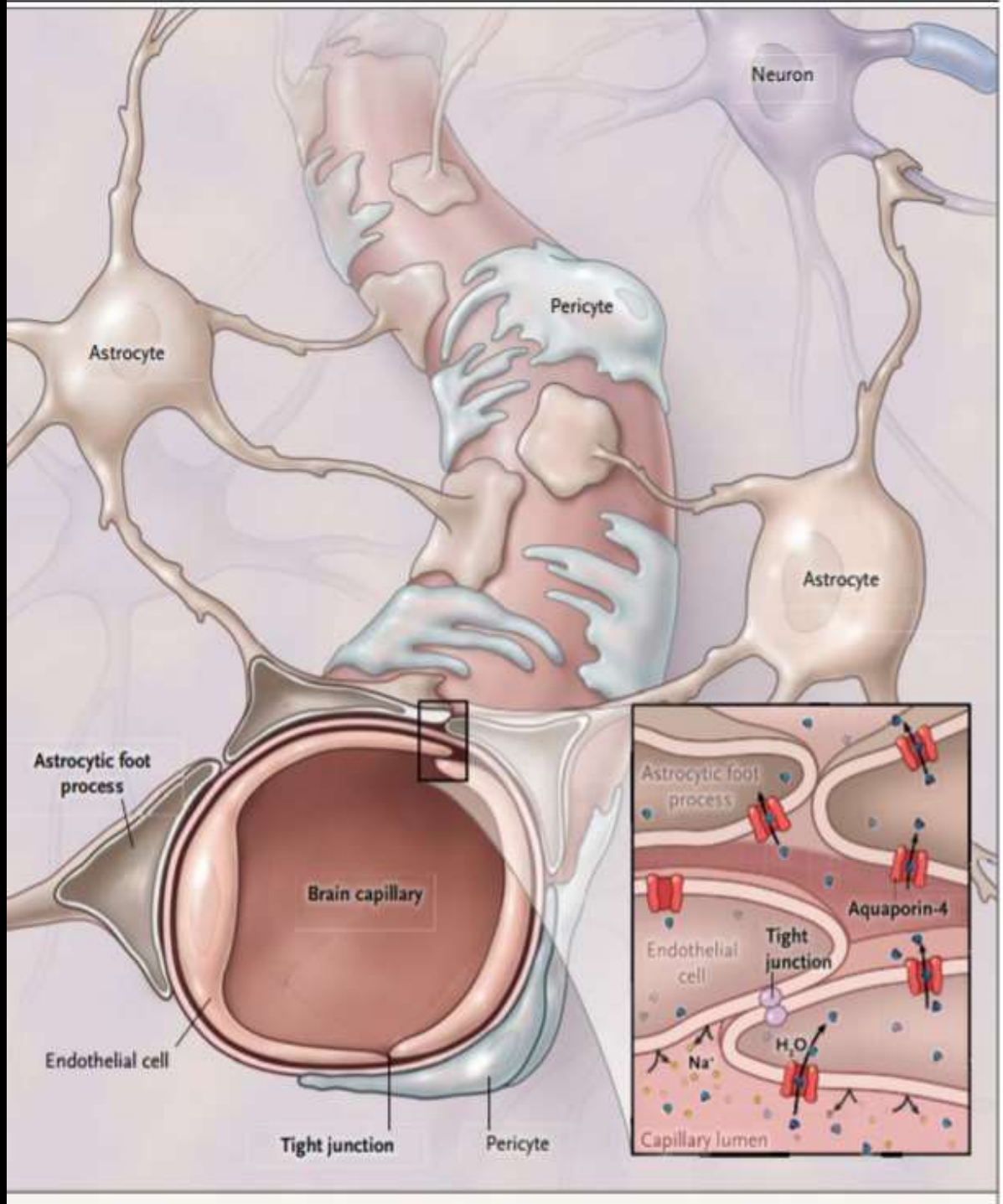


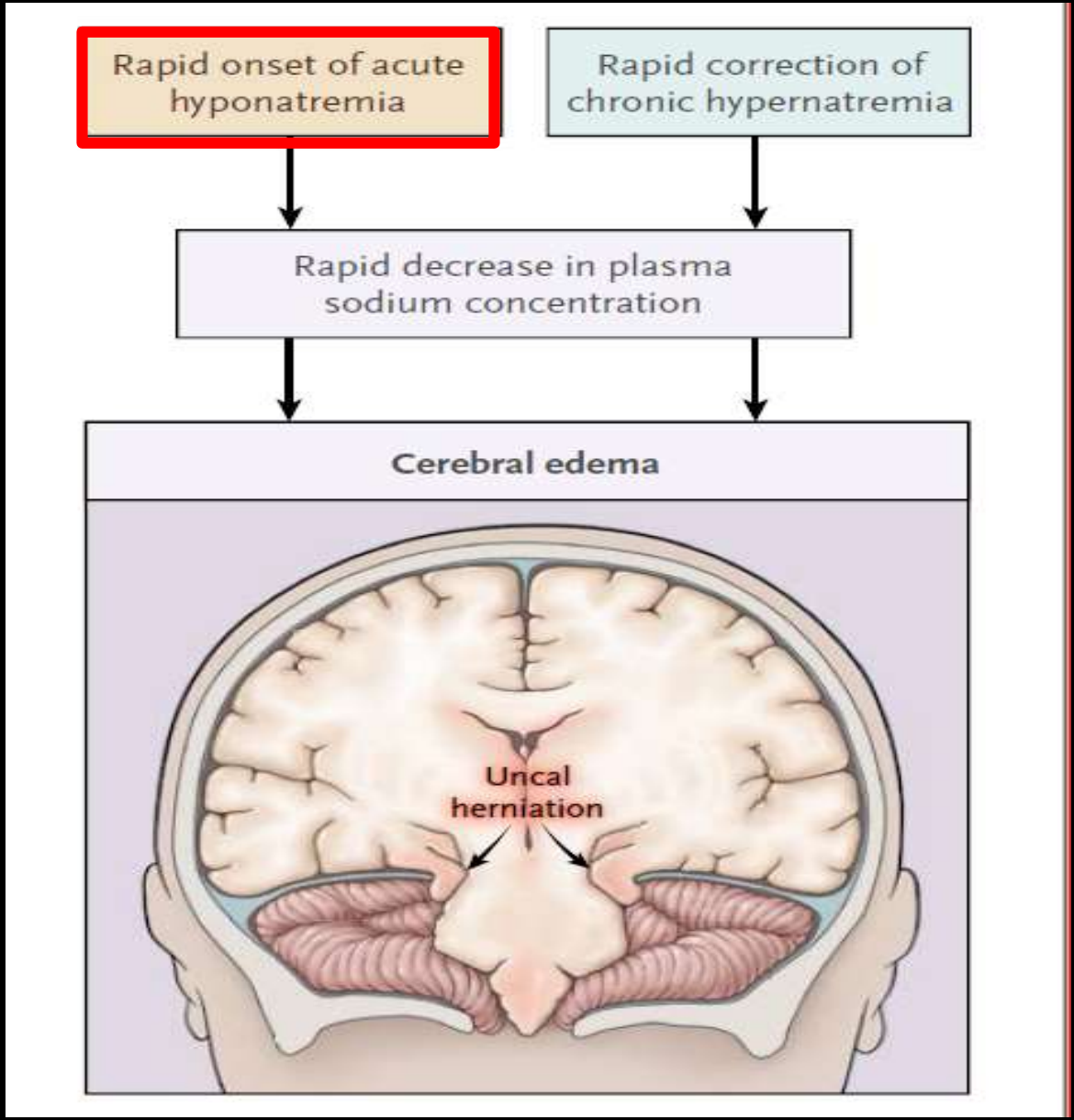
This is not a normal brain

Astrocytes and the neurovascular unit



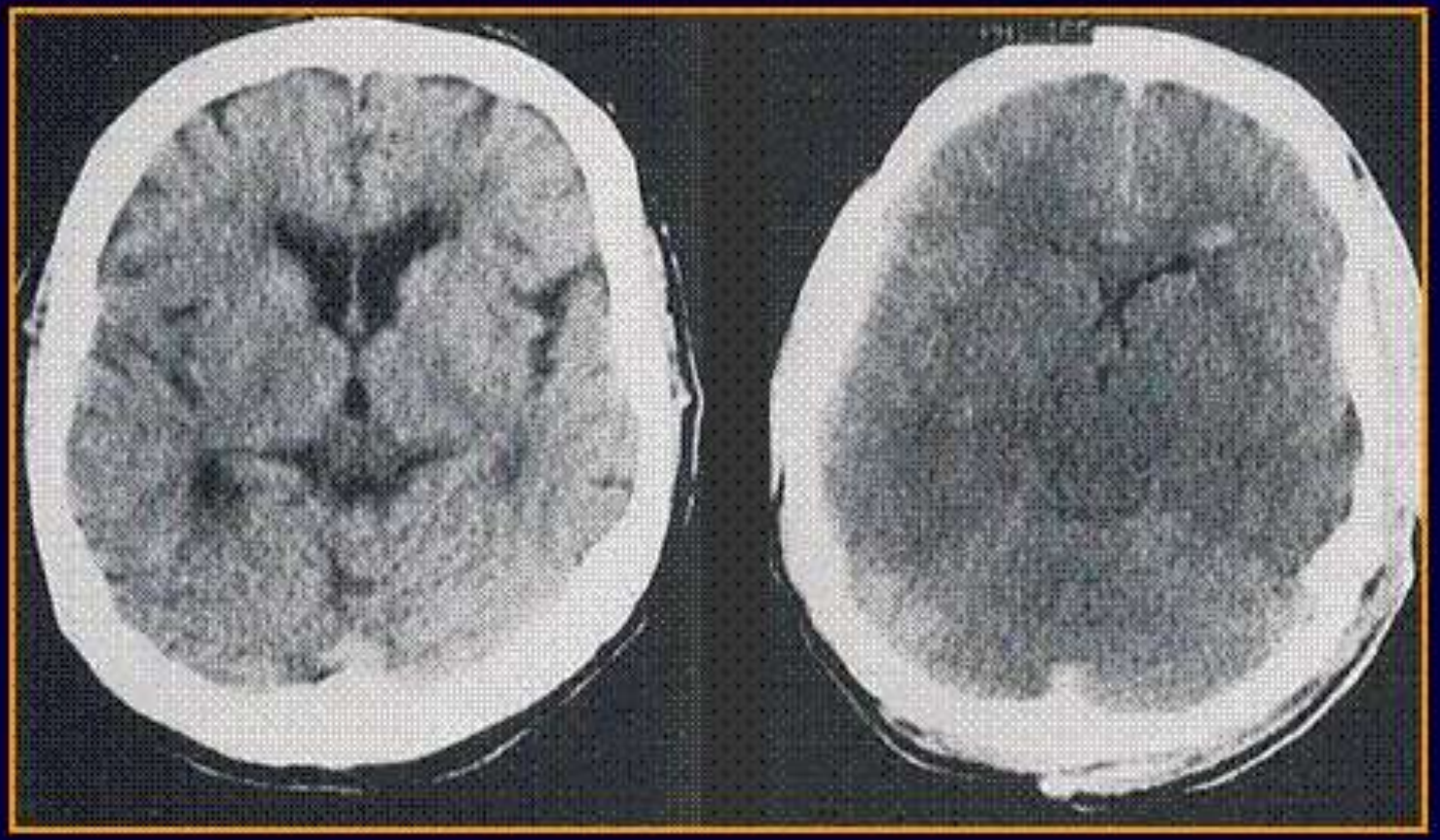
Sterns R N Engl J Med 2015;372:55-65

Consequences of Rapid Changes in the Plasma Na



Sterns RH, **N Engl J Med 2015;372:55-65.**

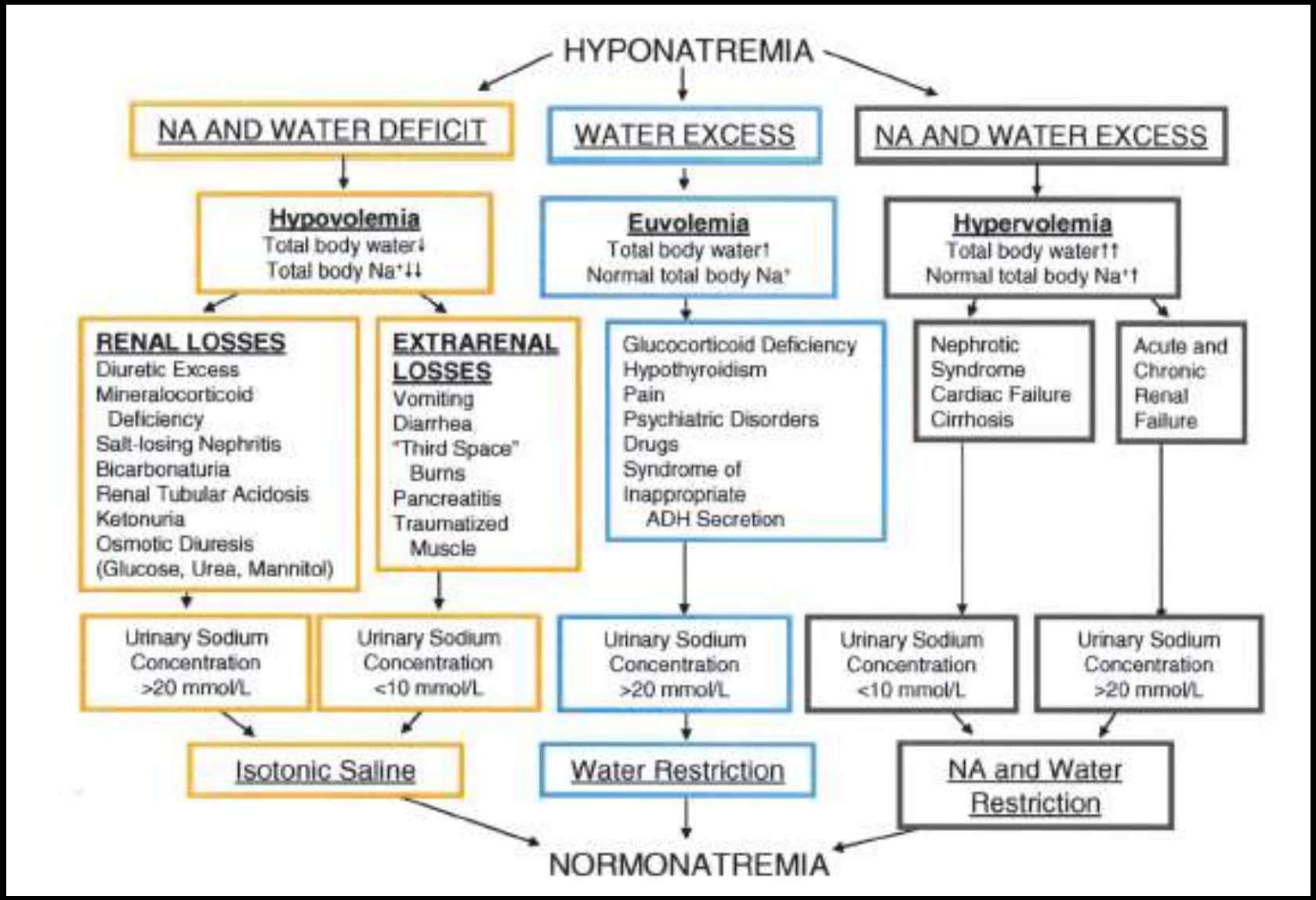
Brain CT Scans



Normal Study

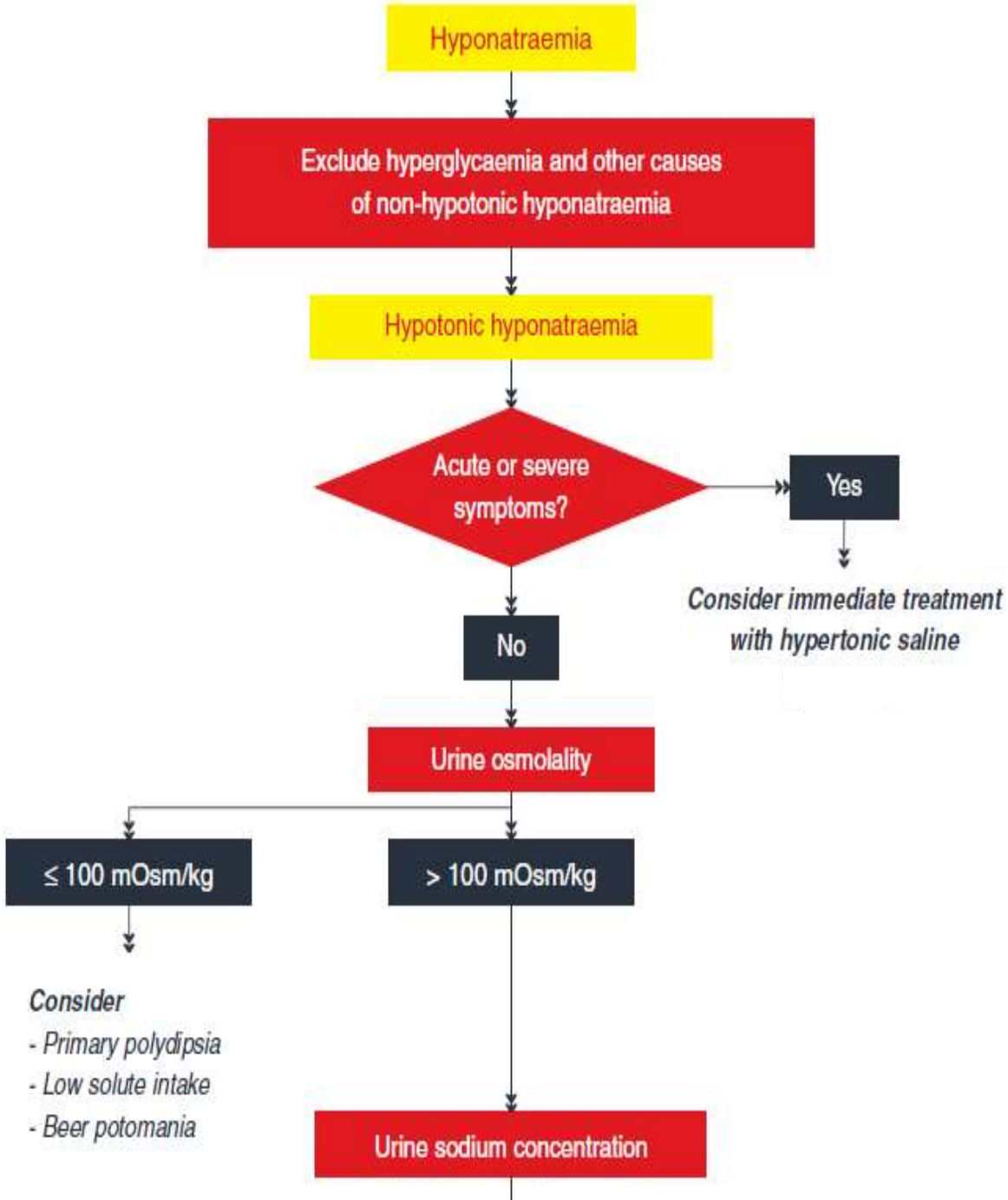
Fatal Hyponatremia

Diagnostic and therapeutic approach to the 3 forms of hyponatraemia



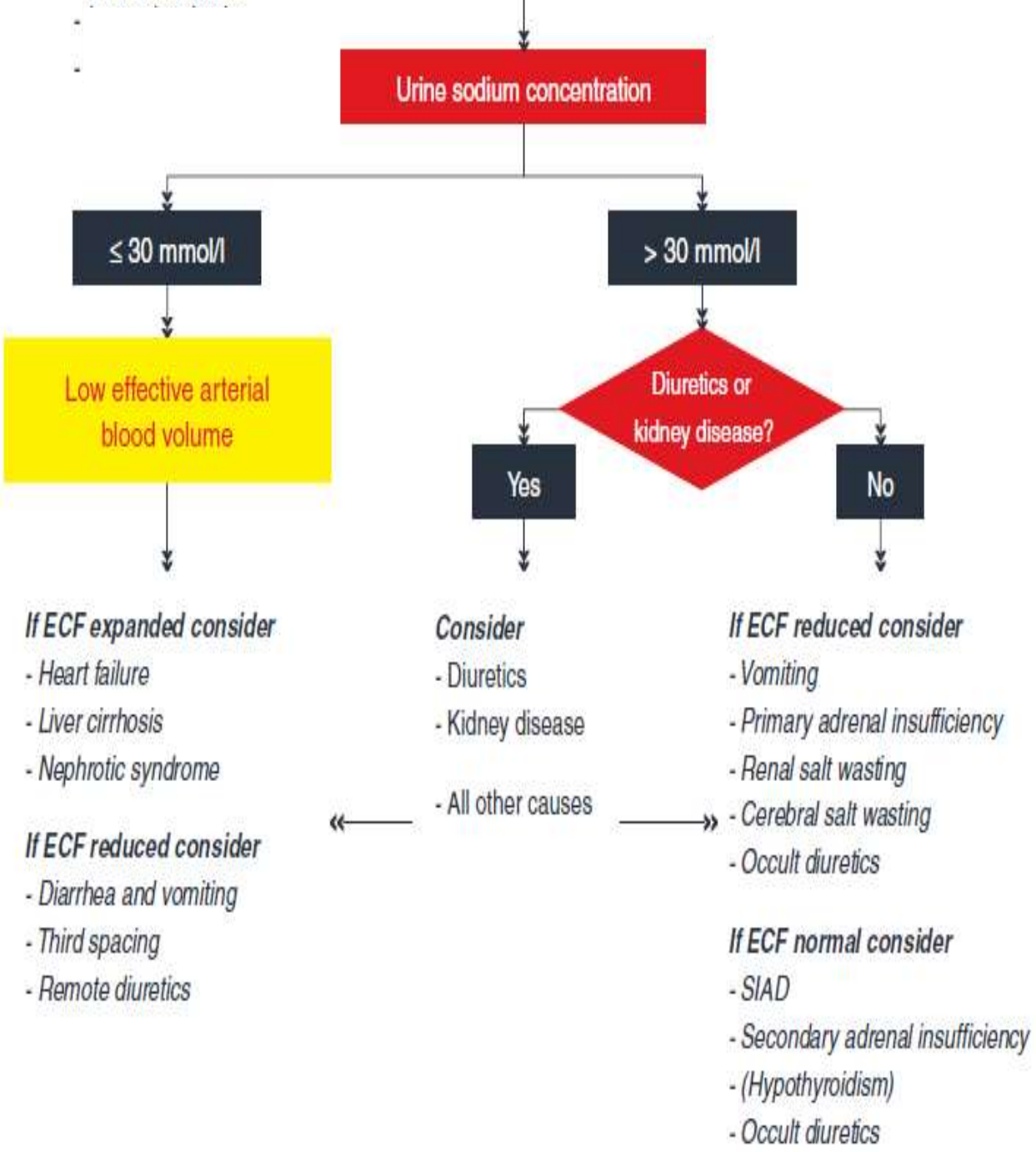
Schrier RW, *J Am Soc Nephrol* 17: 1820–1832, 2006.

An alternative algorithm for the diagnosis of hyponatremia (1)



Spasovski et al, European Journal of Endocrinology (2014) 170, G1–G47

An alternative algorithm for the diagnosis of hyponatremia (2)



Spasovski et al, European Journal of Endocrinology (2014) 170, G1–G47

Conditions and drugs associated with acute hyponatremia (< 48h)

Postoperative phase
Post-resection of the prostate, post-resection of endoscopic uterine surgery
Polydipsia
Exercise
Recent thiazides prescription
3,4-Methylenedioxymethamfetamine (MDMA, XTC)
Colonoscopy preparation
Cyclophosphamide (i.v.)
Oxytocin
Recently started desmopressin therapy
Recently started terlipressin, vasopressin

Recommendations to avoid post-operative hyponatremia

- Never infuse electrolyte-free water in the acute perioperative setting. Give very little water by mouth until a dilute urine can be excreted.
- Even mild symptoms (mild nausea, headache) might be followed by a sudden and catastrophic herniation of the brain.
- Be very suspicious of a “good” urine output because this might be hypertonic to the infused solutions and generate electrolyte-free water- the desalination process.

Criteria for the diagnosis of SIADH

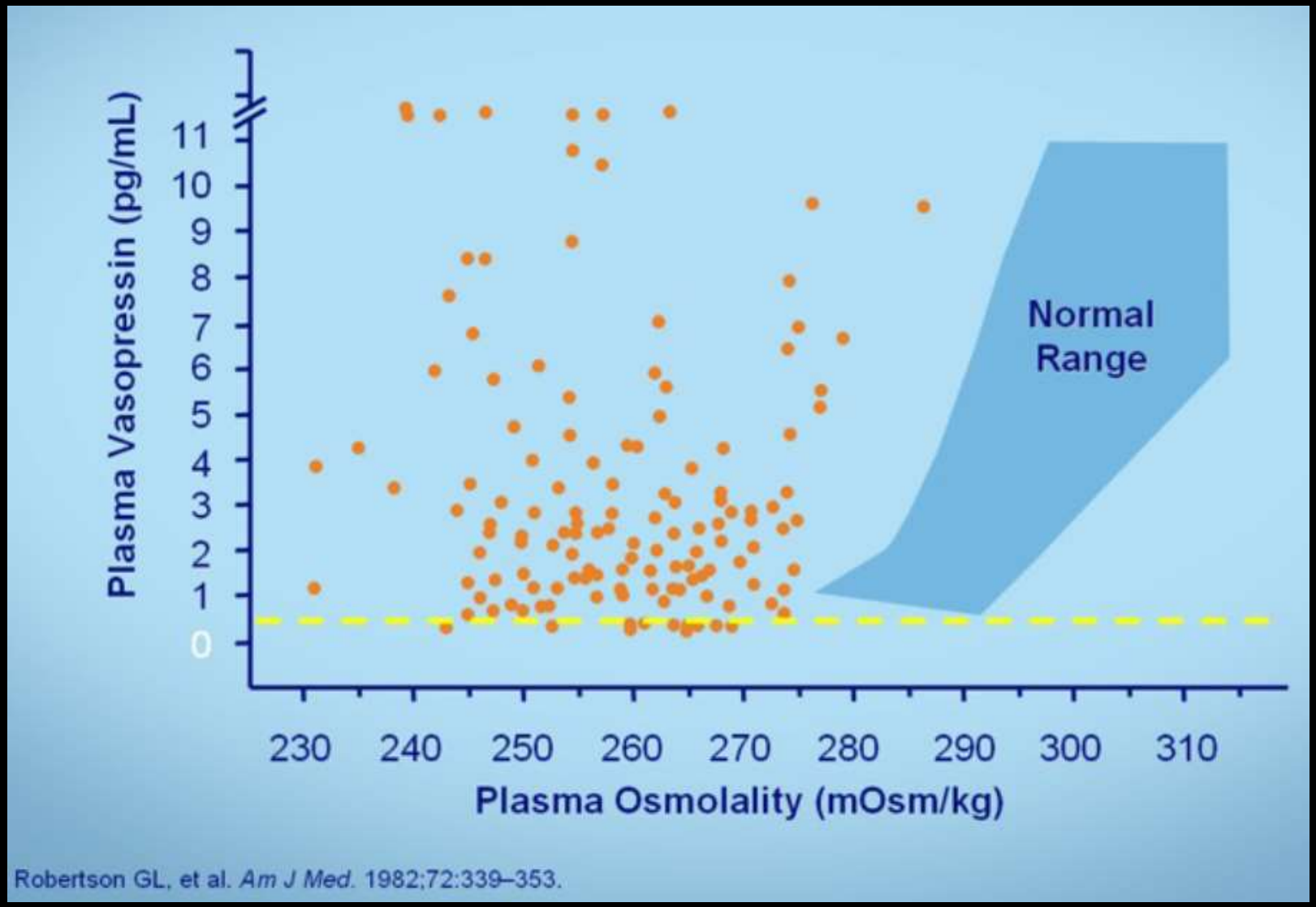
Essential	Supporting
• Hyponatraemia (plasma sodium < 135 mmol/l) • Decreased measured plasma osmolality (< 275 mOsm/kg H_2O) • Urinary osmolality > 100 mOsm/kg H_2O during hypo-osmolality • Clinical euvolaemia – No clinical signs of contraction of extracellular fluid (e.g., no orthostasis*, tachycardia, decreased skin turgor or dry mucous membranes) – No clinical signs of expansion extracellular fluid (e.g., no oedema or ascites) • Urinary sodium > 30 mmol/l with normal dietary salt intake** • Normal thyroid and adrenal function determined by both clinical and laboratory assessment • No use of diuretic agents within the week prior to evaluation	• Plasma uric acid <4 mg/dl (< 0.2 mmol/l) • Blood urea nitrogen <10 mg/dl (< 3.6 mmol/l) • Fractional sodium excretion > 1%; Fractional urea excretion >55%*** • Failure to improve hyponatraemia after 0.9% saline infusion • Improvement of hyponatraemia with fluid restriction

* Orthostatic changes in blood pressure and pulse rate are defined as a >= 20 mm decrease in systolic BP and/or as a >= 20 bpm increase in pulse rate upon going from a supine to a standing position

** Although high urine sodium excretion generally occurs in patients with SIADH, its presence does not confirm the diagnosis, nor does its absence rule out the diagnosis; urine sodium can also be high in renal causes of solute depletion such as diuretic use or Addison's disease, and conversely some patients with SIADH can have low urinary sodium if they become hypovolaemic or solute depleted, which are conditions sometimes produced by imposed sodium and water restriction

*** Fractional sodium excretion = (urinary sodium/plasma sodium) / (urinary creatinine/plasma creatinine) X 100; Fractional urea excretion = (urinary urea/plasma urea) / (urinary creatinine / plasma creatinine) X 100

Plasma levels of vasopressin are inappropriately elevated in most patients with SIADH



Robertson GL, et al. *Am J Med.* 1982;72:339–353.

Causes of the syndrome of inappropriate ADH release (SIADH

Carcinomas	Pulmonary Disorders	Nervous System Disorders	Other
Bronchogenic carcinoma	*Viral pneumonia*	*Encephalitis (viral or bacterial)*	*AIDS–HIV*
Carcinoma of the duodenum	*Bacterial pneumonia*	*Meningitis (viral, bacterial, tuberculous, and fungal)*	*Idiopathic (elderly)*
Carcinoma of the pancreas	*Pulmonary abscess*	*Head trauma*	Prolonged exercise
Thymoma	*Tuberculosis*	*Brain abscess*	
Carcinoma of the stomach	Aspergillosis	*Brain tumors*	
Lymphoma	Positive pressure ventilation	Guillain-Barré syndrome	
Ewing's sarcoma	Asthma	Acute intermittent porphyria	
Carcinoma of the bladder	Pneumothorax	Subarachnoid hemorrhage or subdural hematoma	
Carcinoma of the prostate	Mesothelioma	Cerebellar and cerebral atrophy	
Oropharyngeal tumor	Cystic fibrosis	Carvernous sinus thrombosis	
Carcinoma of the ureter		Neonatal hypoxia Hydrocephalus Shy–Drager syndrome Rocky Mountain spotted fever Delirium tremens Cerebrovascular accident (cerebral thrombosis or hemorrhage) Acute psychosis Peripheral neuropathy Multiple sclerosis	

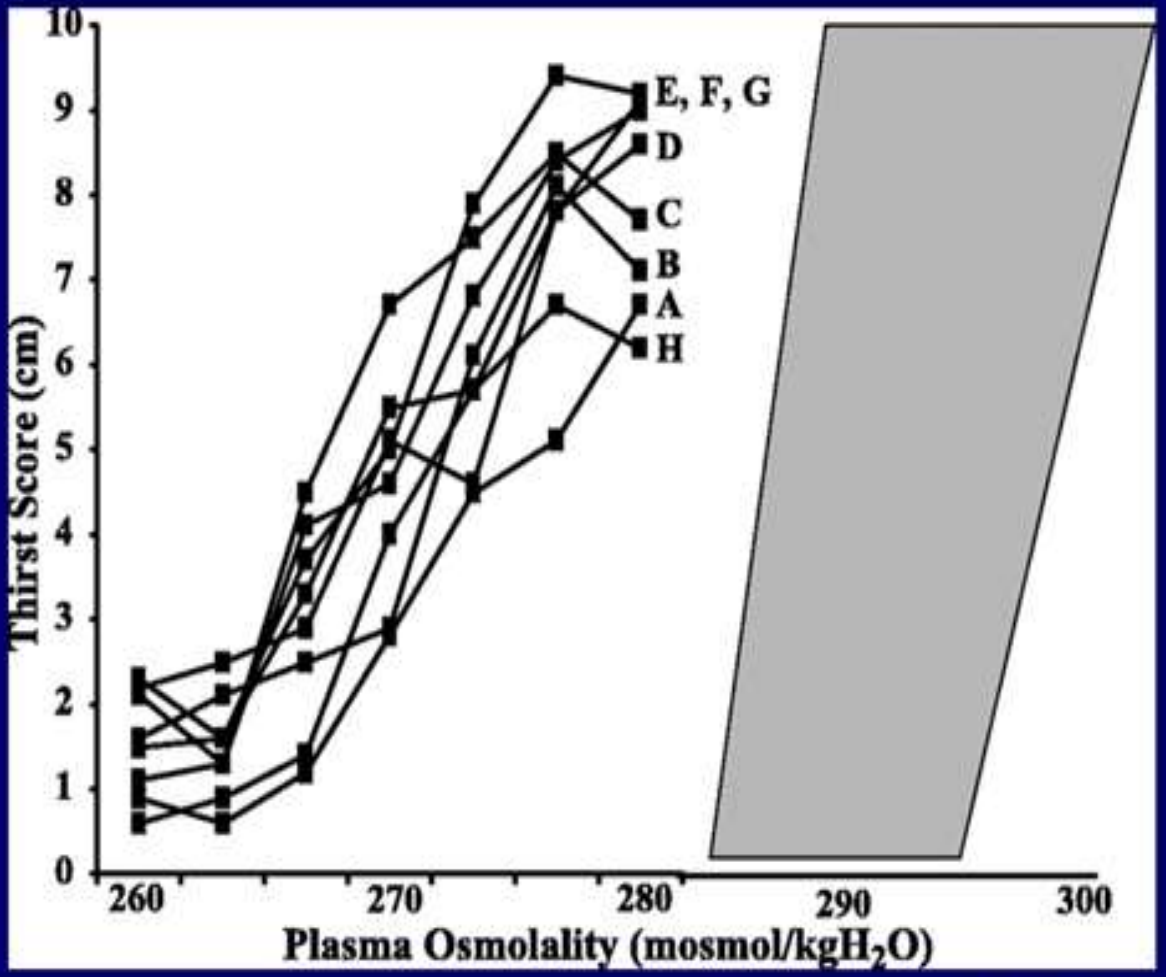
Floege, Johnson, Feehally, Comprehensive Clin Nephrology,4th ed 2010

Drugs associated with hyponatremia

Vasopressin Analogues	Drugs that Potentiate Renal Action of Vasopressin
Desmopressin (DDAVP) Oxytocin	Chlorpropamide Cyclophosphamide Nonsteroidal anti-inflammatory drugs (NSADs) Acetaminophen
Drugs that Enhance Vasopressin Release	**Drugs that Cause Hyponatremia by Unknown Mechanisms**
Chlorpropamide Clofibrate *Carbamazepine-oxycarbazepine* Vincristine Nicotine Narcotics *Antipsychotics/antidepressants (SSRI)* Ifosfamide	*Haloperidol* Fluphenazine Amitriptyline Thioridazine Fluoxetine *Methamphetamine (MDMA or ecstasy)* IVIG

Comprehensive Clin Nephrology
Eds Floege, Feehally, Johnson 2010

Leftward shift of the thirst response in SIADH, i.e. thirst is also abnormal



A-H: SIADH pts
Grey: Controls

Smith et al, *AJP Endocrinol*, 2004

Duration of hyponatremia and differences in treatment

	Acute (< 48 hours)	Chronic (> 48 hours)
	When brain cannot adapt rapidly	Brain swelling is minimized
Symptoms	• Cerebral edema • Seizures • Delirium • Possible brain herniation	• Headache • Nausea/vomiting • Fatigue
Treatment	Urgent correction to prevent brain herniation	If corrected too rapidly, can cause osmotic demyelination syndrome

Verbalis JG, et al. *Am J Med*. 2013;126(10 Suppl 1):S1-S42.[3]

ERBP recommendations for treatment of hyponatremia with severe symptoms

7.1.1.1. We recommend prompt i.v. infusion of 150 ml 3% hypertonic over 20 min (1D).

7.1.1.2. We suggest checking the serum sodium concentration after 20 min while repeating an infusion of 150 ml 3% hypertonic saline for the next 20 min (2D).

7.1.1.3. We suggest repeating therapeutic recommendations 7.1.1.1 and 7.1.1.2 twice or until a target of 5 mmol/l increase in serum sodium concentration is achieved (2D).

7.1.1.4. Manage patients with severely symptomatic hyponatraemia in an environment where close biochemical and clinical monitoring can be provided (not graded).

Spasovski et al, European Journal of Endocrinology (2014) 170, G1–G47

Effect of different therapies in SIADH with fixed Uosm of 680 mosm/kg

	NaCl, mosmol	Water, ml
Isotonic saline		
In	**308**	**1000**
Out	**308**	**453**
Net	**0**	**+547**
Hypertonic saline		
In	**1026**	**1000**
Out	**1026**	**1500**
Net	**0**	**-500**
Hypertonic saline + loop diuretic (Uosm= 300 mosmol/kg)		
In	**1026**	**1000**
Out	**1026**	**3400**
Net	**0**	**-2400**

Conditions in which overly rapid correction of hyponatremia may occur, caused by restoring electrolyte free water excretion

- ✓ Volume repletion in hypovolemia
- ✓ Lowering excessive fluid intake in polydipsia
- ✓ Nausea & alcohol withdrawal
- ✓ Stopping of “antidiuretic” drugs (f.e. SSRI’s)
- ✓ Stopping thiazides
- ✓ Treatment of glucocorticoid deficiency

Caveats in thiazide-induced hyponatremia

- Thiazide-induced hyponatremia often is associated with significant hypokalemia
- Correction of hypokalemia is associated with a predictable increase in serum sodium levels
- In chronic hyponatremia (duration >48 h), the increase in serum sodium plus potassium levels should not exceed 12 mEq/L in the first 24 h and 18 mEq/L in the first 48 h
- In patients with a more rapid increase with or without symptoms of osmotic demyelinating syndrome, it is advisable to reverse the process by the use of free water and, if needed, desmopressin

Berl, Rastegar, Am Journal of Kidney Dis, 55, 742-748,2010

Hyponatremia and glucocorticoid deficiency

All patients with euvolemic hyponatremia should be evaluated for glucocorticoid deficiency before concluding they have SIADH

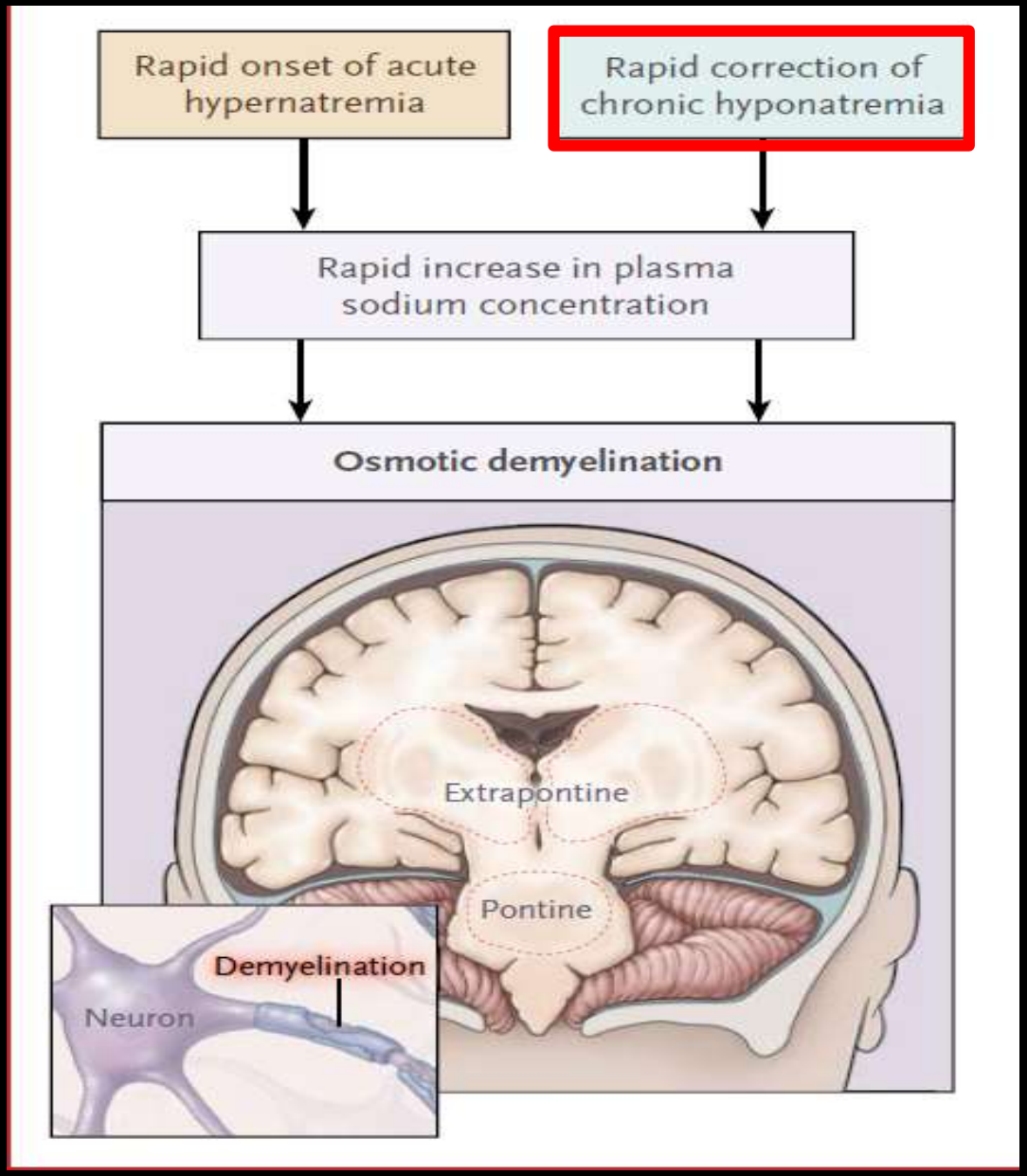
Although glucocorticoid deficiency can be ruled out in some patients with a random or early morning cortisol level ≥ 18 mg/dL, failure to achieve this level will require consideration of a cosyntropin stimulation test for a definitive diagnosis unless clinical judgment makes this possibility unlikely

Unless the patient has severe symptoms of hyponatremic encephalopathy, primary treatment of the hyponatremia should consist of glucocorticoid replacement at either maintenance or stress doses, depending on the degree of intercurrent illness

Because glucocorticoid replacement can result in a spontaneous large aquaresis with rapid correction of serum [Na^+], both serum [Na^+] and urine volume should be followed carefully, particularly in patients with serum [Na^+] < 120 mmol/L or with risk factors for ODS

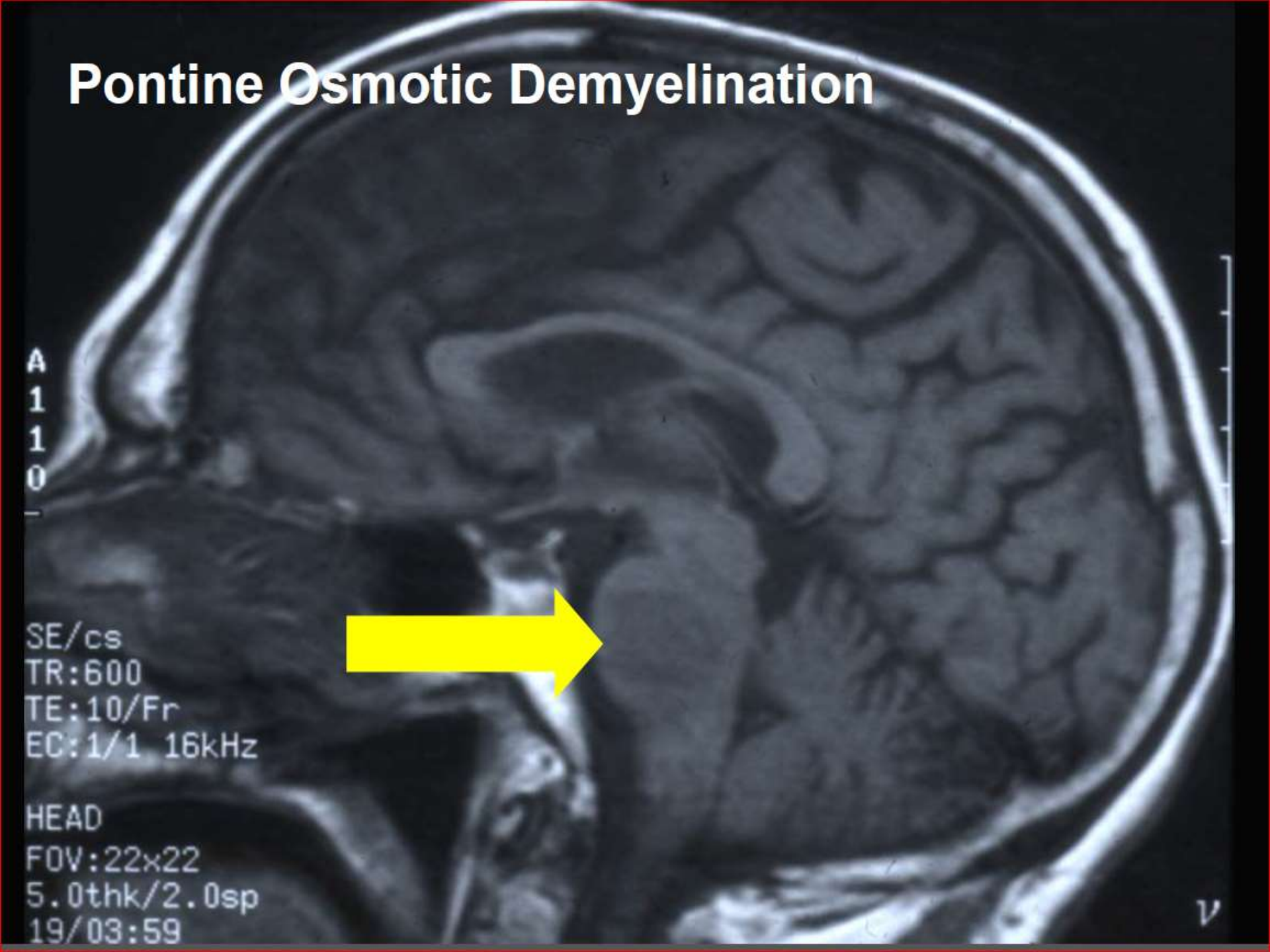
Verbalis JG, et al. *Am J Med.* 2013;126:S1-S42.

Consequences of Rapid Changes in the Plasma [Na+]



Sterns RH, **N Engl J Med 2015;372:55-65.**

Pontine Osmotic Demyelination

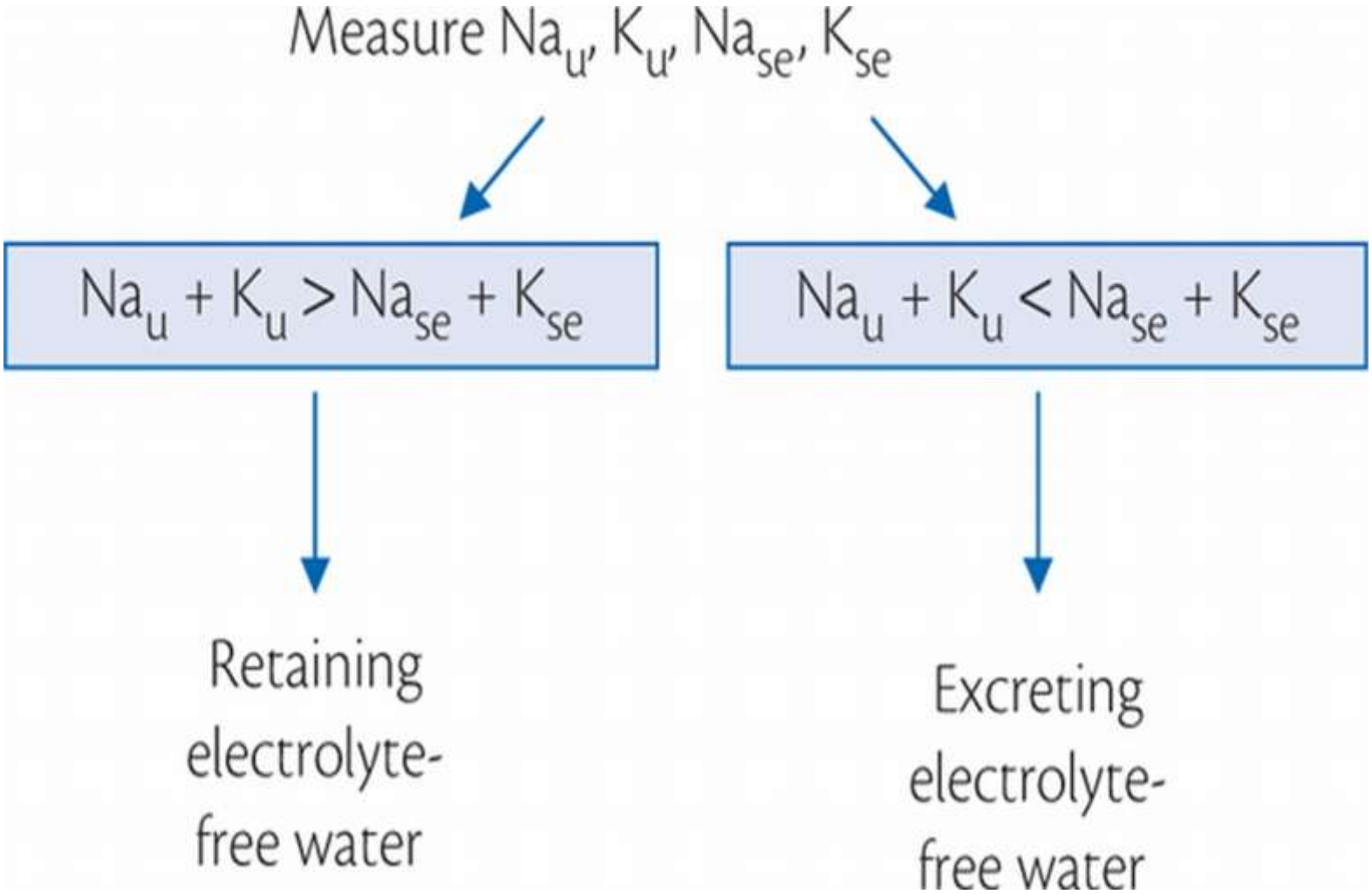


Advantages and disadvantages of therapies for hyponatremia

Therapy	Advantages	Disadvantages
Fluid restriction	Generally effective; inexpensive	Noncompliance
Demeclocycline	Consistently effective	Reversible azotemia and nephrotoxicity; polyuria
Lithium	Effective in some patients	Inconsistent efficacy; significant adverse effects
Loop diuretics (e.g. furosemide) plus increased salt intake	Effective in some patients	Imbalance between diuretic action and salt ingestion can lead to volume depletion or overload
Urea	Consistently effective	Poor palatability; gastrointestinal adverse effects; development of azotemia at higher doses
Hypertonic (3% or 5%) saline with or without coadministration of loop diuretics	Corrects serum sodium concentration	Rate of correction is variable and difficult to control; overly rapid correction is associated with myelinolysis

Chen et al , Clin Pract Nephrol, 3: 81-95, 2007

Measurement of serum and urinary electrolytes can determine whether the patient is retaining or excreting electrolyte-free water.

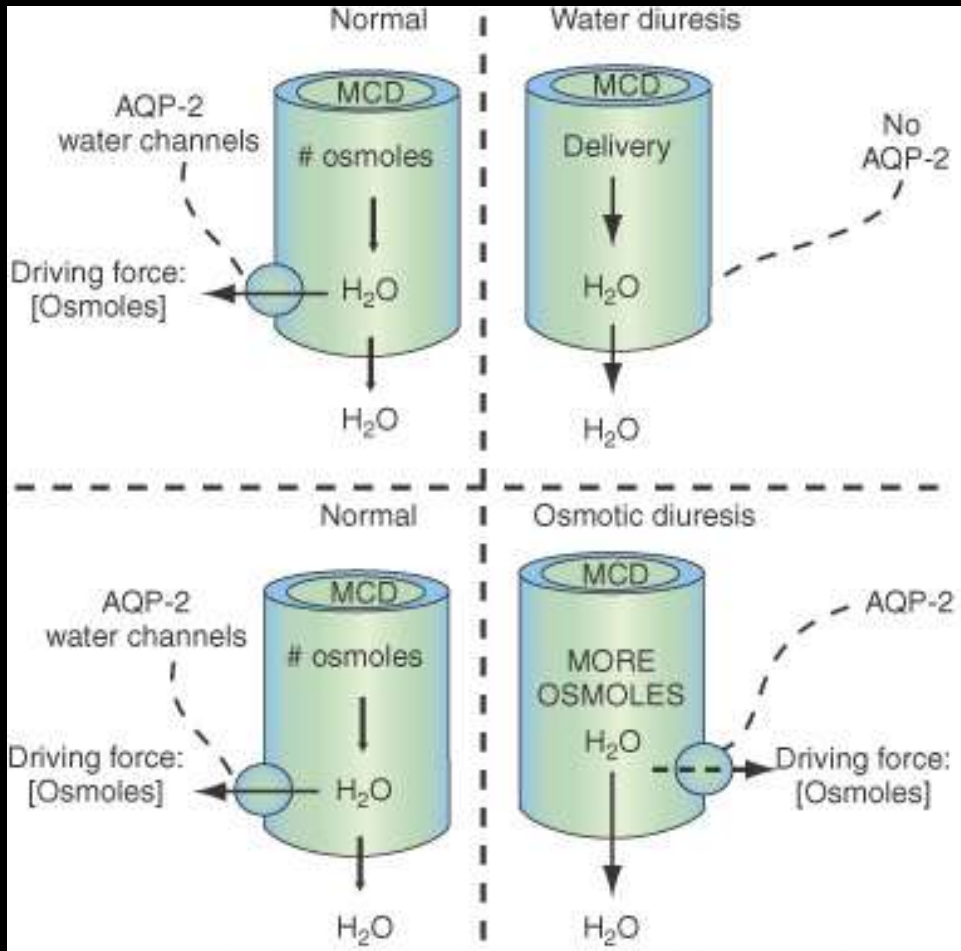


Use of urine electrolytes to predict stringency of fluid restriction in the treatment of hyponatremia

Urine/Plasma Electrolyte Ratio	Recommended Fluid Consumption
> 1.0	0 mL
0.5–1.0	Up to 500 mL
< 0.50	Up to 1 L

$(U_{Na} + U_K/P_{Na})$

Furst et al, Am J Med Sci 319, 240-244,2000



Major concept in the control of the excretion of water. The barrel-shaped structure represents the late distal nephron. The major concept is shown to the left of the *vertical dashed line*. When vasopressin acts, water channels (AQP2, shown by the *circle*) are inserted in the luminal membrane of collecting duct cells, making these nephron segments permeable to water. The driving force to reabsorb water is a high "effective" osmolality in the medullary interstitial compartment. In a water diuresis *(top right portion)*, AQP2 are absent; hence the urine flow rate is regulated by the distal volume delivery. In contrast, during an osmotic diuresis *(lower right portion)*, AQP2 are present so the urine flow rate is dependent on the number of "effective" osmoles delivered to this nephron segment and the osmolality in the medullary interstitial compartment.

"Brussels Champagne" Formulation of Urea.*
Urea, 10 g
Sodium bicarbonate, 2 g
Citric acid, 1.5 g
Sucrose, 200 mg
To be dissolved in 50–100 ml of water

* We prescribe this effervescent solution for the minority (10 to 15%) of patients who find the taste of urea aversive. This solution was used in the past to treat gastric ulcers, even when they were bleeding.

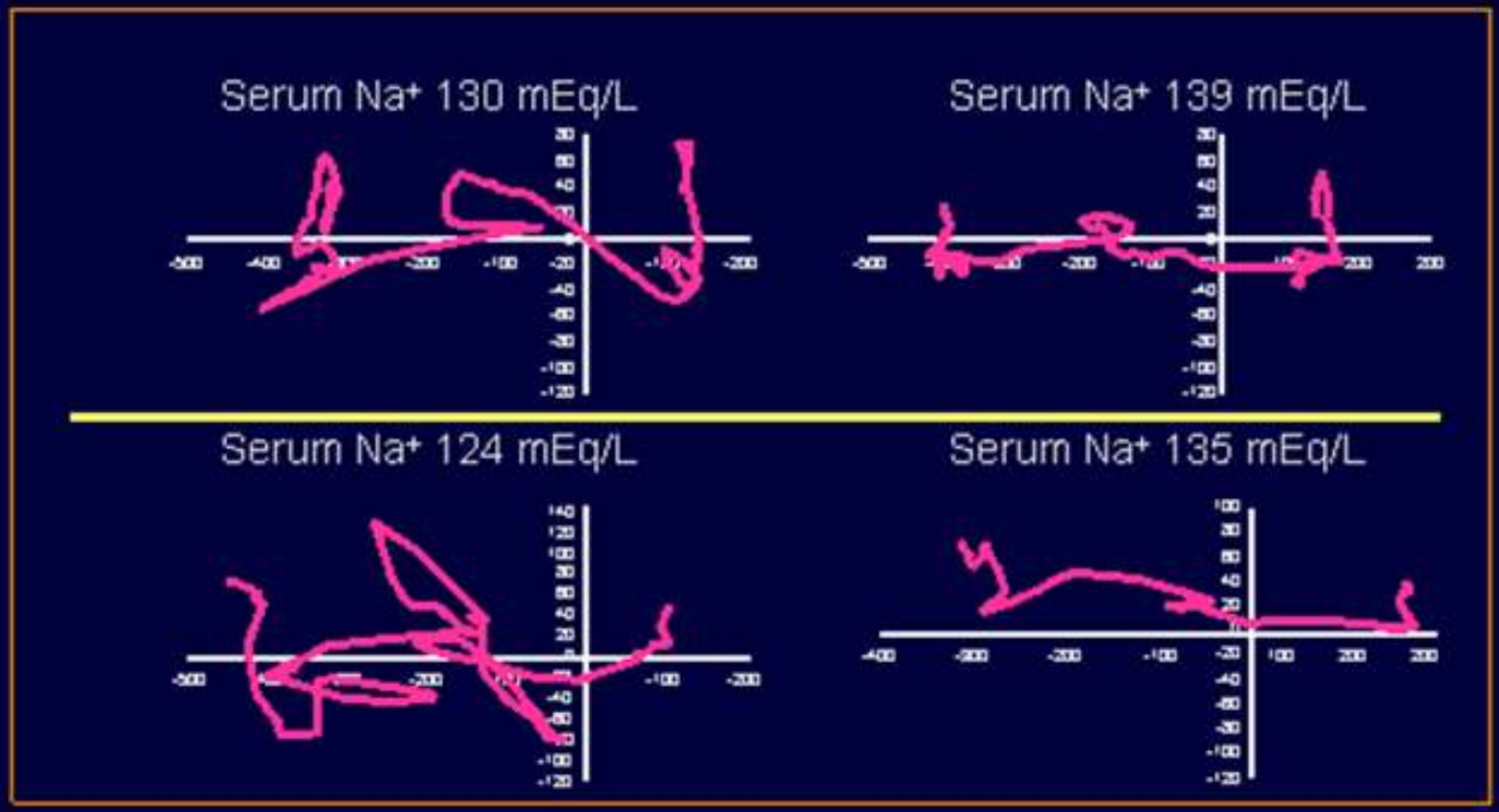
Decaux et al, N Engl J Med 373;10 september 3, 2015

"Asymptomatic" Hyponatremia

- Patients presenting to the ER of a single medical center with hyponatremia & neither edema nor ascites
- 151 patients (SNa 115 to 132 mmol/L)
  - 10 with seizures (7 %)
    - 6 with psychotic polydipsia
    - 2 with known epilepsy
  - 19 with acute water intoxication (no seizure)
- 122 patients with chronic, "asymptomatic" hyponatremia
  - Serum Na 125 ± 5 mmol/L
  - Normal neurologic and mini-mental status exam

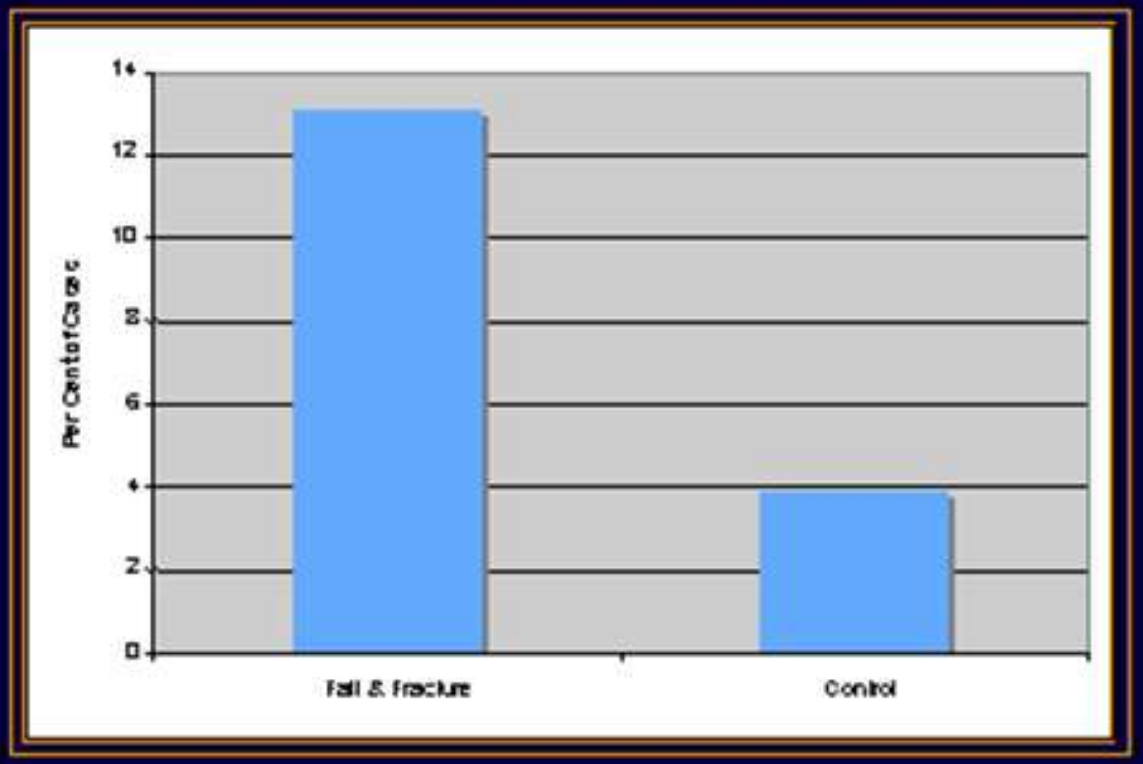
Renneboog. Am J Med. 2006;119:71.e1-71.e8.

"Asymptomatic" Hyponatremia



Renneboog. Am J Med. 2006;119:71.e1-71.e8.

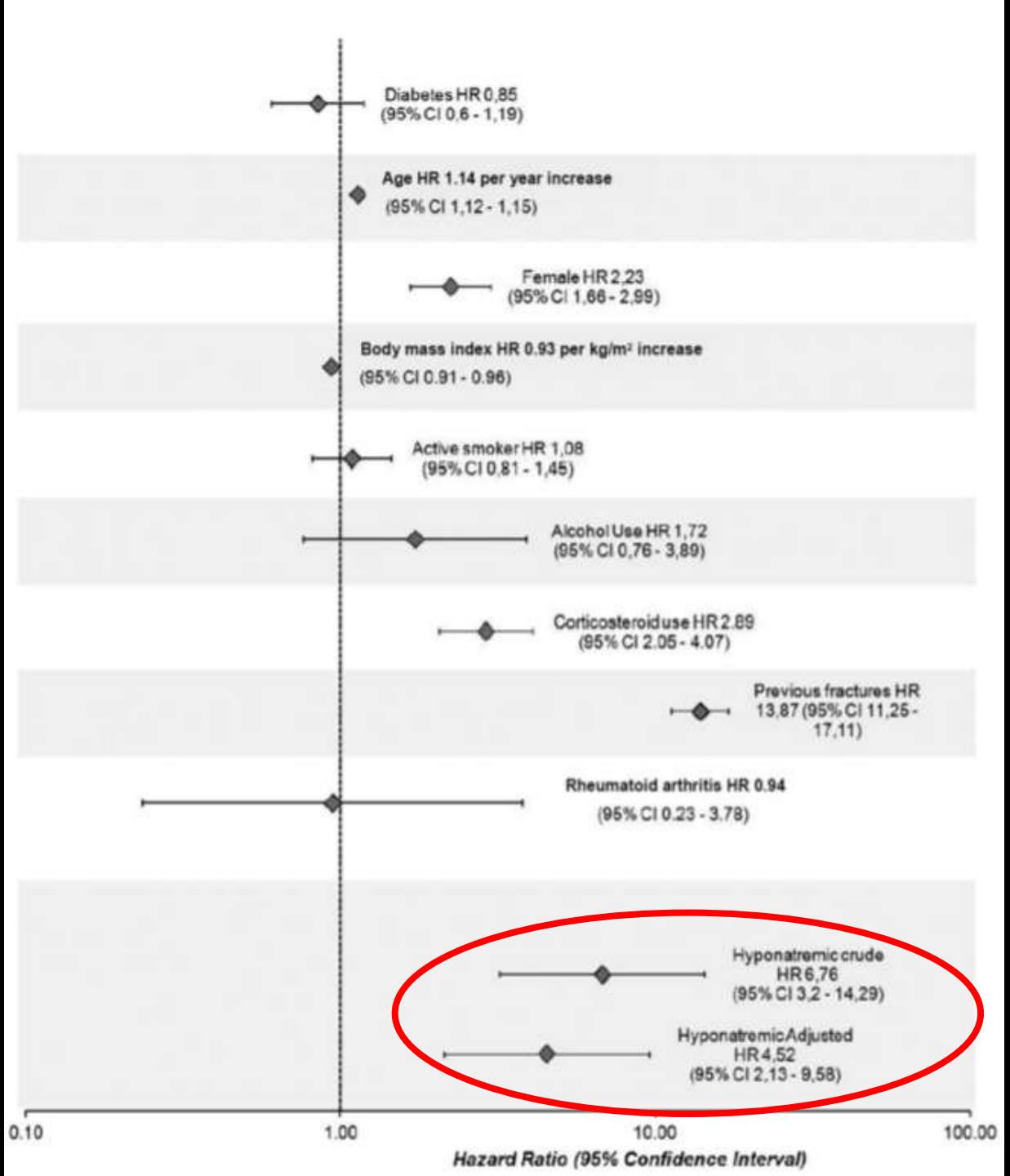
Asymptomatic Hyponatremia: Association with Fractures



Incidence of hyponatremia significantly higher in patients presenting with falls and fractures than in age-matched controls

Gankam Kengne F. QJM. 2008 May 13

Associations of prolonged hypoNa+ and other risk factors for hip fracture in elderly

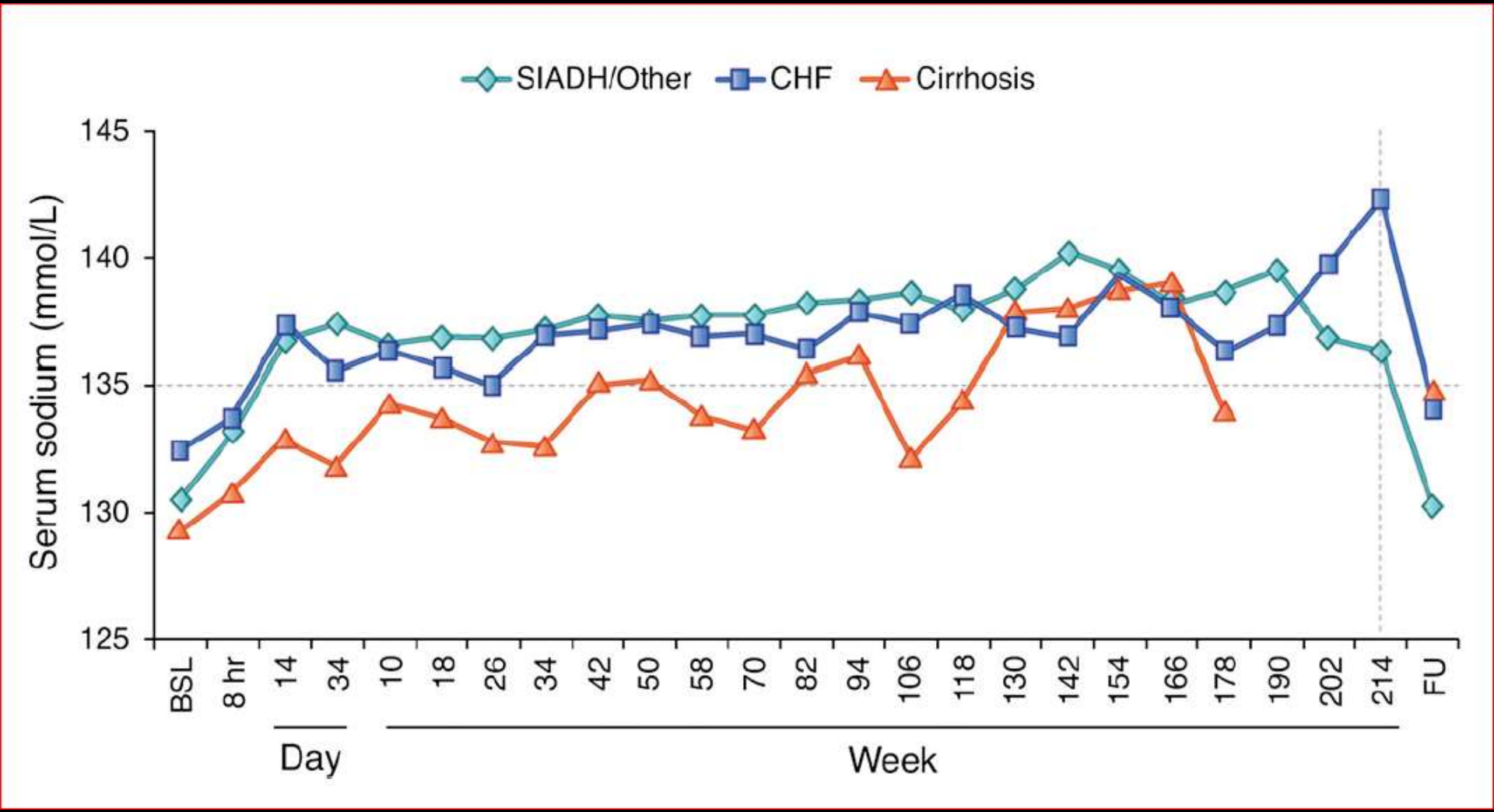


Ayus et al , Nephrol Dial Transplant (2016) 31: 1662–1669

Pros and Cons of the Vaptans

- What are the indications in clinical practice?
- Significant expense, e.g. ~$200/day for oral tolvaptan
- Risk of overcorrection – minimize by frequent monitoring of serum Na during the first 48 hours
- Tolvaptan can be used in liver disease (conivaptan should **NOT**)
- Conivaptan is IV but not PO; tolvaptan is PO but not IV.....

Long-term effect of tolvaptan on serum sodium in the SALTWATER trial.



Berl et al, J Am Soc Nephrol 21:705–712, 2010

Hypernatremia
General remarks

- Is not a specific disease - look for its cause and treat the underlying disease
- In hypernatremia the ICF volume is always contracted
- CNS hemorrhage is most to fear if hypernatremia is acute and/or severe
- Hypernatremia is almost always due to net water loss
- At least one of two defenses to water loss are impaired: thirst and /or excretion of a maximally concentrated urine.

Patient groups at risk for development of severe hypernatremia

Elderly patients or infants

Hospitalized patients receiving hypertonic infusions, tube feedings, osmotic diuretics, lactulose, mechanical ventilation

Altered mental status

Uncontrolled diabetes mellitus

Underlying polyuric disorders

Causes of hypernatremia

Etiology	Underlying Cause
Incapacitated, unable to obtain water	Stroke Chronic medical illness
Dehydration secondary to elevated temperature Osmotic diuresis secondary to hyperalimentation	Oral hyperalimentation Parenteral hyperalimentation
Loss of free water via the kidneys	Diabetes insipidus Chronic renal failure
Dialysis malfunction Intervenous hypertonic sodium (NaCl or NaHCO3)	Proportioning system disorder Metabolic acidosis Cardiac arrest Therapeutic abortion Fluid therapy for burns
Certain brain lesions	Pineal, superopticohypophyseal, subcommisural
Extrarenal loss of water	Perspiration Osmotic diarrhea Infectious diarrhea