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Founding Member, Mass General Brigham

Sodium Disorders

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Research Focus: Urate transport

Clinical Focus: Glomerulonephritis,

Electrolyte disorders, Gout,

Consultative Nephrology



Financial Disclosures

Author, peer reviewer – UpToDate, McGraw Hill
Consultant/advisory boards
– Gout: Shanton Pharma
– ANCA-associated vasculitis: Amgen



OVERVIEW

Hyponatremia

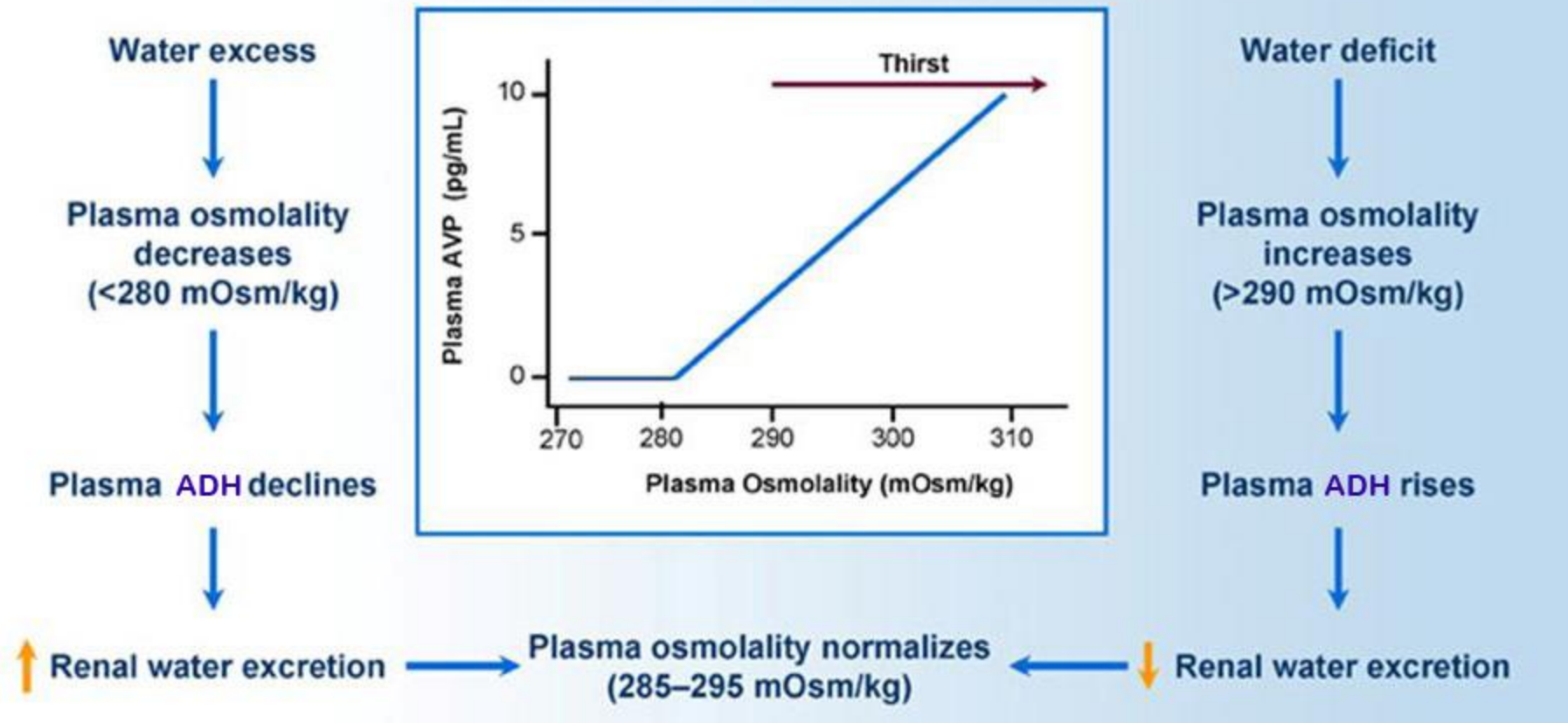
- Pathophysiology
- Diagnostic approach
- Clinical sequelae
 - Acute hyponatremia
 - Chronic hyponatremia
- Management

Hypernatremia/polyuria

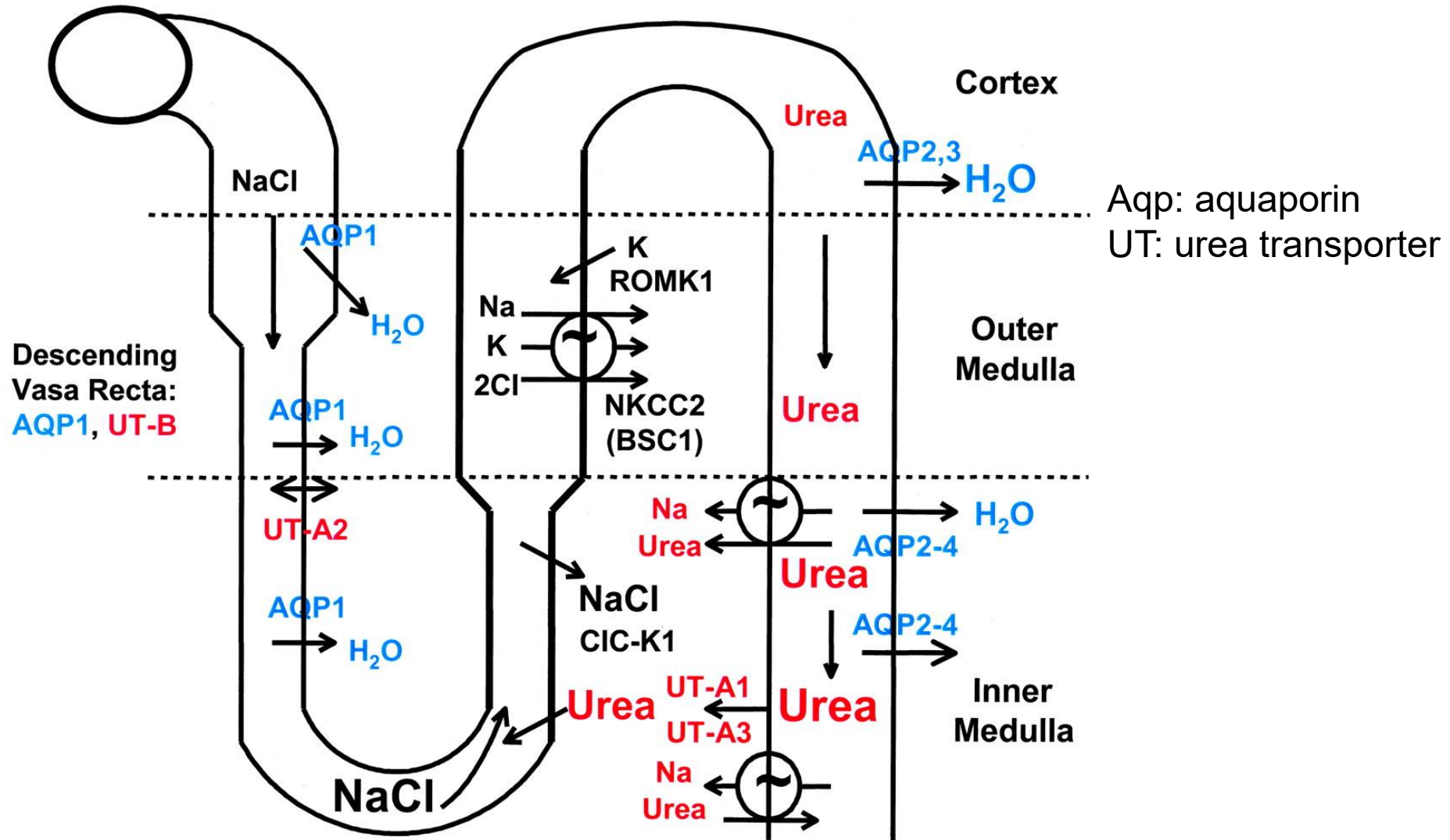
- DD_x and diagnostic approach
- Management



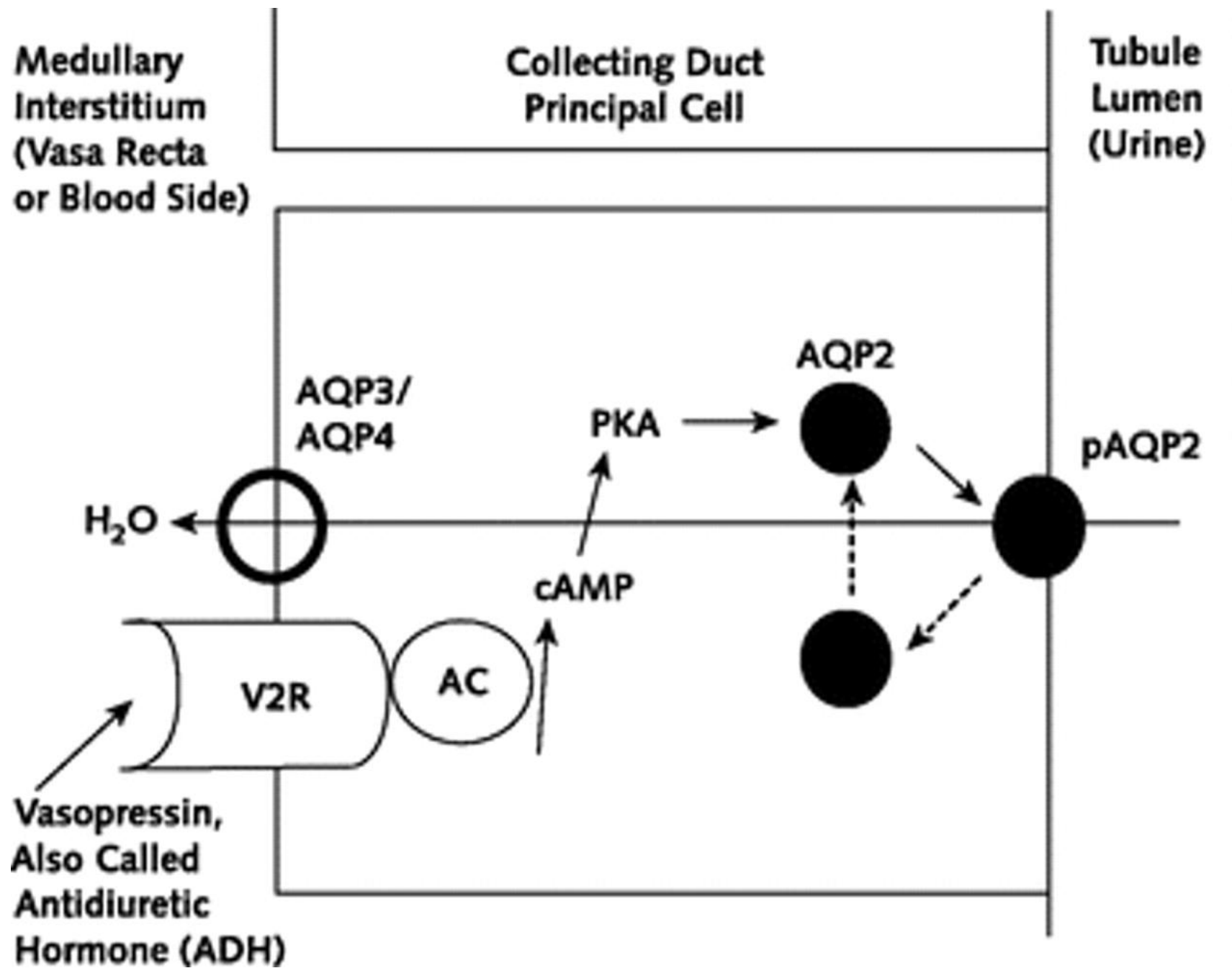
Vasopressin (AVP, ADH) Regulates Water Homeostasis and Osmolality



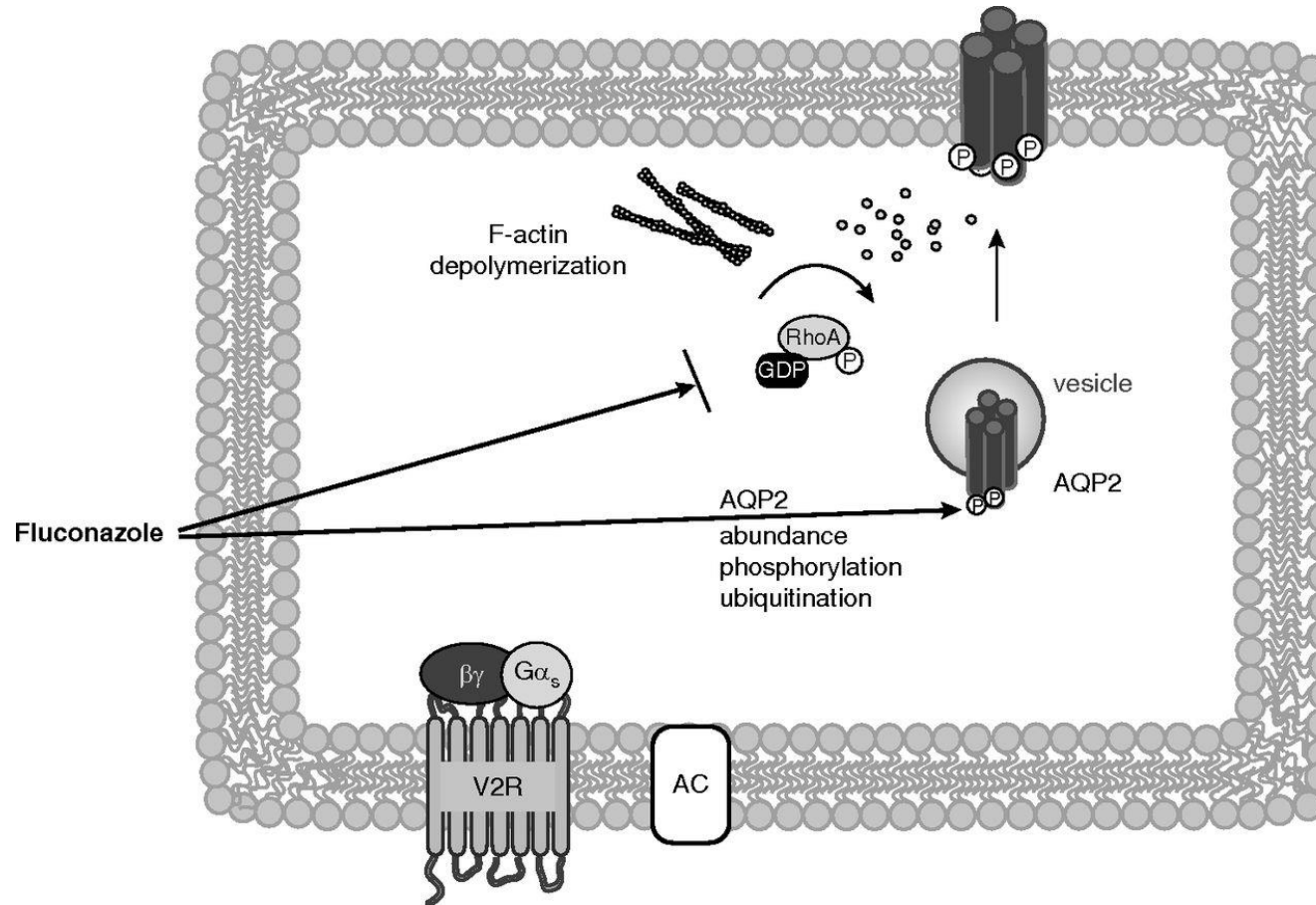
The Renal Concentrating Mechanism in the 21st Century!



Sands, *J Am Soc Nephrol*, 2002



Novel Therapies Where You Yeast Expect Them: Fluconazole for Nephrogenic DI



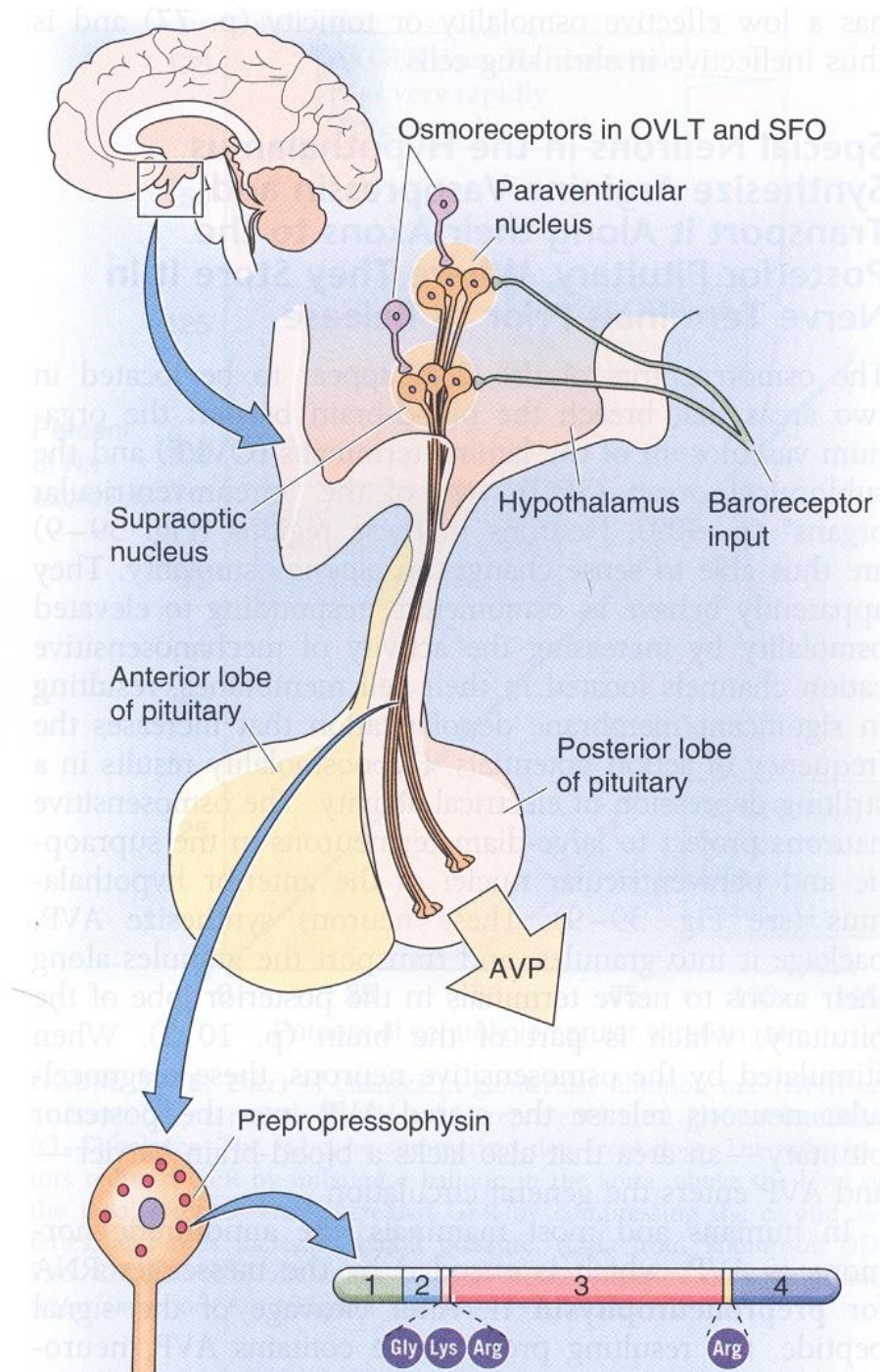
Osmoregulation versus Extracellular Volume Regulation

	<i>Osmoregulation</i>	<i>Volume regulation</i>
<i>What is being sensed</i>	Plasma osmolality	Arterial perfusion pressure
<i>Sensors</i>	Hypothalamic osmoreceptors	Carotid sinus Afferent arteriole Atria
<i>Effectors</i>	ADH/Vasopressin Thirst	Sympathetic nervous system Renin-angiotensin-aldosterone system ANP/BNP <u>VASOPRESSIN</u>
<i>What is affected</i>	Urine osmolality Water intake	Urinary sodium excretion

Black and Rose, *Manual of Clinical Problems in Nephrology*, 1988



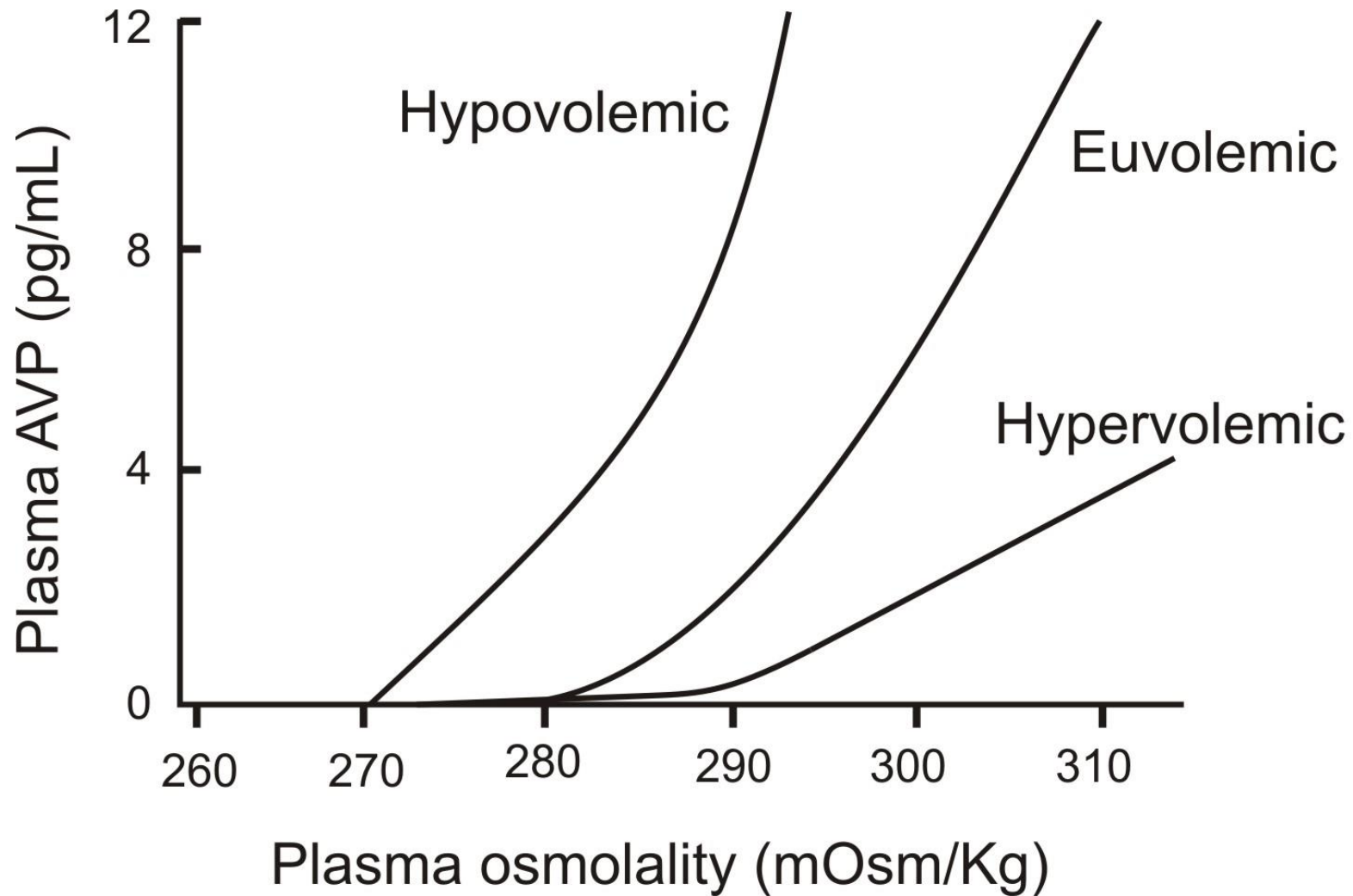
Hypothalamic Control of Vasopressin Secretion



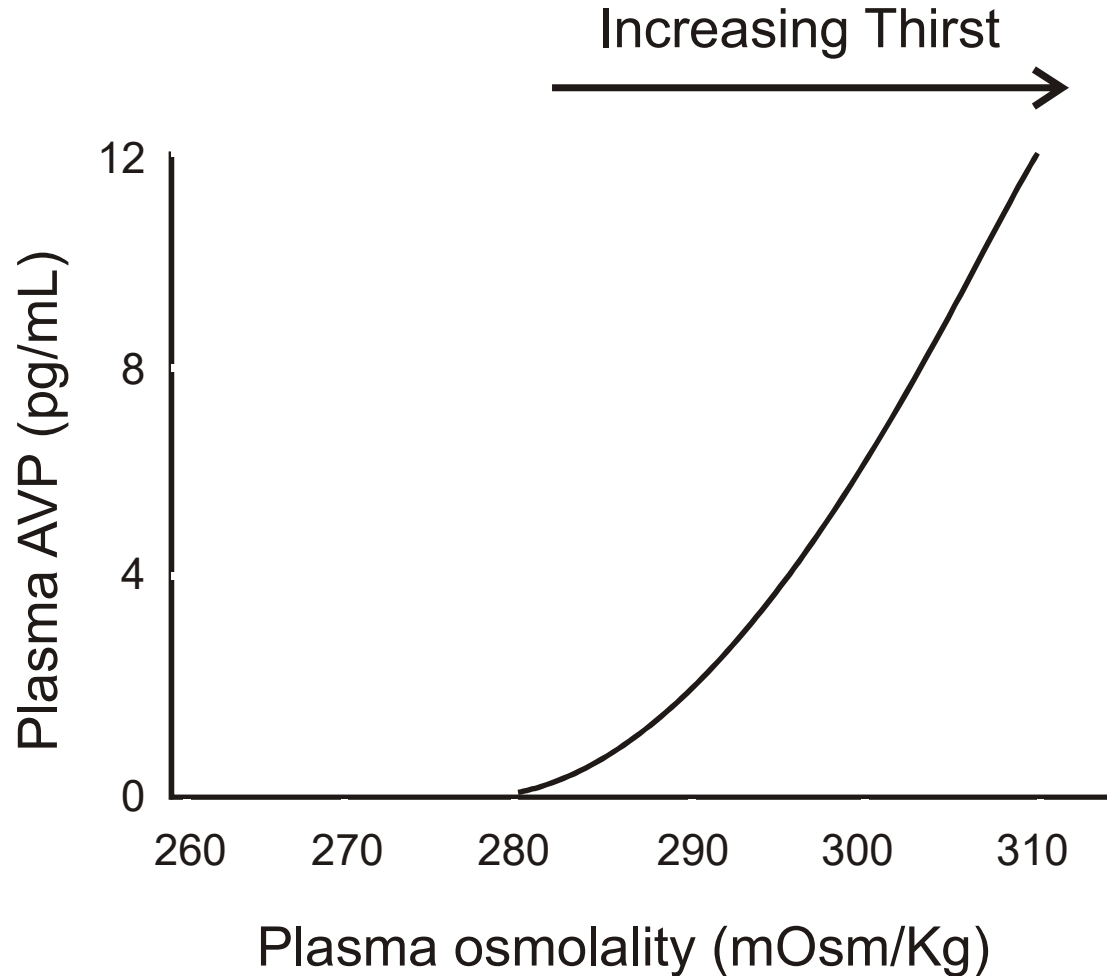
OVLT – organum vasculosum of the lamina terminalis (periventricular, 3rd ventricle)
SFO – subfornical organ



Volume Status and AVP Release



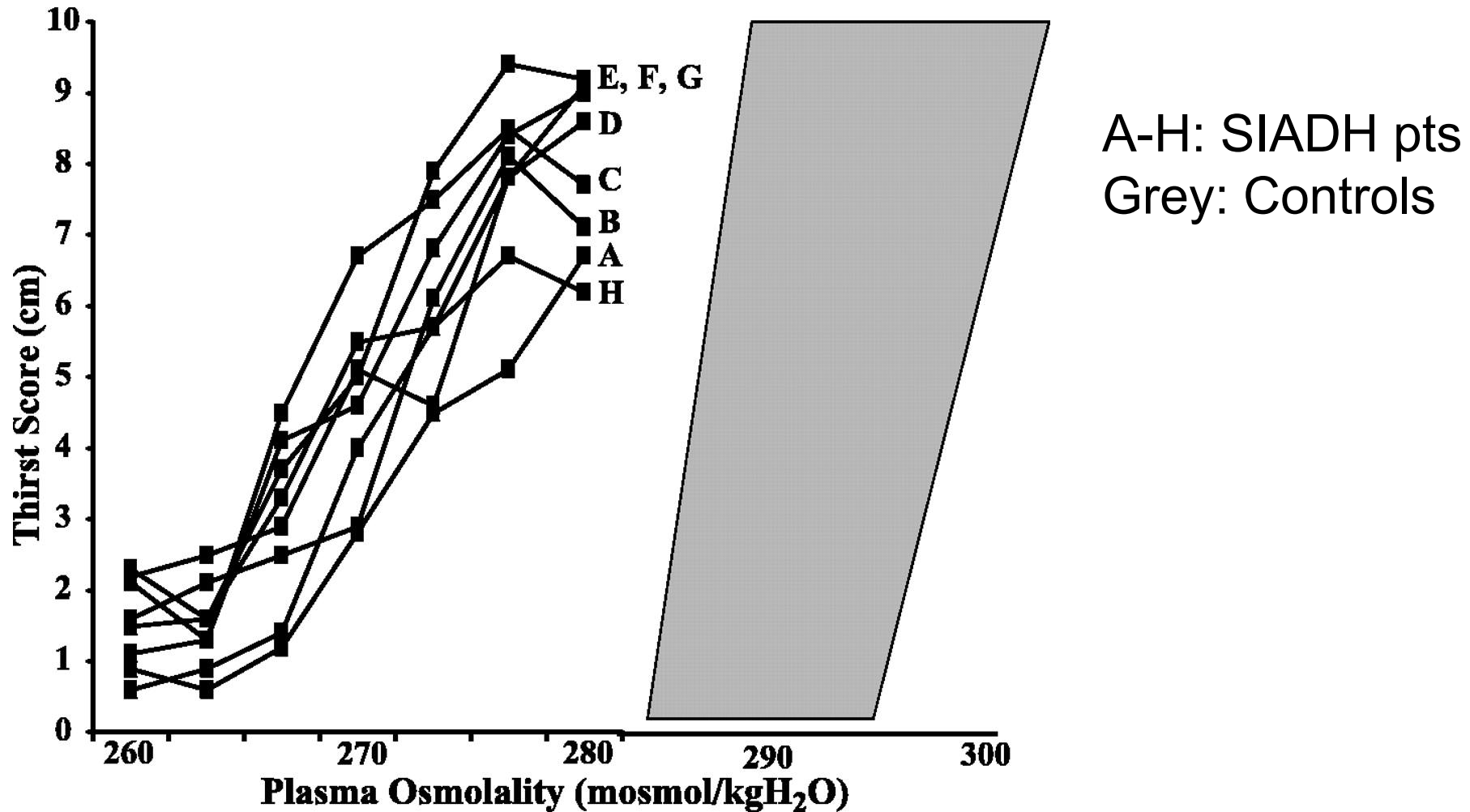
What About Thirst??



Thirst is stimulated over same range of osmolality as AVP, via activation of central osmoreceptors

Typically need intake of H₂O to generate hyponatremia

Leftward Shift of the Thirst Response in SIADH, i.e. Thirst Also Abnormal



Smith et al, *AJP Endocrinol*, 2004



Initial Evaluation of Hyponatremia

H&P

- Medications. SSRIs are the most common contemporary cause of SIADH.
- PMH. For example, prior pituitary surgery....
- ROS. Symptoms attributable to acute or chronic hyponatremia.

Symptoms suggestive of a cause, e.g. profuse diarrhea → hypovolemic hyponatremia.

Chronicity; acute versus chronic (>48 hours).

Exam

- Hypovolemic? Orthostatics, JVP
- Hypervolemic? JVP, edema, chest exam



Initial Lab Evaluation of Hyponatremia

Plasma osmolality

- Low: true hyponatremia
- Normal or elevated:
pseudohyponatremia or renal failure

Urine osmolality

- <100 mosmol/kg: primary polydipsia
- >100 mOsmol/kg: reduced H_2O excretion

Urine Na^+ concentration

- <20 mEq/L: **effective** volume depletion
- >20 mEq/L: “euvolemic” causes or renal Na^+ wasting



Question #1

63 yo male relapsed alcoholic, >12 beers/day
Patient had been to his PCP two days before,
was found to have serum Na of 115 and told to
return to the ED.

On exam he is barely rousable but responds to
commands slowly. Supine BP 124/67 HR 80;
standing BP 170/71 HR 114, then 105/84 HR
105 after 5 minutes

Na <110, K 4.8, Cl 73, HCO₃ 27, BUN 9, Cr 0.8,
Gluc 193, Urine Osm 227, Urine Na <20, Serum
Osm 236.



Which of the following is the most likely cause of this presentation?

- A. Beer potomania
- B. Pure hypovolemic hyponatremia
- C. SIADH
- D. Polydipsia



Low Solute Hyponatremia?

Patient hx of ETOH dependence with suspicion of recent drinking.

Low Urine Osmoles

Rapid initial correction with IV NS soln.

Exam appears euvolemic (orthostatics confusing). But management would be similar for hypovolemic hyponatremia (avoid rapid saline/solute intake).



Beer Potomania

Vasopressin-independent cause of hyponatremia.

Free water excretion in the urine requires a minimum amount of solute.

Beer provides carbohydrates that can sustain, but with no salt or protein it generates minimal urinary solute excretion.

Combined with high free water intake from beer, patients become hyponatremic.

Classically low urine Na/Osm but can be generous.

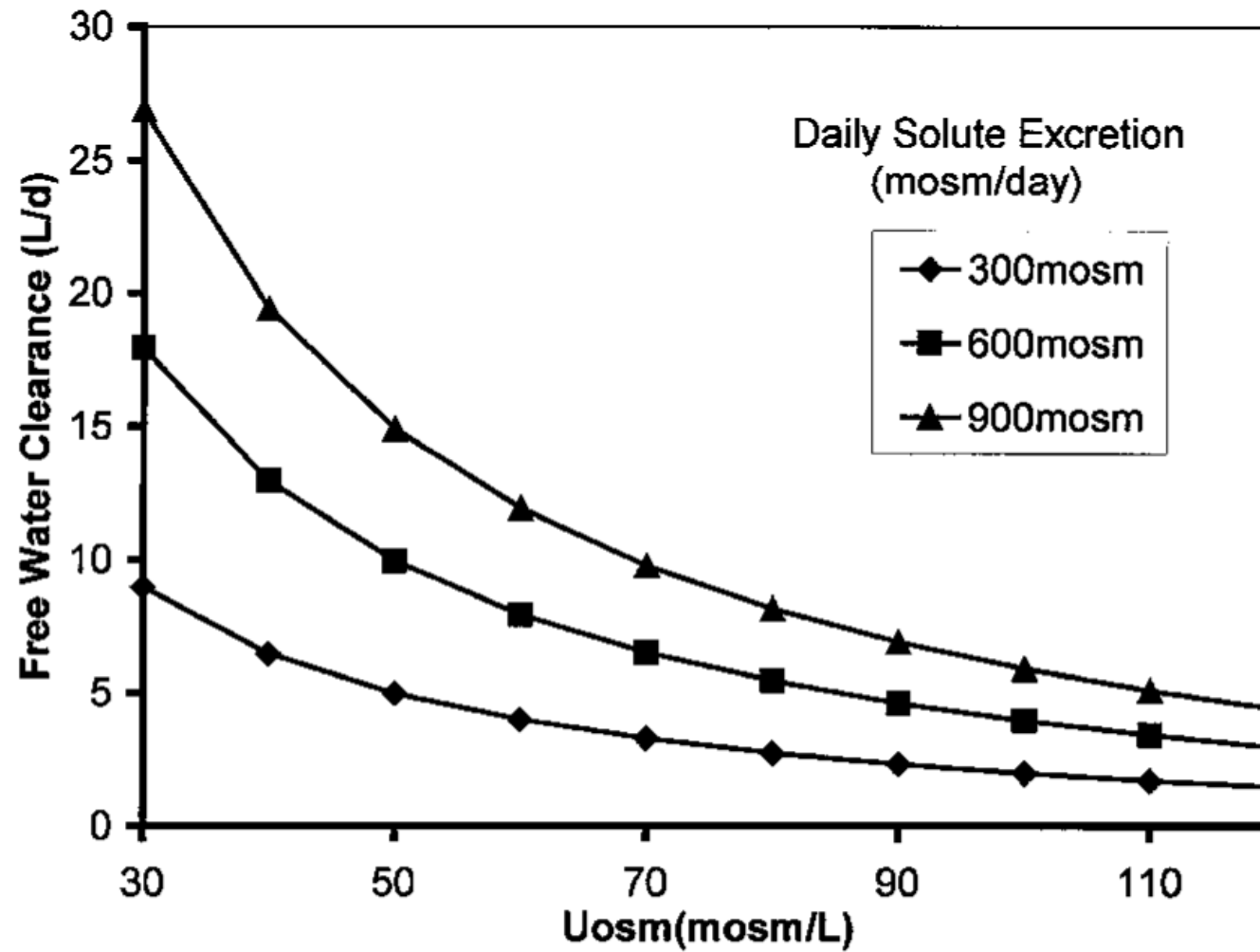


Lab Data in Beer Potomania

Author (year)	Patients no.	Neurological Symptoms on Presentation	Presentation Laboratory Results					Treatment	Serum Na Change	Outcome
			Na (mEq/L)	K (mEq/L)	BUN (mg/dL)	U osm (mosm/L)	U Na (mos m/L)			
Demanet (71)	1	Unconscious, seizure	107	2.6	12	N/A	N/A	N/A	N/A	N/A
	2	Weakness	105	1.3	15	N/A	N/A	N/A	N/A	Death - brain autopsy with atrophy of mammillary bodies
	3	Weakness	104	2.6	30	N/A	N/A	N/A	N/A	Death - no brain autopsy
	4	Unconscious	103	2.5	13	N/A	N/A	300 MEQ Na IV d 1 and 2	10 mmol/48 h	N/A
	5	Weakness, "grand mal"	101	1.4	19	N/A	N/A	N/A	N/A	Death - normal brain autopsy
	6	Unconscious, "grand mal"	99	1.8	18	N/A	N/A	N/A	N/A	Death - brain autopsy with CPM
	7	Unconscious, "grand mal"	98	4.4	30	N/A	N/A	N/A	N/A	N/A
Gwinup (72)	8	Weakness	122	5.1	N/A	N/A	N/A	Fluid restriction	20 mmol/72 h	No neurological sequelae reported
Hilden (75)	9	Debility, dizziness, confusion	123	2.7	N/A	N/A	N/A	0.9% NS 2-3 L	12 mmol/48 h	No neurological sequelae reported
	10	Debility, dizziness, confusion	109	2.5	N/A	79	N/A	No IVFs	15 mmol/48 h	No neurological sequelae reported
	11	Debility, dizziness, confusion	108	2.7	N/A	69	N/A	0.9% NS 2-3 L	19 mmol/48 h	No neurological sequelae reported
	12	Debility, dizziness, confusion	127	2.5	N/A	N/A	N/A	No IVFs	2 mmol/48 h	No neurological sequelae reported
	13	Debility, dizziness, confusion	117	3.1	N/A	N/A	N/A	No IVFs	9 mmol/48 h	No neurological sequelae reported
Swenson (76)	14	Weakness	106	3.8	N/A	199	5.6	Fluid restriction	8 mmol/48 h	No apparent neurological sequelae
Evans (85)	15	Confused, restless	118	4.1	2.3	N/A	N/A	1.8% NS × 6 h then 10 DW or 0.9% NS	9 mmol/48 h	Long-term impaired memory, confabulation
Joyce (86)	16	Agitation, confusion, seizures	110	3	N/A	N/A	N/A	3% NS × 30 mL, 0.9% NS @ 300 mL/h	14 mmol/24 h	Discharged d 2, lost to follow-up
Ferves (95)	17	Tremor	121	3.6	4	50	1	0.9% NS @ 100 mL/h	13 mmol/13 h	Not reported
	18	Unconscious, seizures	97	3.6	2	338	12	0.9% NS @ 150 mL/h and 3% NS @ 20 mL/h × 160 MI	30 mmol/48 h	No apparent neurological sequelae
Kelly (98)	19	Unconscious	109	3.6	16	340	<10	NS 3 L/24 h	20 mmol/48 h	ODS
Lens (01)	20	Confusion/weakness	97	2.1	14	N/A	N/A	0.45 NS + KCl supplements	21 mmol/48 h	ODS
Sanghvi (06)	21	Weakness	100	2.7	4	218	53	NS, later fluid restriction with D5	15 mmol/24 h, 24 mmol/48 h	ODS
	22	Weakness	104	4.3	7	547	10	Fluid restriction	7 mmol/24 h, 14 mmol/48 h	No apparent neurological sequelae



Free Water Clearance and Solute Excretion



Further Testing in Hyponatremia

TSH – rule out hypothyroidism

Random cortisol – primary or secondary adrenal failure. Check other indices of pituitary function if hypopit likely

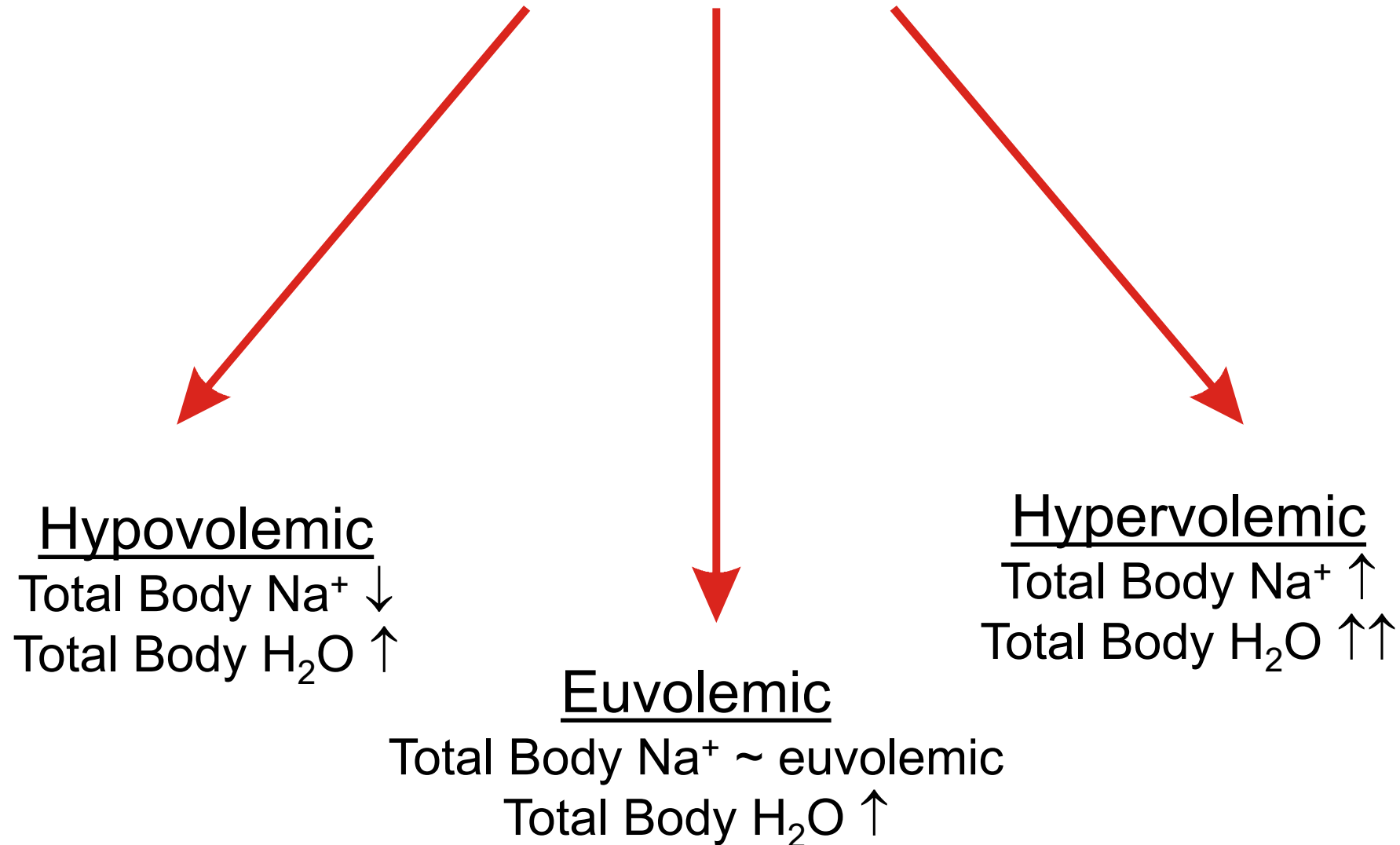
Cosyntrophin stimulation test – if primary adrenal failure likely

CXR; if negative and high likelihood of small cell CA → chest CT

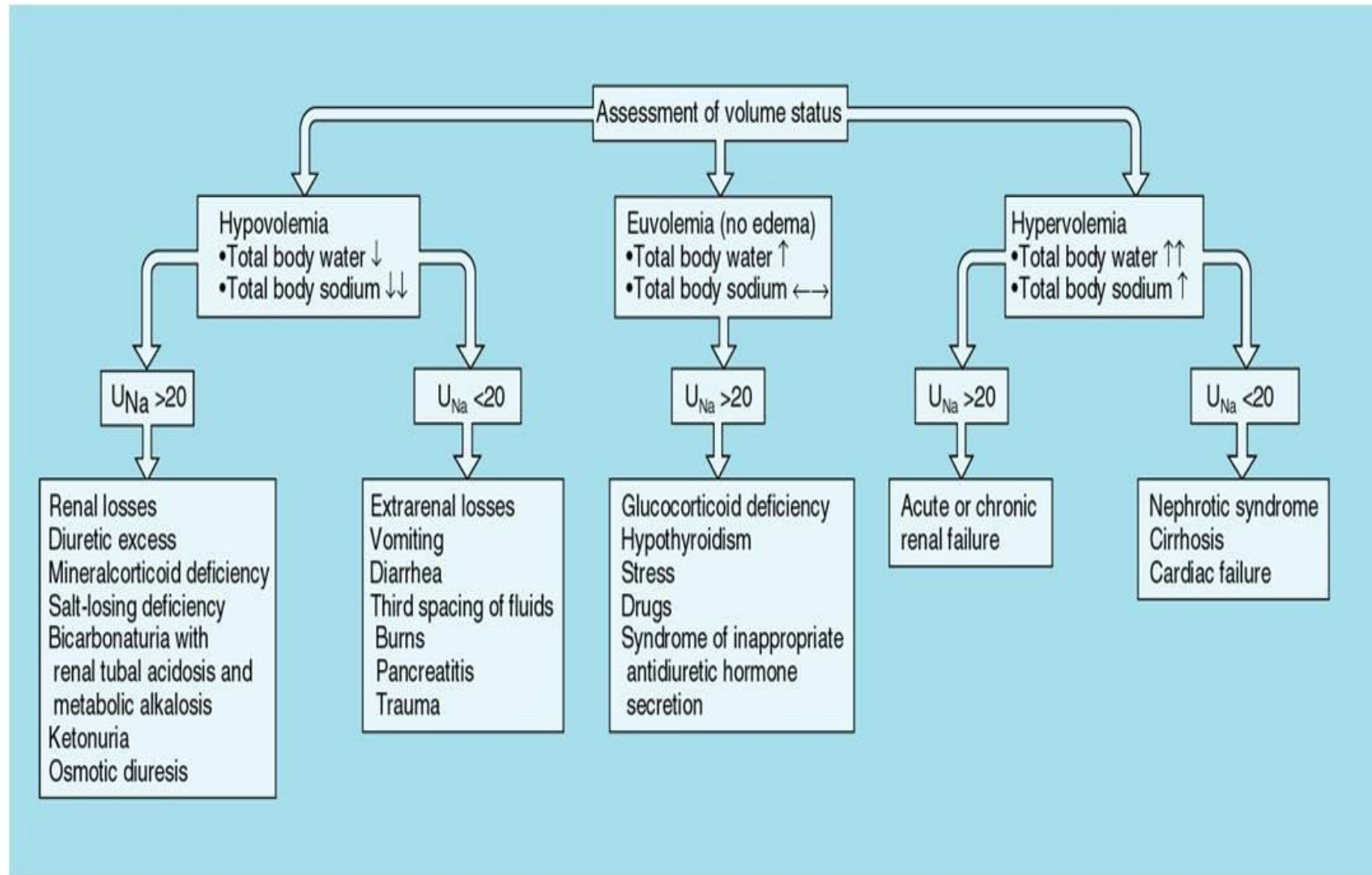
Head CT – look also at sinuses and nasal cavity (squamous cell CA, olfactory neuroblastoma)



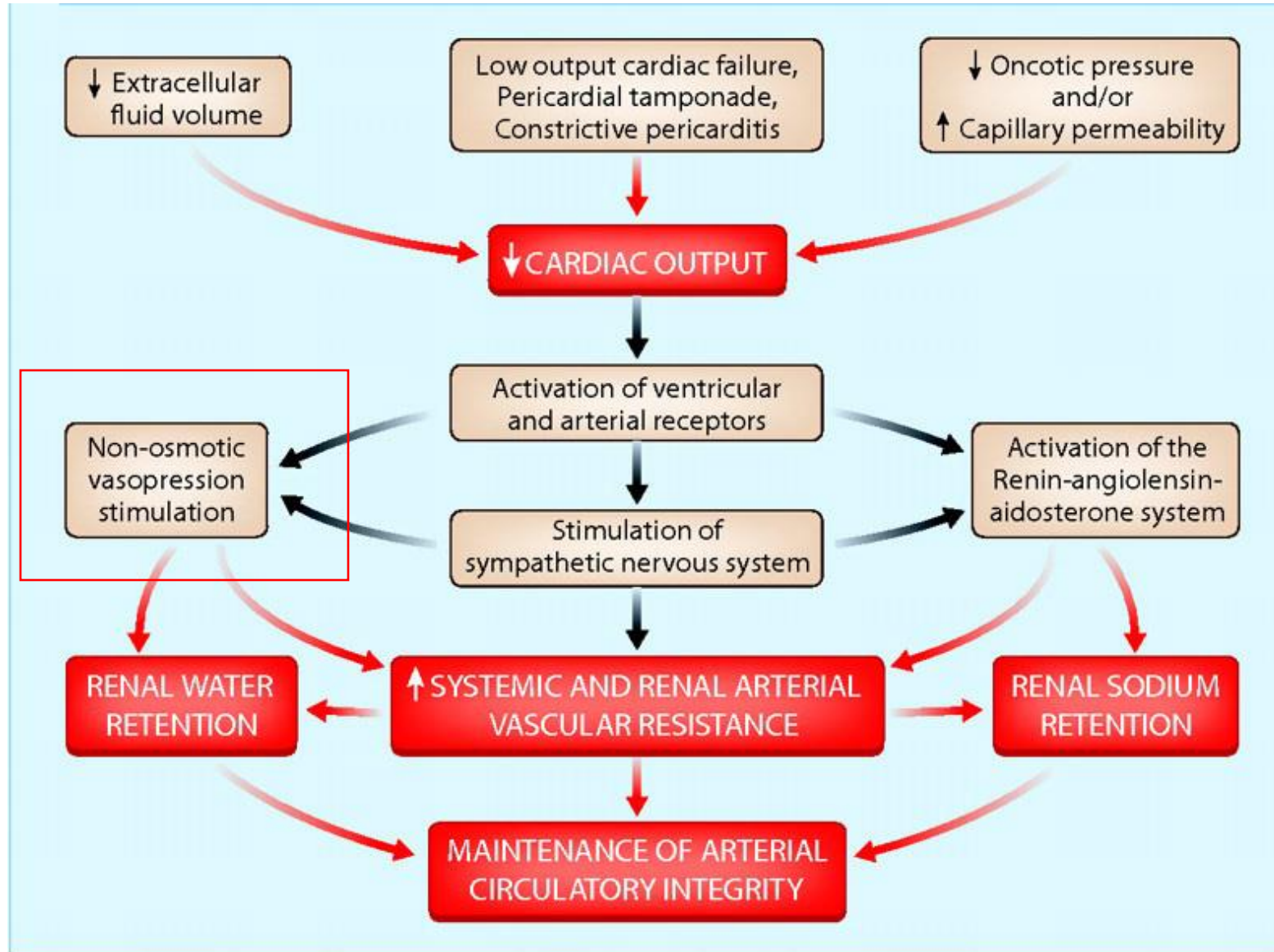
Approach to the Hyponatremic Patient with $U_{\text{osm}} > 100 \text{ mOsm/kg}$



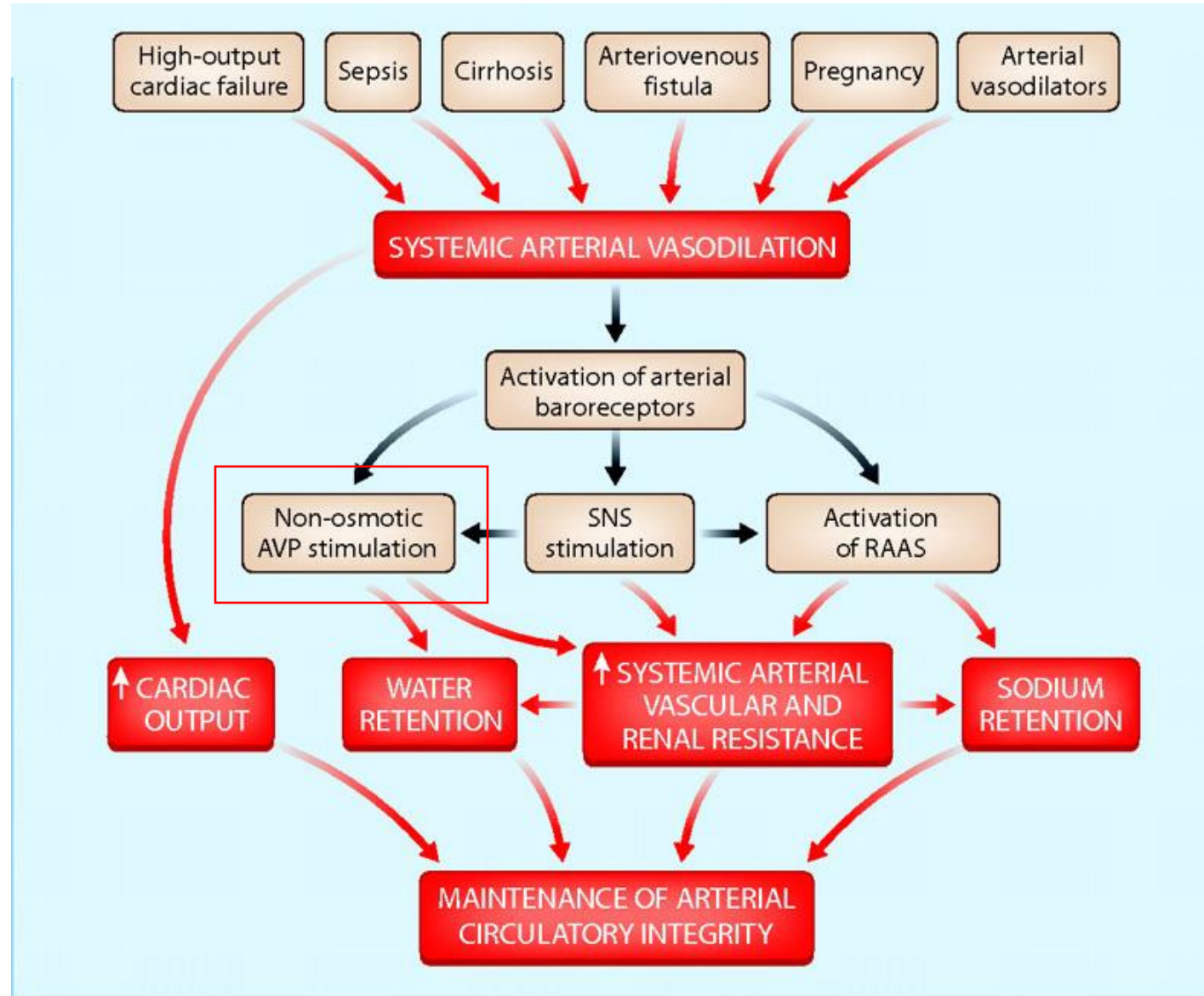
Diagnostic Algorithm



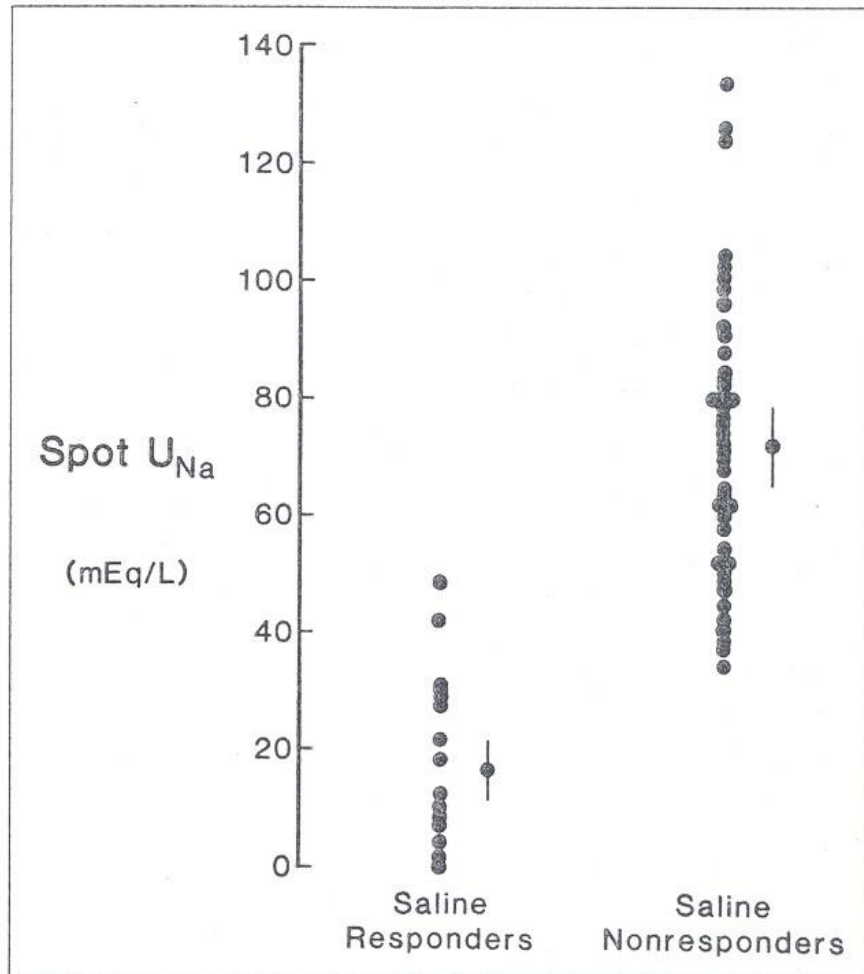
Defense of Circulatory Integrity in ↓ Cardiac Output



Defense of Circulatory Integrity in Vasodilatory States



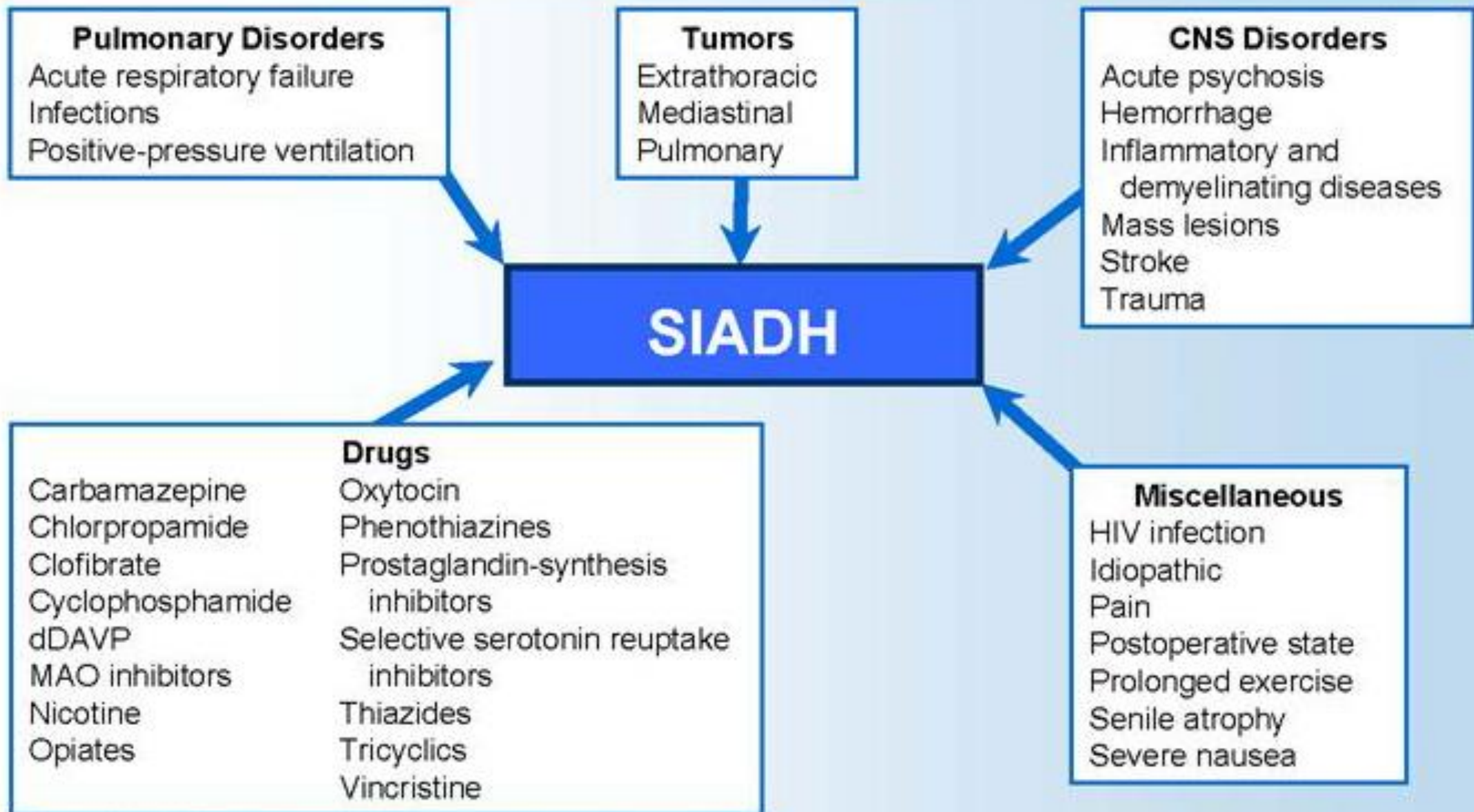
Spot Urinary Na^+ and the D_x of Hypovolemic Hyponatremia



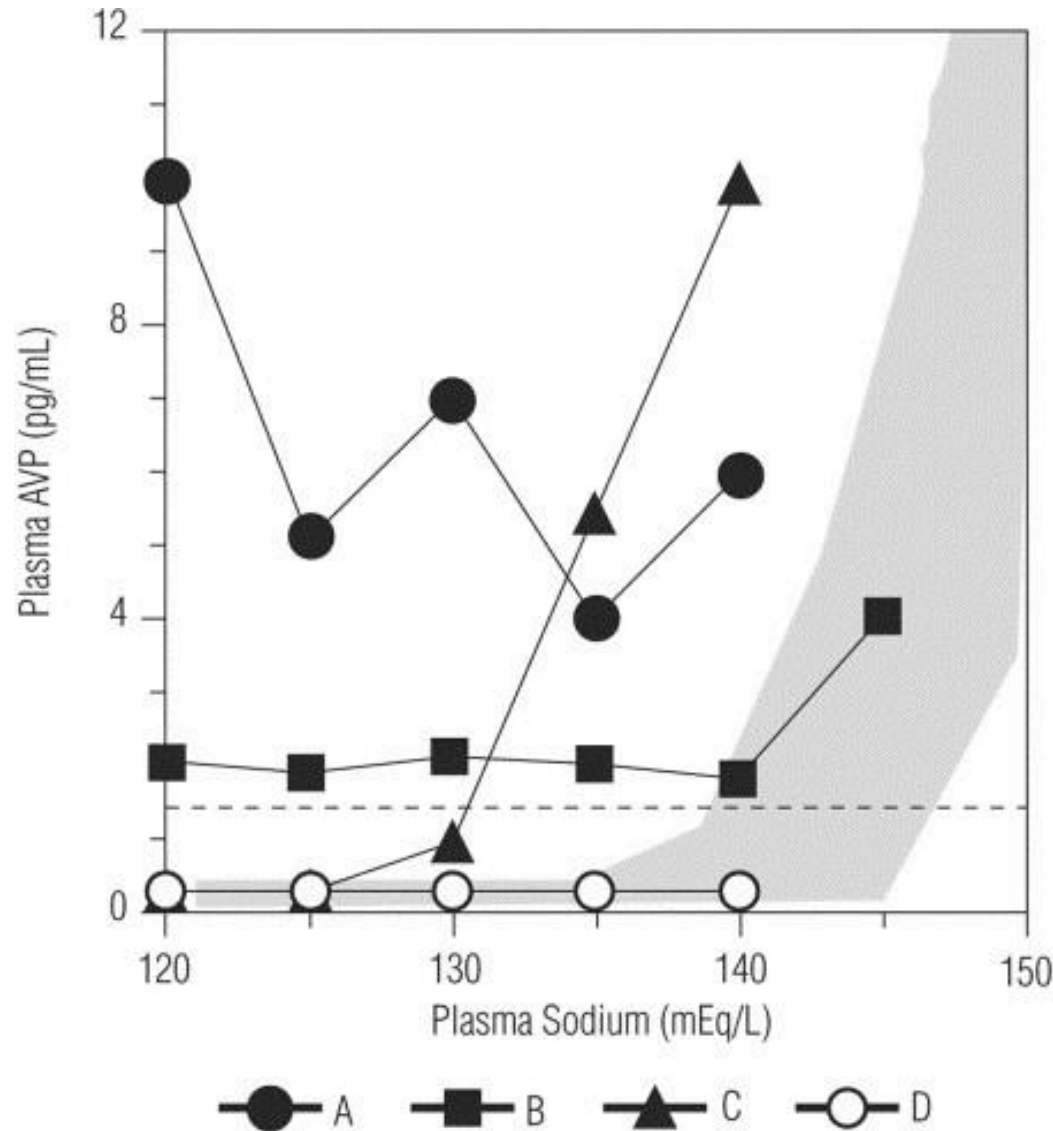
Urine Na^+ in “non-edematous” patients with hyponatremia, who do or do not respond to saline infusion with $\uparrow$ serum Na^+

Na^+ -avid patients have $\uparrow$ vasopressin due to hypovolemia $\rightarrow$ suppressed by normal saline infusion.

Am J Med 83: 905-908, 1987



Patterns of AVP Release in SIADH



- A) Unregulated, erratic**
- B) Baseline increase, normal osmotic response**
- C) "Reset osmostat"**
- D) Suppressed AVP**

Question #2

A 19 yo woman is brought to the emergency department with altered mental status. She had been at a “rave” the night before. She became drowsy at ~2 AM, and vomited several times. At 4 AM she had a generalized seizure that lasted ~15 seconds. On exam, she is unresponsive, ventilated HR 84, bp 145/85. Heart sounds normal, inspiratory crackles on chest exam. Head & neck WNL, no evidence of trauma.

Laboratory Studies:

Na ⁺	121	Creat	0.5
K ⁺	3.6	uric acid	3.7
Cl ⁻	90	Osm	242

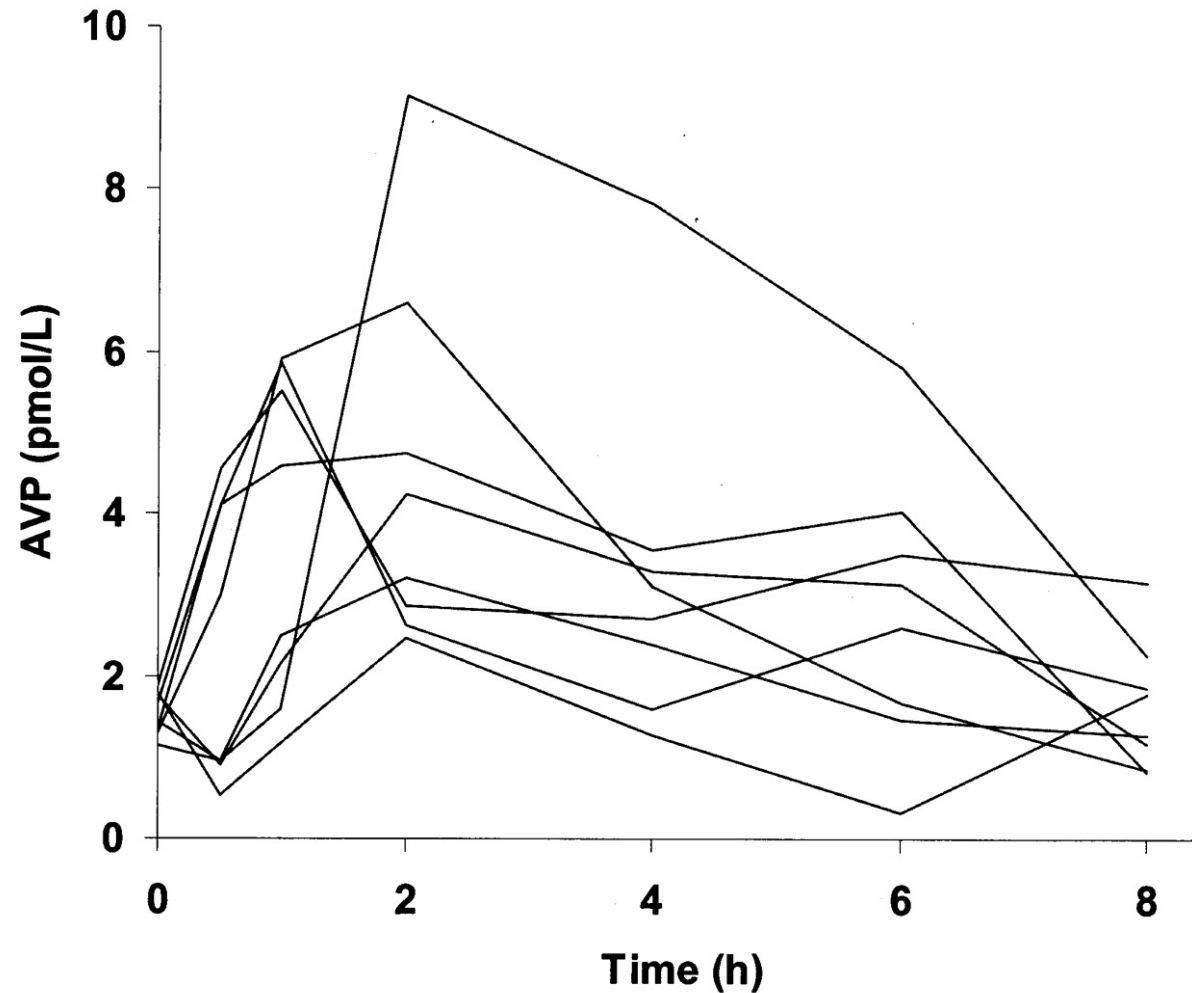


Which of the following is the most likely cause of this syndrome?

- A. Ecstasy-induced hyponatremia
- B. Hyponatremia secondary to seizure
- C. Exercise-associated hyponatremia
- D. Acute intracerebral bleed
- E. Compulsive drinking



MDMA (Ecstasy) Ingestion Causes SIADH In Healthy Volunteers



Fallon et al, *Ann. N.Y. Acad. Sci.*, 2002



Ecstasy and Hyponatremia

Due to a combination of factors:

- Acute, massive increase in AVP – serotonin activates central osmoreceptors → ↑ AVP release from posterior pituitary
- Acute stimulation of thirst – serotonin activates central osmoreceptors
- Deliberate water intake – recommendations have been to increase water intake at raves, given exertion and possible hyperthermia



Causes of Acute Hyponatremia

Iatrogenic

- Postoperative – premenopausal women
- Hypotonic fluids with cause of ↑ vasopressin
- Glycine irrigant – TURP, uterine surgery
- Colonoscopy preparation
- Recent institution of thiazides

Polydipsia

Ecstasy ingestion

Exercise induced

Multifactorial, e.g. thiazide and polydipsia



Symptoms/Signs of Acute Hyponatremic Encephalopathy

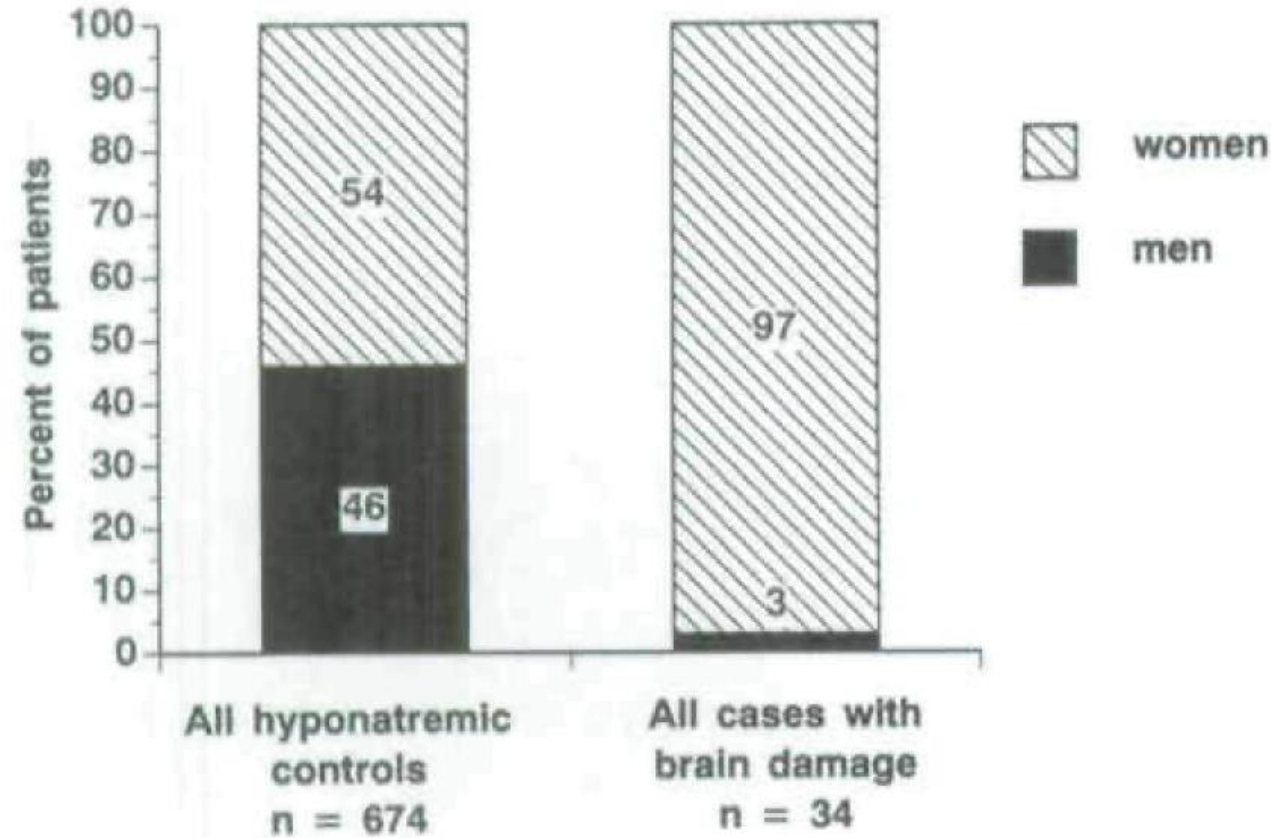
Early: headache, nausea, vomiting

Advanced: ↓ response to verbal or painful stimuli, inappropriate behavior, asterixis, obtundation, incontinence

Far advanced: decorticate and/or decerebrate posturing, hyper/hypotension, dilated pupils, **seizures**, **respiratory arrest**, polyuria (central DI), hyperglycemia



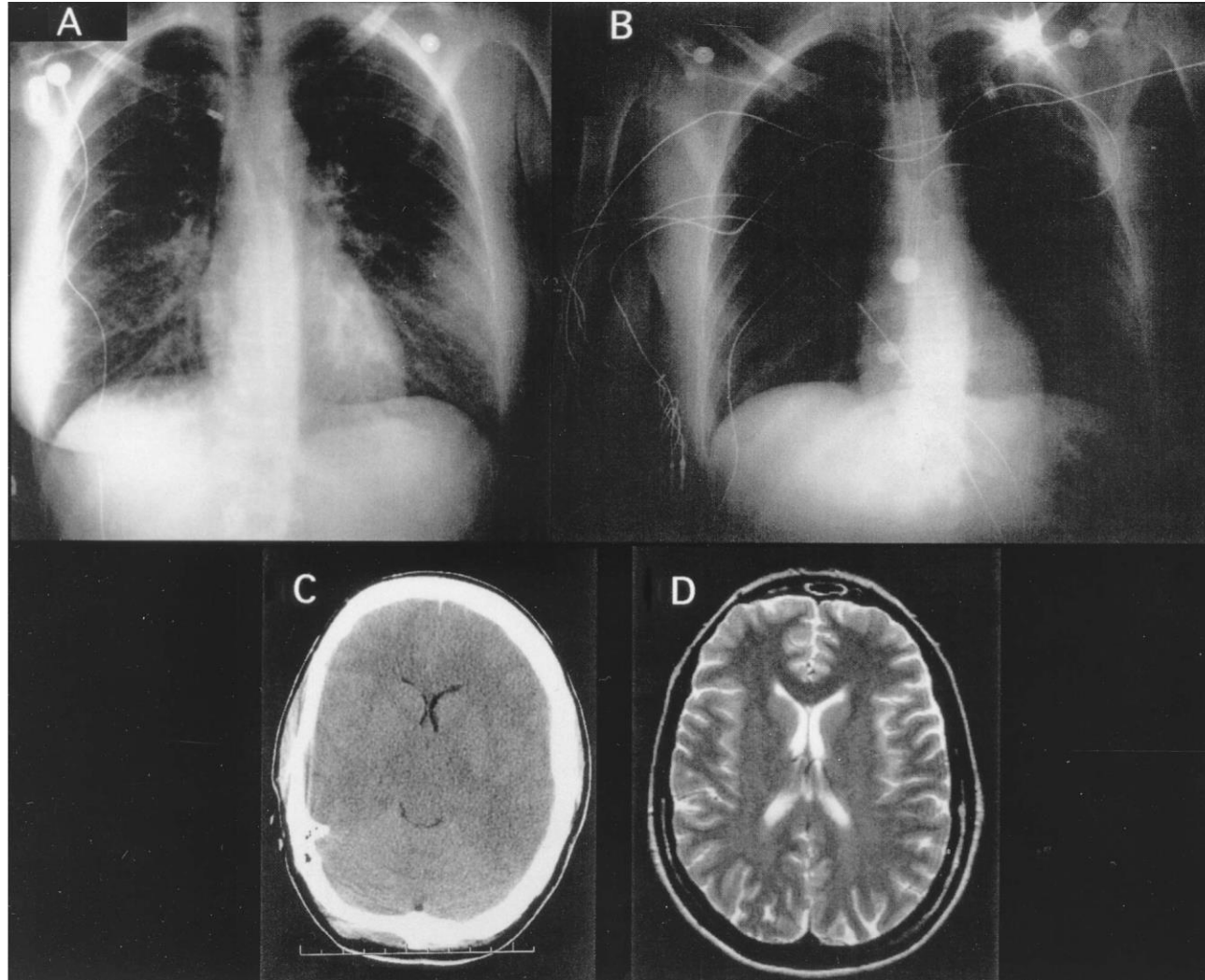
The Marked Female Preponderance in Hyponatremic Brain Injury



Ayus et al, *Ann Int Med*, 1992



Cerebral Edema and Non-Cardiogenic Pulmonary Edema in Acute Hyponatremia



A&C – @ ER
B&D – after 24 hrs

44 yo female
marathon runner

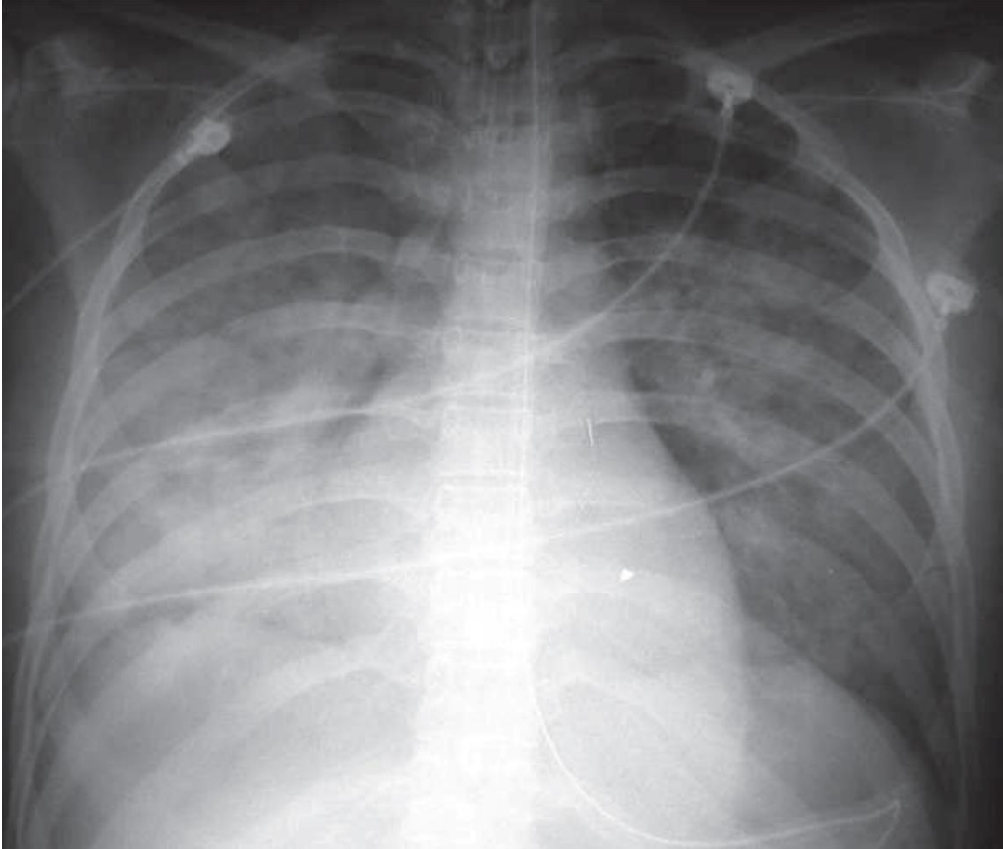
Ayus et al,
Ann Int Med, 2000



CT head

MRI

Pulmonary Edema After Ecstasy Ingestion



20 year-old female
college student

[Na⁺] 117 mM

Chronic Hyponatremia

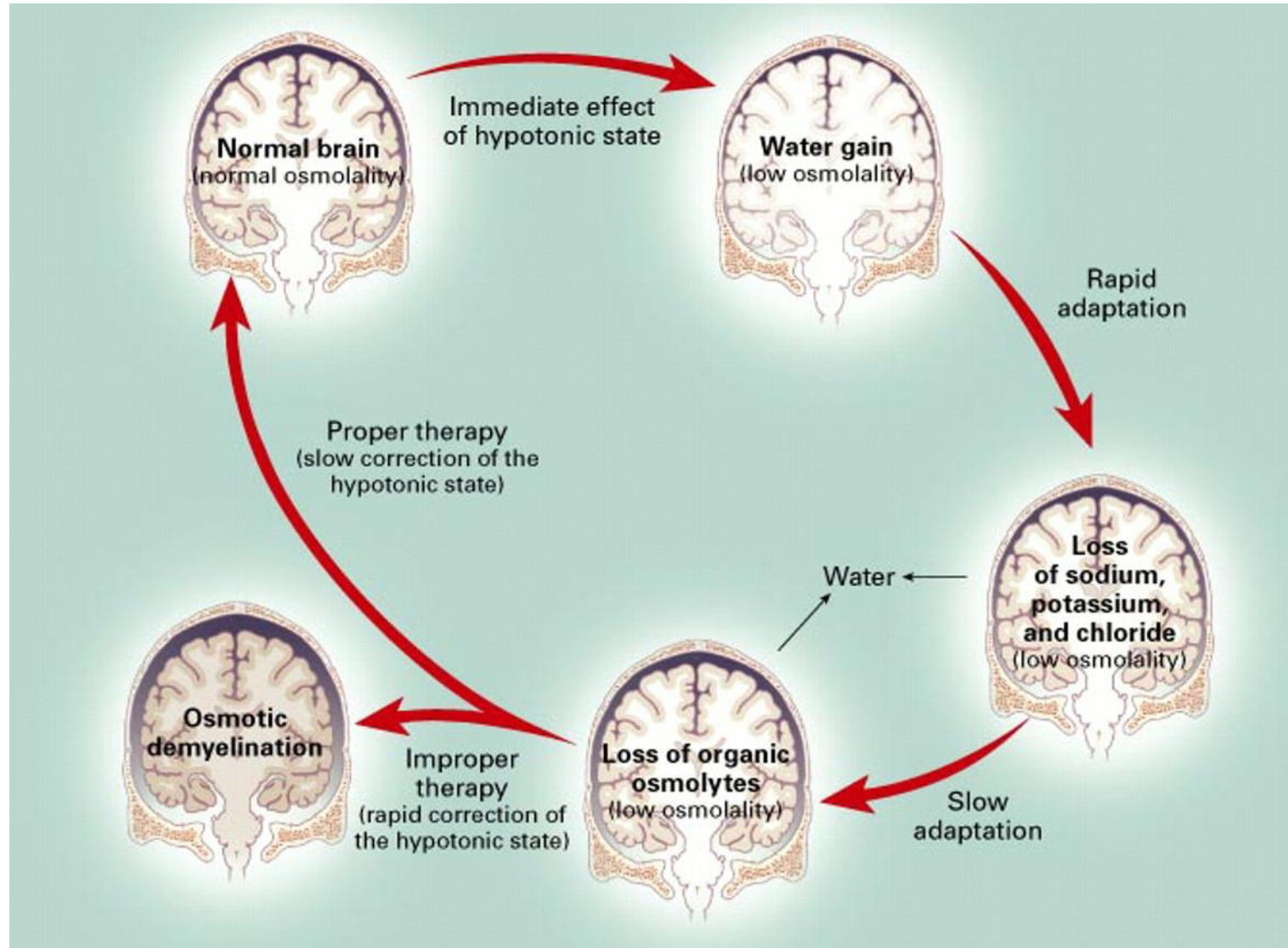
> 48 hours or of unknown duration
CNS response to hyponatremia induces sensitivity to correction rate, wrt osmotic demyelination syndrome (ODS)

Symptoms classically taught as “absent” but may include:

- Nausea and vomiting
- Muscle cramps and weakness
- Ataxia
- Confusion, change in mental status
- Seizures (if Na^+ ↓↓↓)

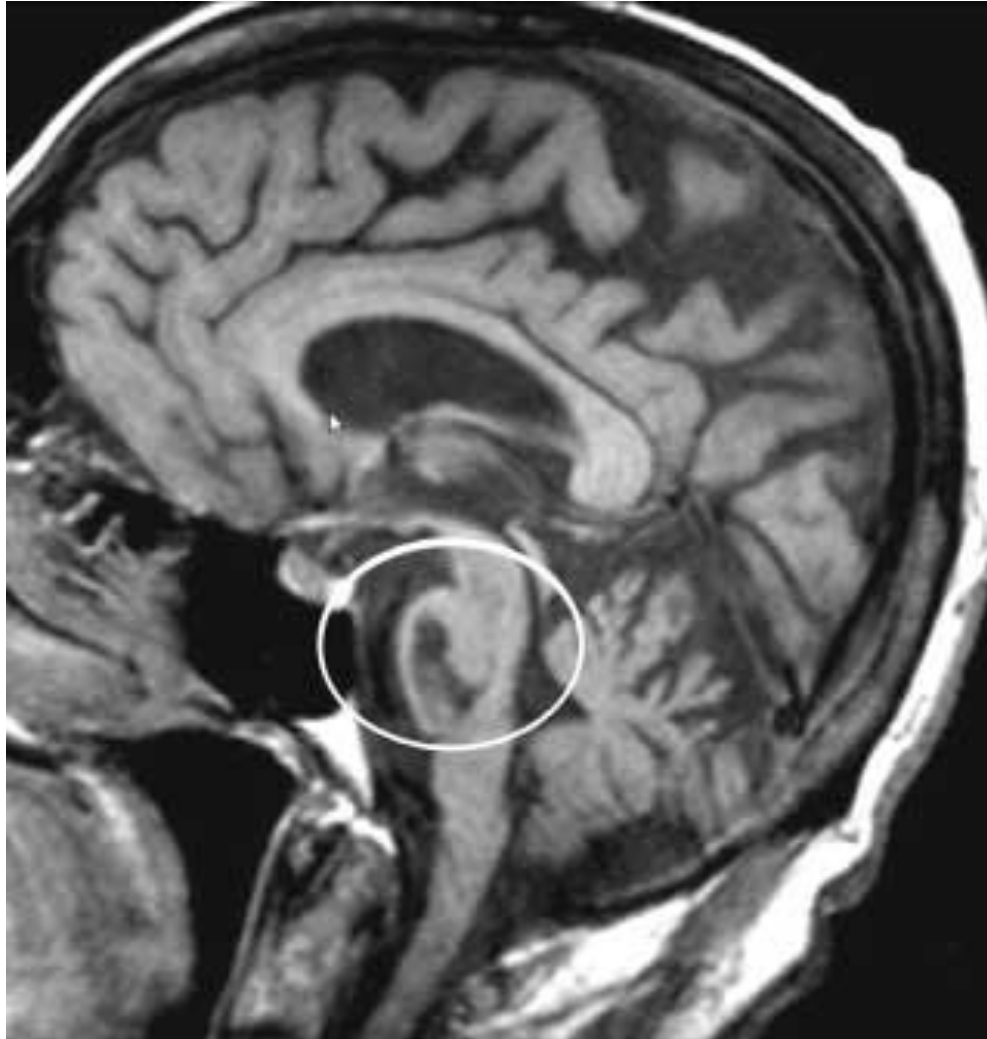


The CNS Response to Hyponatremia



Adrogué and Madias, *NEJM*, 2000

Central Pontine Myelinolysis (CPM) From Osmotic Demyelination Syndrome (ODS)



Flaccid quadriparesis, Δ
corticospinal tract
Dysphagia, from
corticobulbar tract
Locked-in syndrome
Symptoms from extra-
pontine pathology are
variable, depending on
region involved

Risk Factors for Osmotic Demyelination

Rate of correction (although CPM/ODS can occur at accepted rates.....)

Hypokalemia – role in genesis of hyponatremia, with increase in Na after K repletion, along with potential CNS effects

Alcoholism

Malnutrition, e.g. with anorexia/bulimia

Liver failure, liver transplantation

- Similar changes in cerebral osmolytes in liver failure



Pathogenesis of Osmotic Demyelination

Disruption of the blood-brain barrier – leakage of Ig's, complement, cytokines into perivascular brain.

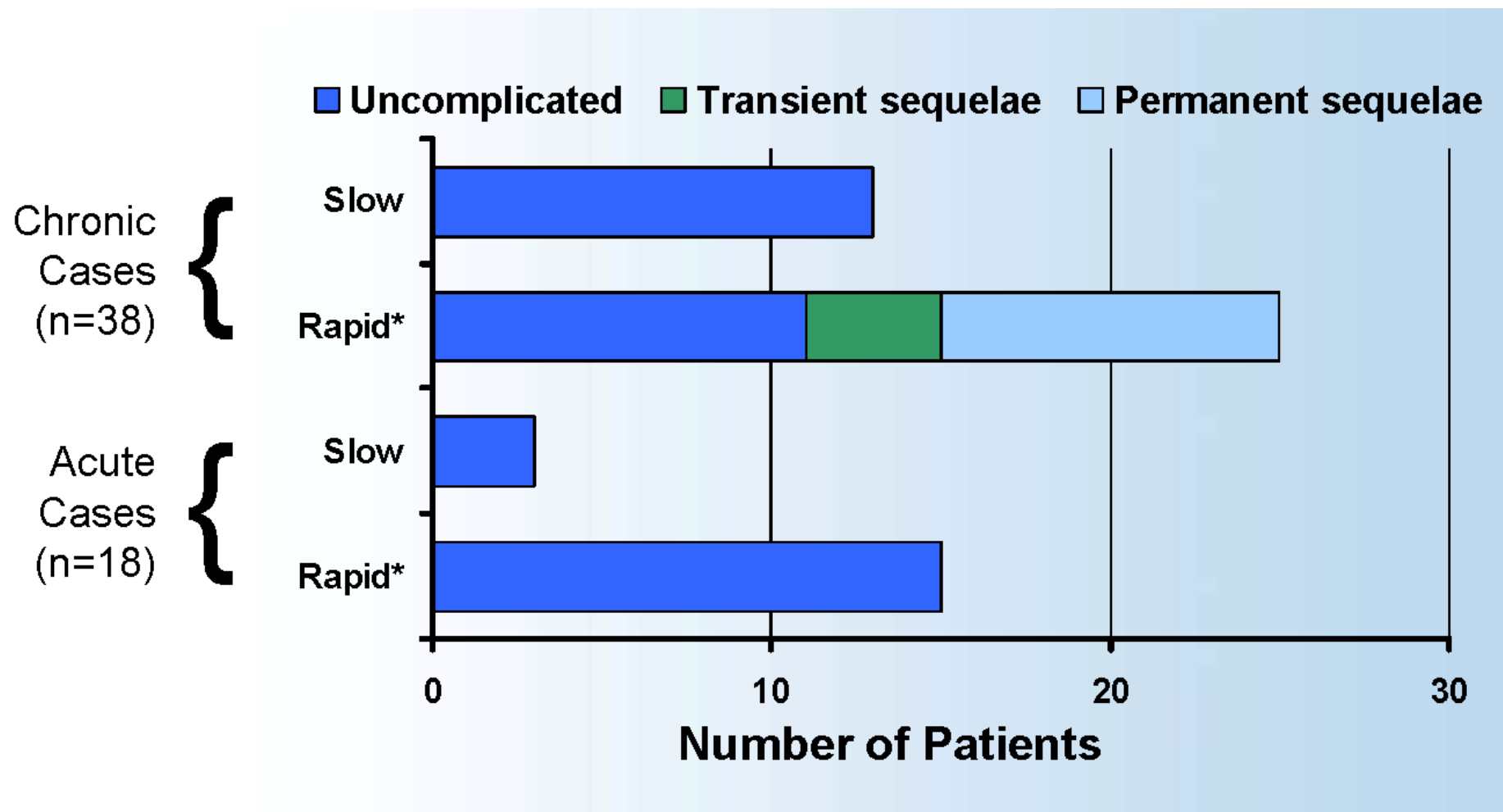
Delayed induction of osmolyte transporters after correction of hyponatremia → ↓ osmoregulatory capacity and cell swelling/death.

Apoptotic or excitotoxic (glutamate-dependent) cell death after correction of hyponatremia.

Defective glial proteostasis – unfolded protein response and ER stress induced by correction*



Rate of Correction from $[\text{Na}^+] \leq 105 \text{ mEq/L}$ and Neurological Outcome



Sterns et al, *JASN*, 1994

Is Chronic Hyponatremia Really That Asymptomatic?

Case-control series of 122 consecutive asymptomatic hyponatremia patients.

Na ranged from 115-135

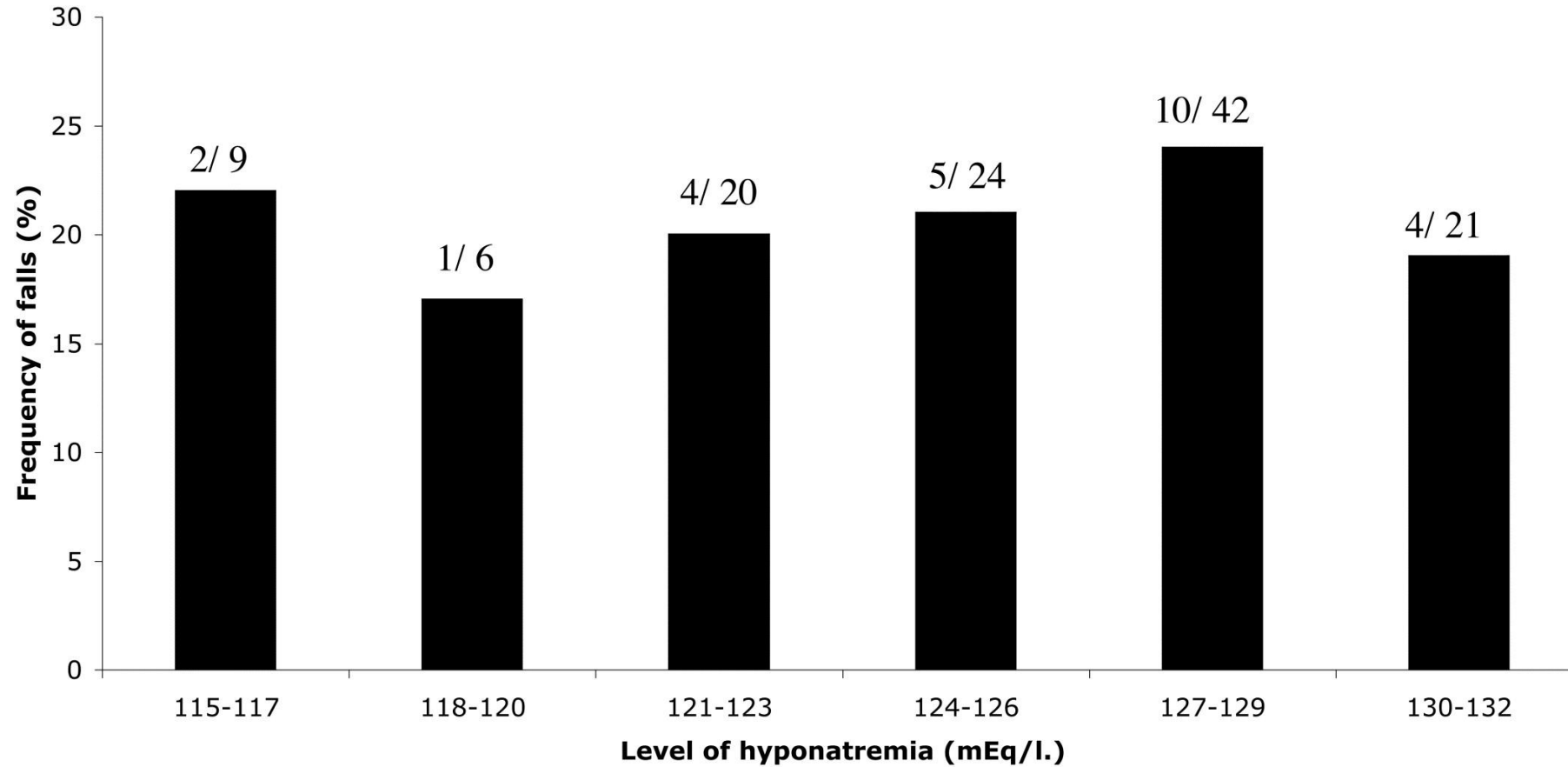
Prevalence of falls was 21.3% versus 5.4 % in case controls ($p < 0.001$).

Fall was often reason for admission.

Subtle gait and attention defects in a separate cohort of hypoNa patients.



Falls and the Magnitude of Hyponatremia: Occurrence at All Levels



Renneboog, et al, *Am J Med*, 2006

Hyponatremia-Induced Osteoporosis

Joseph G Verbalis,¹ Julianna Barsony,¹ Yoshihisa Sugimura,^{1,2} Ying Tian,^{1,3} Douglas J Adams,⁴ Elizabeth A Carter,⁵ and Helaine E Resnick^{5,6}

¹Division of Endocrinology and Metabolism, Georgetown University, Washington, DC, USA

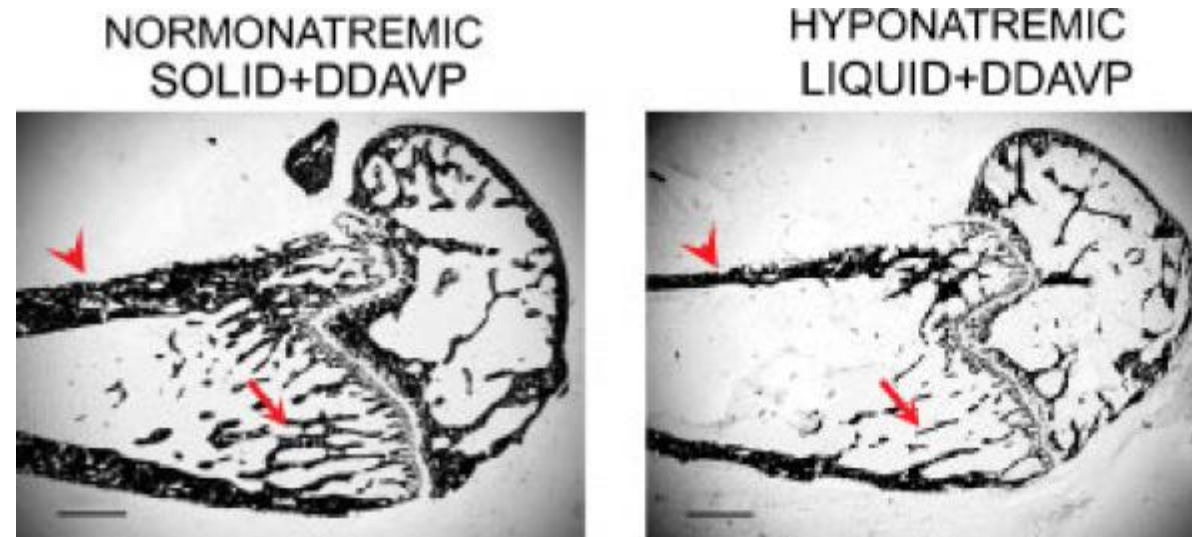
²Presently: Department of Endocrinology and Diabetes, Nagoya University Graduate School of Medicine, Nagoya, Japan

³Presently: Geriatrics and Clinical Gerontology Program, National Institute on Aging, National Institutes of Health, Bethesda, MD, USA

⁴Department of Orthopaedic Surgery, New England Musculoskeletal Institute, University of Connecticut Health Center, Farmington, CT, USA

⁵Department of Epidemiology and Statistics, MedStar Research Institute, Hyattsville, MD, USA

⁶Presently: American Association of Homes and Services for the Aging, Washington, DC, USA



J Bone Miner Res. 2010 Mar;25(3):554-63.

Treatment of Hyponatremia

Management of acute, symptomatic hyponatremia

Management of chronic hyponatremia

- Fluid restriction
- Furosemide and salt tabs - ↓ countercurrent mechanism and repletion of excreted NaCl
- Demeclocycline - ↓ V_2 R response
- Oral urea – “Ure-na”TM – palatable form of oral urea
- Vasopressin antagonists



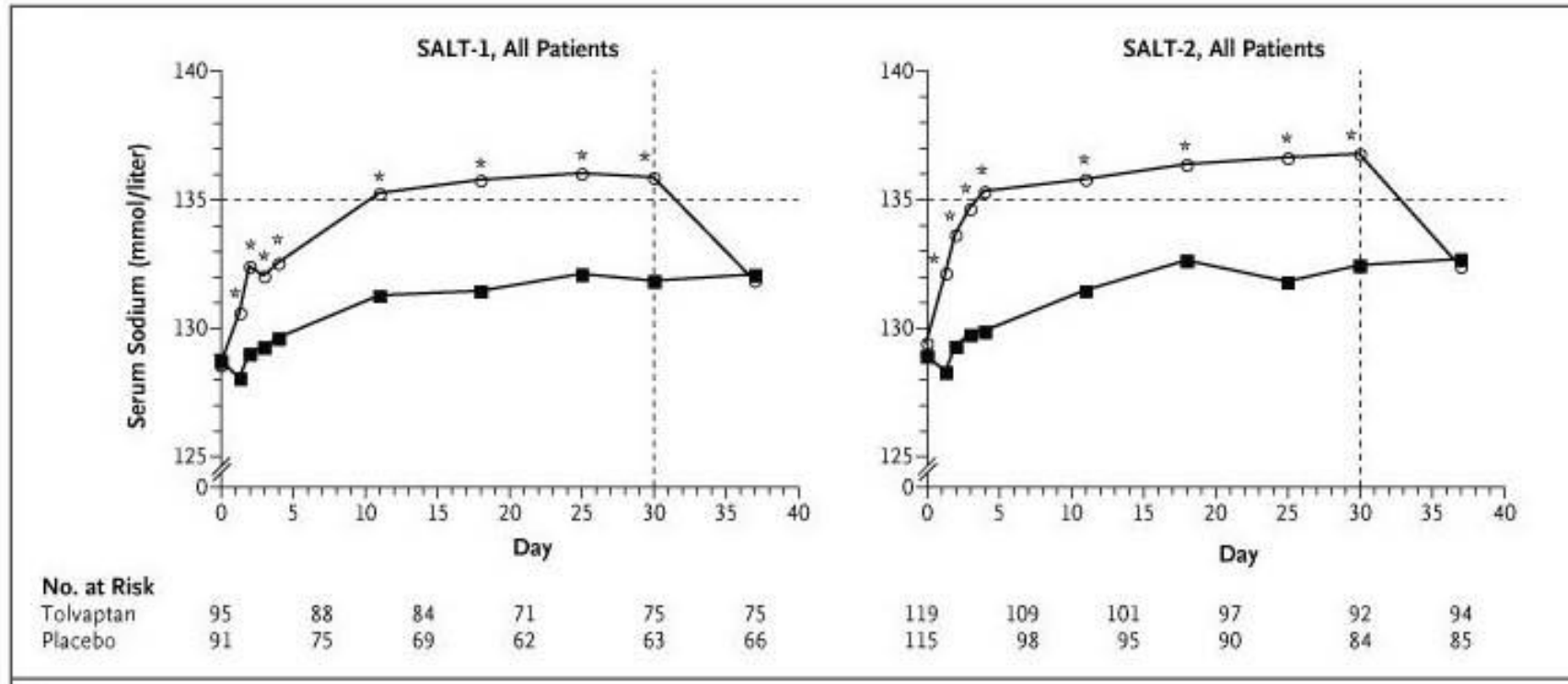
Vasopressin Antagonists

<i>Drug</i>	<i>Antagonism</i>	<i>Route</i>	<i>Dose</i>
<i>Conivaptan</i>	V1A/V2	IV	20-40 mg/day
<i>Tolvaptan</i> *	V2	PO	15-60 mg/day
<i>Lixivaptan</i>	V2	PO	100-200 mg/day
<i>Satavaptan</i>	V2	PO	12.5-50 mg/day

* FDA advisory, 2013 → 2.5 ↑ in LFTs is more common in patients given Tolvaptan versus placebo in the TEMPO PKD trial. Therefore, do not use in liver disease or for >30 days.



Tolvaptan in Hyponatremia: The SALT Trials



Schrier et al, *NEJM*, 2006

Pros and Cons of the Vaptans

What are the indications in clinical practice?

Significant expense

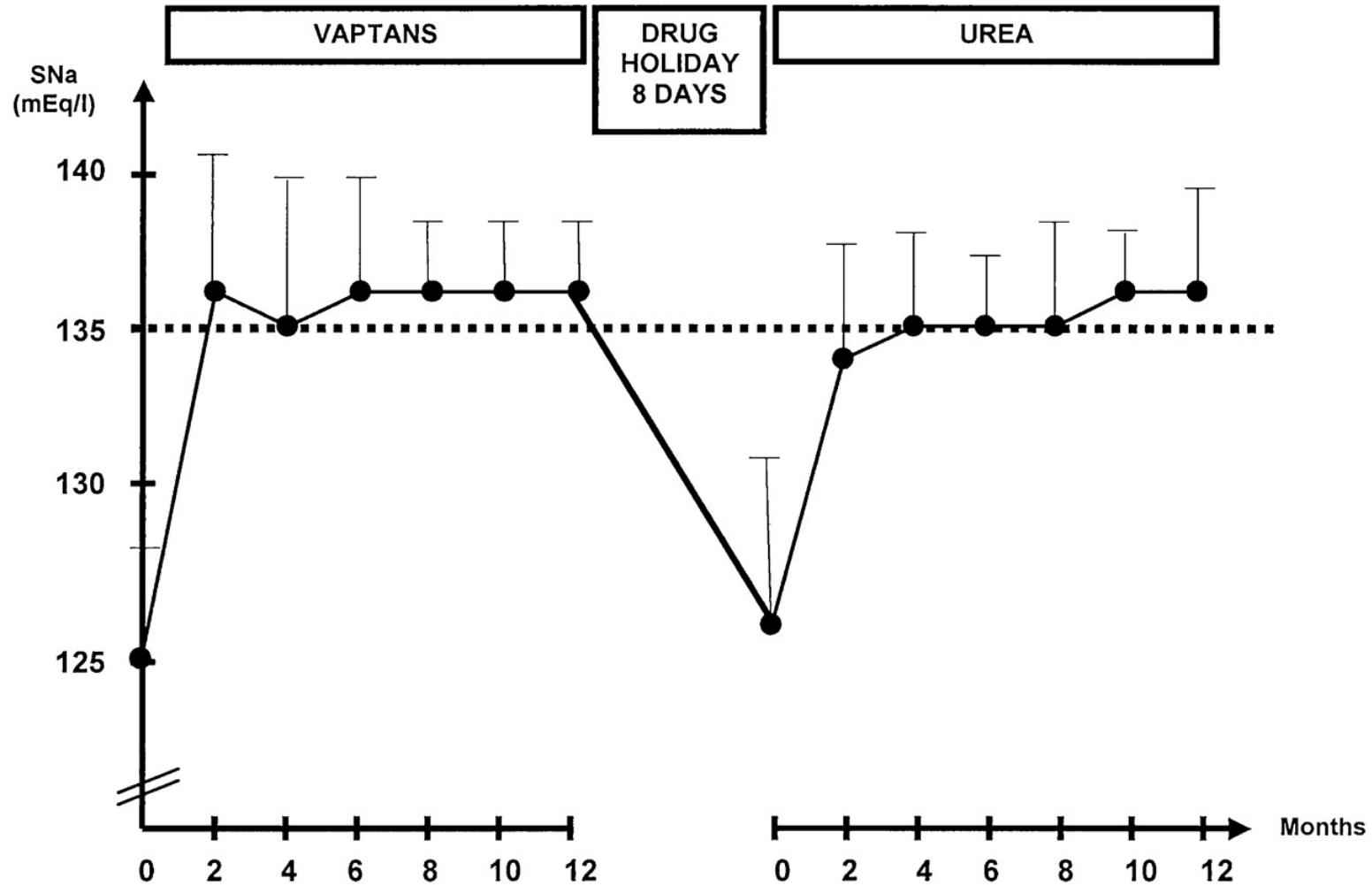
Risk of overcorrection – minimize by frequent monitoring of serum Na during the first 48 hours and > 2 liters/day water intake

****FDA advisory regarding liver toxicity of tolvaptan****

Primary utility is in severe CHF-associated hyponatremia



Oral Urea for SIADH



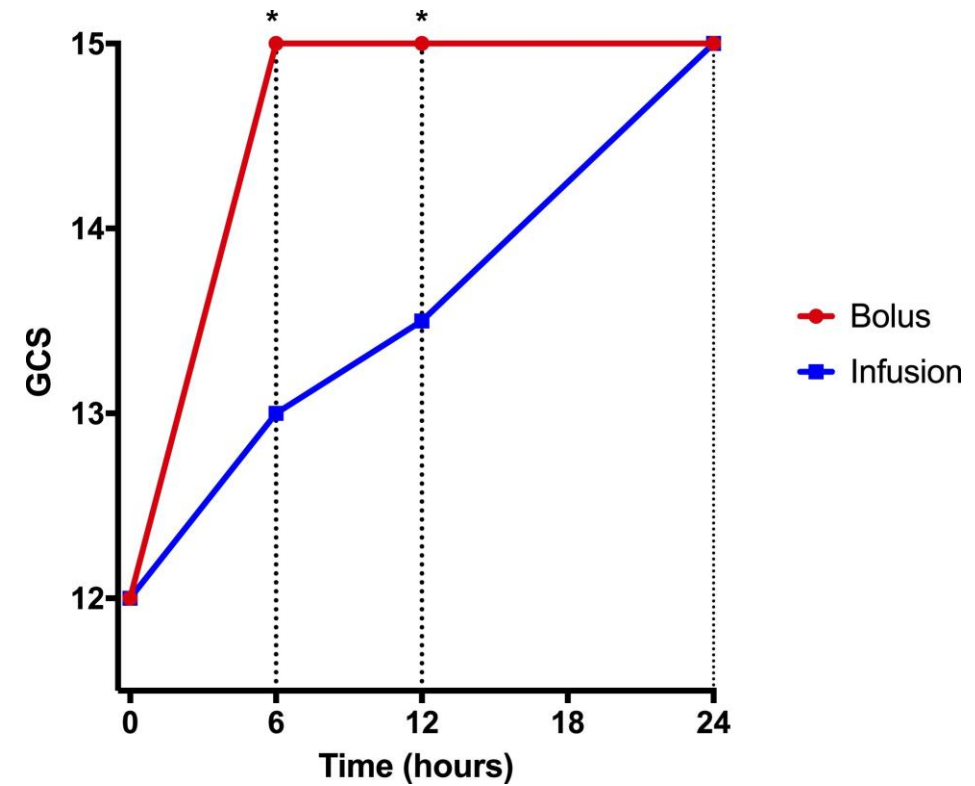
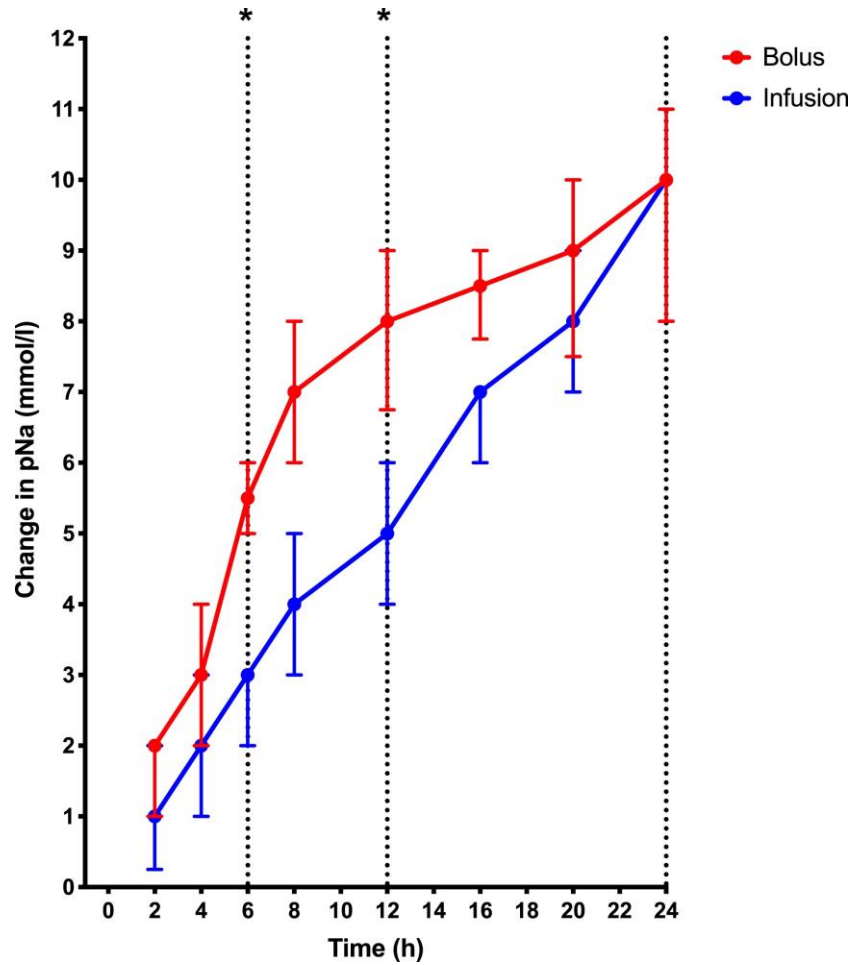
We Hopefully Agree.....

Treatment of acute, symptomatic hyponatremia can be life-saving
Management should include:

- hypertonic saline
- ABG, CXR, and CNS imaging (if available – but do **NOT** delay therapy)
- supplemental O₂ prn
- loop diuretic (R_x of pulmonary edema and ↓ countercurrent mechanism)



Bolus Hypertonic Versus Infusion



Rate of Correction

Acute (< 48 hr) symptomatic hyponatremia

- 1-2 mEq/l per hour, correcting by 4-6 mEq/L and/or until correction of severe symptoms, then chronic criteria
- hypertonic saline, plus furosemide (particularly if in pulmonary edema)
- Close attention to oxygenation

Chronic hyponatremia (> 48 hr)

- 0.5 mEq/l per hour, $\leq$ 10 mEq/L first 24 hours, and $\leq$ 18mEq/L first 48 hours
- Most experts advocate even more conservative approach in patients at $\uparrow\uparrow$ risk of ODS, 4-6 mEq/L first 24 hours then no $>$ 8 mEq/L subsequent 24 hour periods



What If You “Over-Correct”: Treatment of Osmotic Demyelination

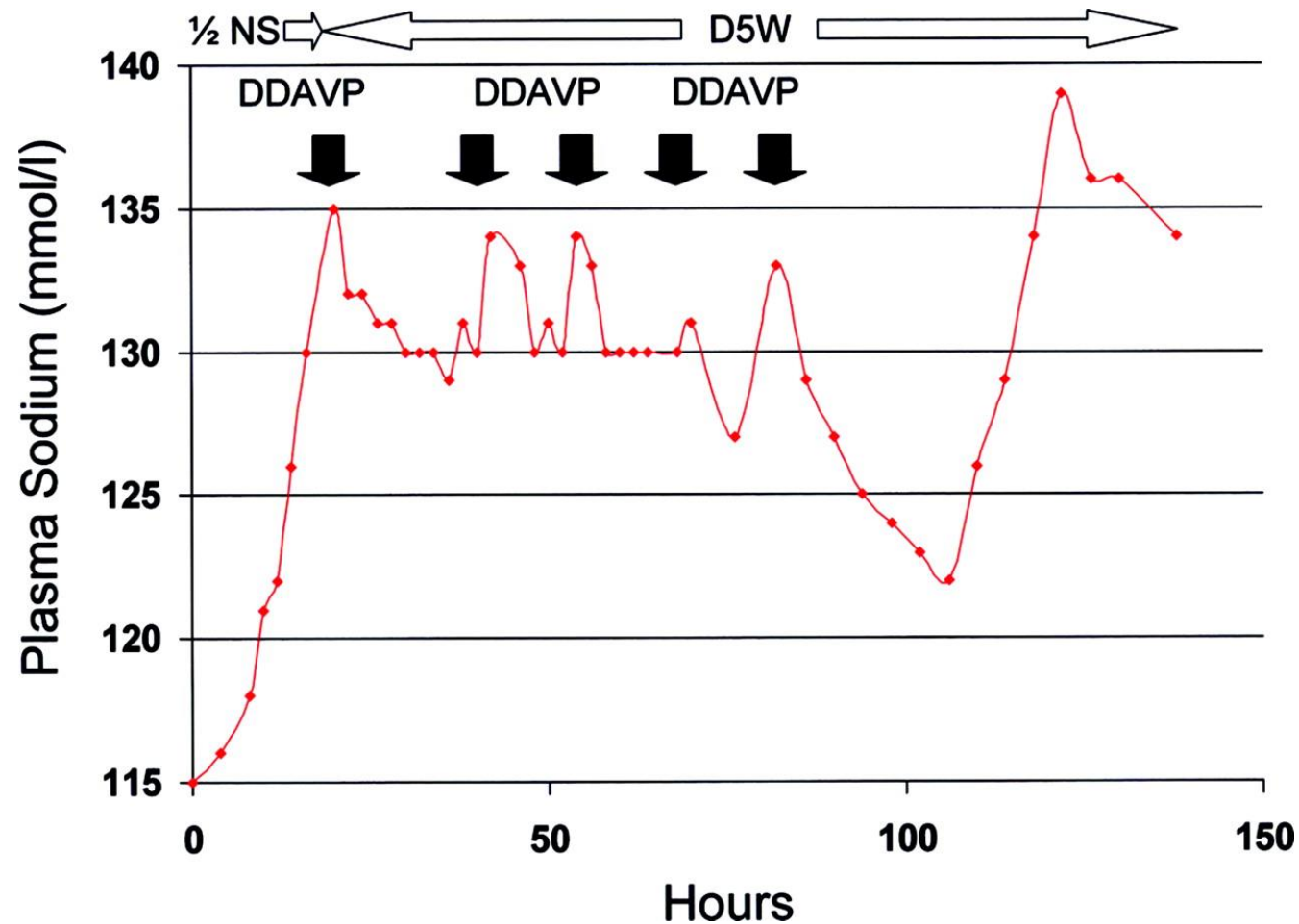
DDAVP and D5W to re-induce hyponatremia – animal and human data

Myo-inositol supplementation during correction – animal data

Dexamethasone to restore blood brain barrier function – animal data



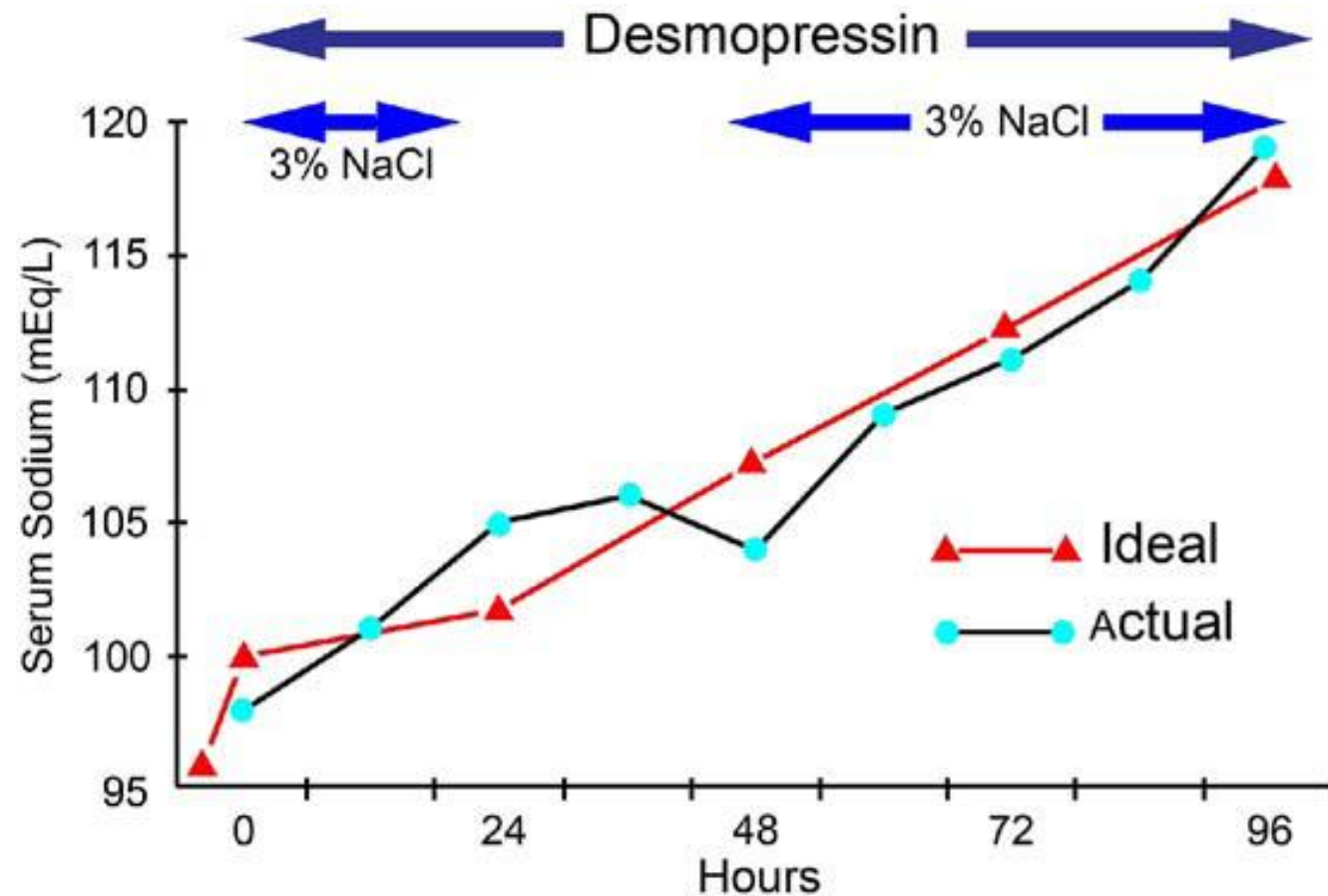
Re-Induction of Hyponatremia With DDAVP + Free H₂O



Sterns et al, CJASN, 2008



Alternative Approach: DDAVP “Clamp” with Hypertonic Saline



Am J Kidney Dis 56:774-779, 2010

Question #2

You admit a 40 yo woman with a one-week history of flu-like illness and profuse diarrhea. She has received 1.5 liters of N/S.

On exam, HR is 80 supine, 105 standing, bp 11/70. JVP is seen at 5 cm.

Admission Laboratory Studies:

Na ⁺	121	K ⁺	3.6
Urine Na ⁺	12	Urine Osm	450

Current Labs (6 hours after admission to ER):

Na ⁺	130	K ⁺	3.5
Urine Na ⁺	18	Urine Osm	300



Which of the following therapies is the *most* appropriate?

- A. Normal saline at 200 ml/hr
- B. Normal saline with 40 mEqu/l at 200 ml/hr
- C. Conivaptan 40 mg load then continuous infusion at 20 mg/day
- D. D5W at 75 ml/hr
- E. D5W at 75 ml/hr, after 1 μ g of DDAVP



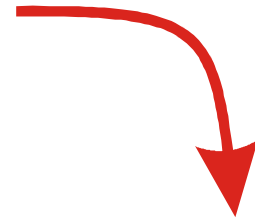
Hyponatremic Causes Associated With “Overcorrection”

- Hypovolemic hyponatremia, after volume resuscitation with saline and ↓ AVP (half-life of AVP is 10-20 minutes)
- Hypopituitarism with 2° adrenal failure, after treatment with cortisol and ↓ AVP
- Thiazide-associated hyponatremia, after discontinuation and saline hydration
- Rapid spontaneous resolution of SIADH or of a “non-osmotic” increase in AVP
- Discontinuation of DDAVP
- Beer potomania/low solute intake hyponatremia



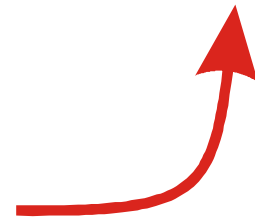
Hypernatremia

Increase the Numerator



$$\text{Serum [Na}^+] \propto \frac{\text{Na}^+_E + \text{K}^+_E}{\text{Total Body Water}}$$

Decrease the Denominator



Water Intake Disorders

Insufficient water intake – very common

High sodium intake without adequate water - rare

Thirst/Osmoreceptor (CNS) lesions – rare



Thirst / Osmoreceptor Defects

Infiltrating CNS tumor

Granulomatous disease, e.g. sarcoidosis

Ischemia

Primary hyperaldosteronism

↑ Age



Inappropriately High Water Losses

Insensible losses (sweat, breath)

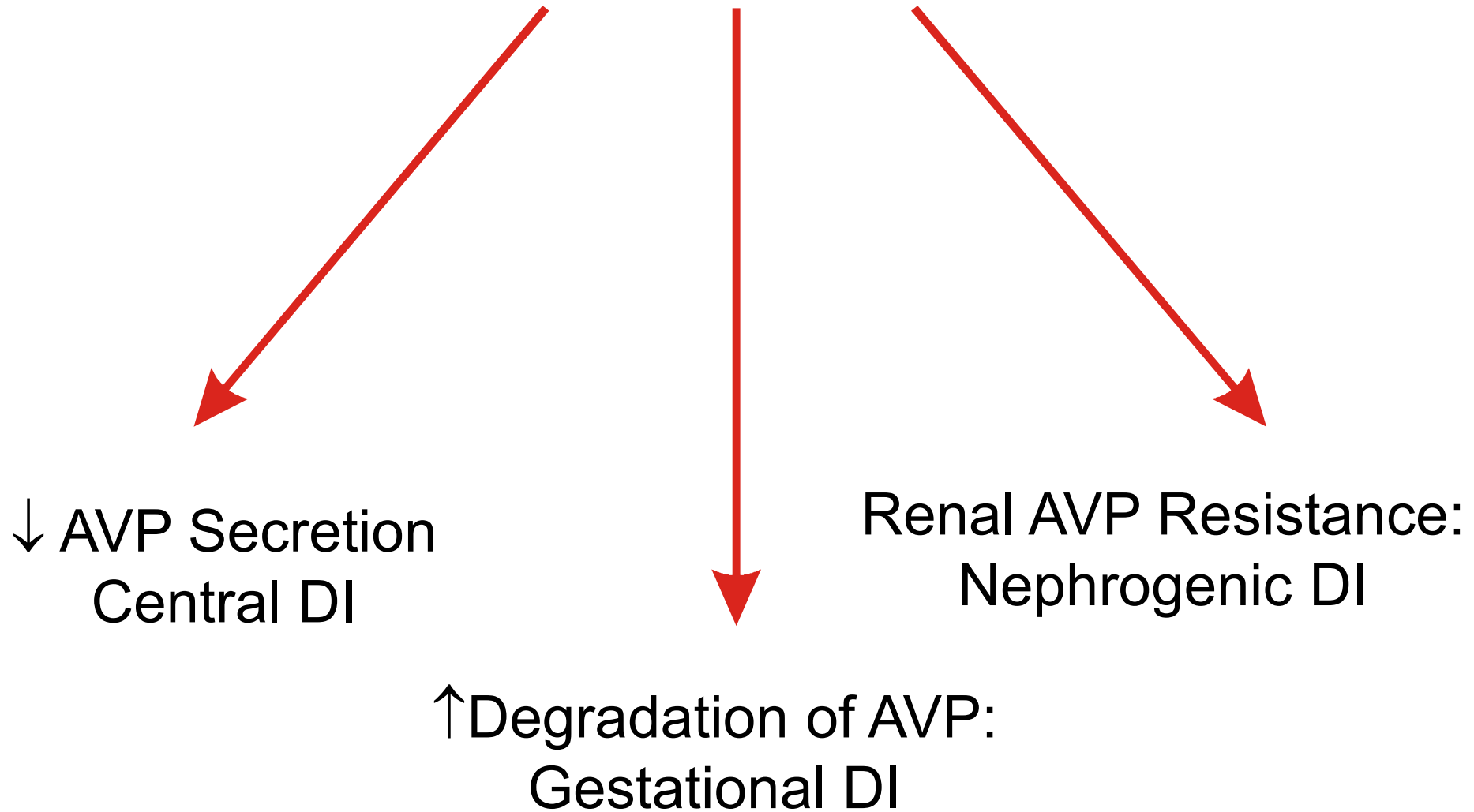
Gastrointestinal (vomiting, diarrhea)

- Gastric losses usually hypotonic
- Diarrhea isotonic
 - Secretory – $[\text{Na}^+] + [\text{K}^+] = 140$
 - Osmotic – $[\text{Na}^+] + [\text{K}^+] < 100$, i.e. free water loss

Kidney loss of free water



Renal Water Loss: Diabetes Insipidus



Causes of Central DI

Pituitary surgery

Head trauma

Tumors

CVA or hypoxic encephalopathy

Infections

Idiopathic - ? autoimmune

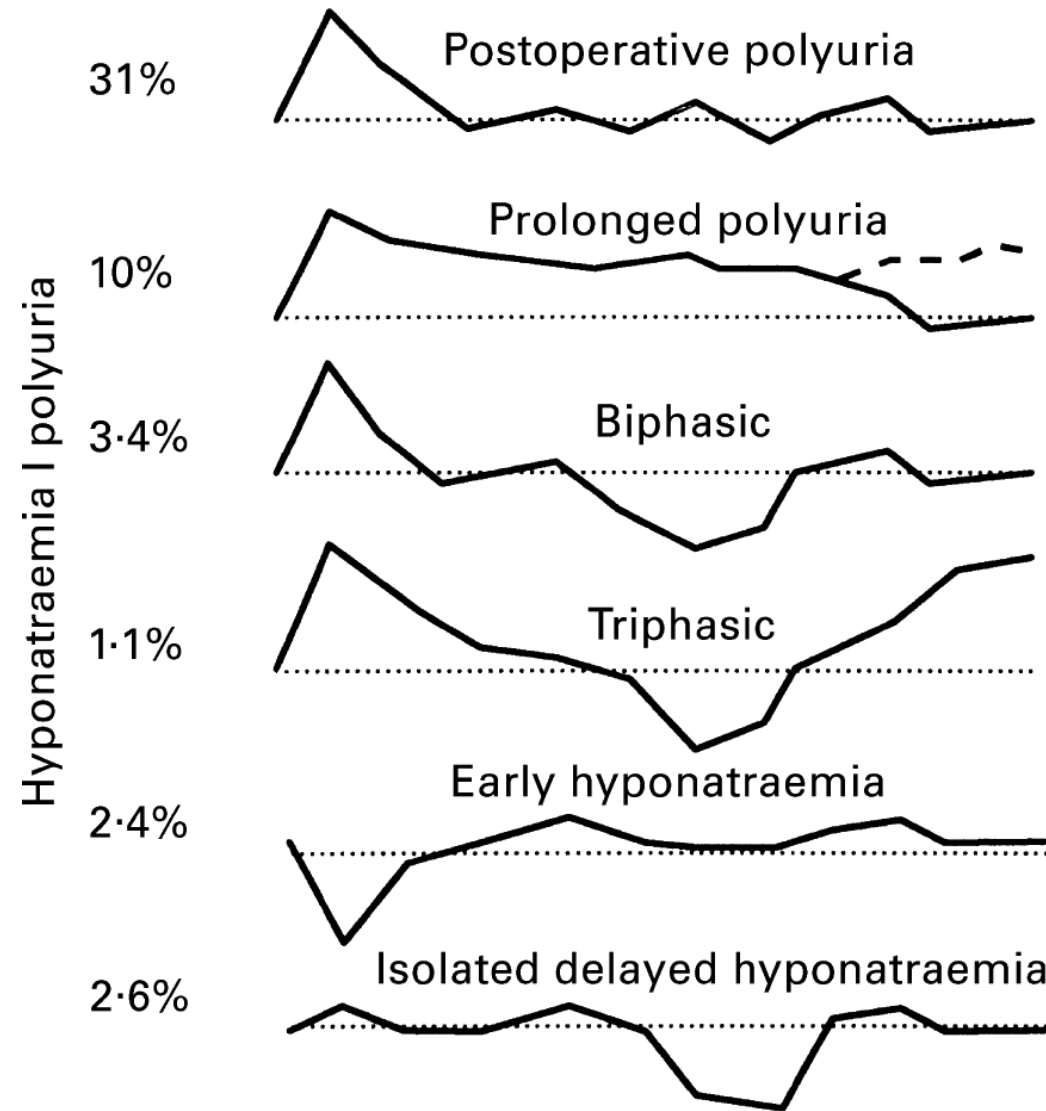
Granulomatous disease – sarcoid, histiocytosis

X

Hereditary – AD mutations in
preprovasopressin/neurophysin, Wolfram
syndrome



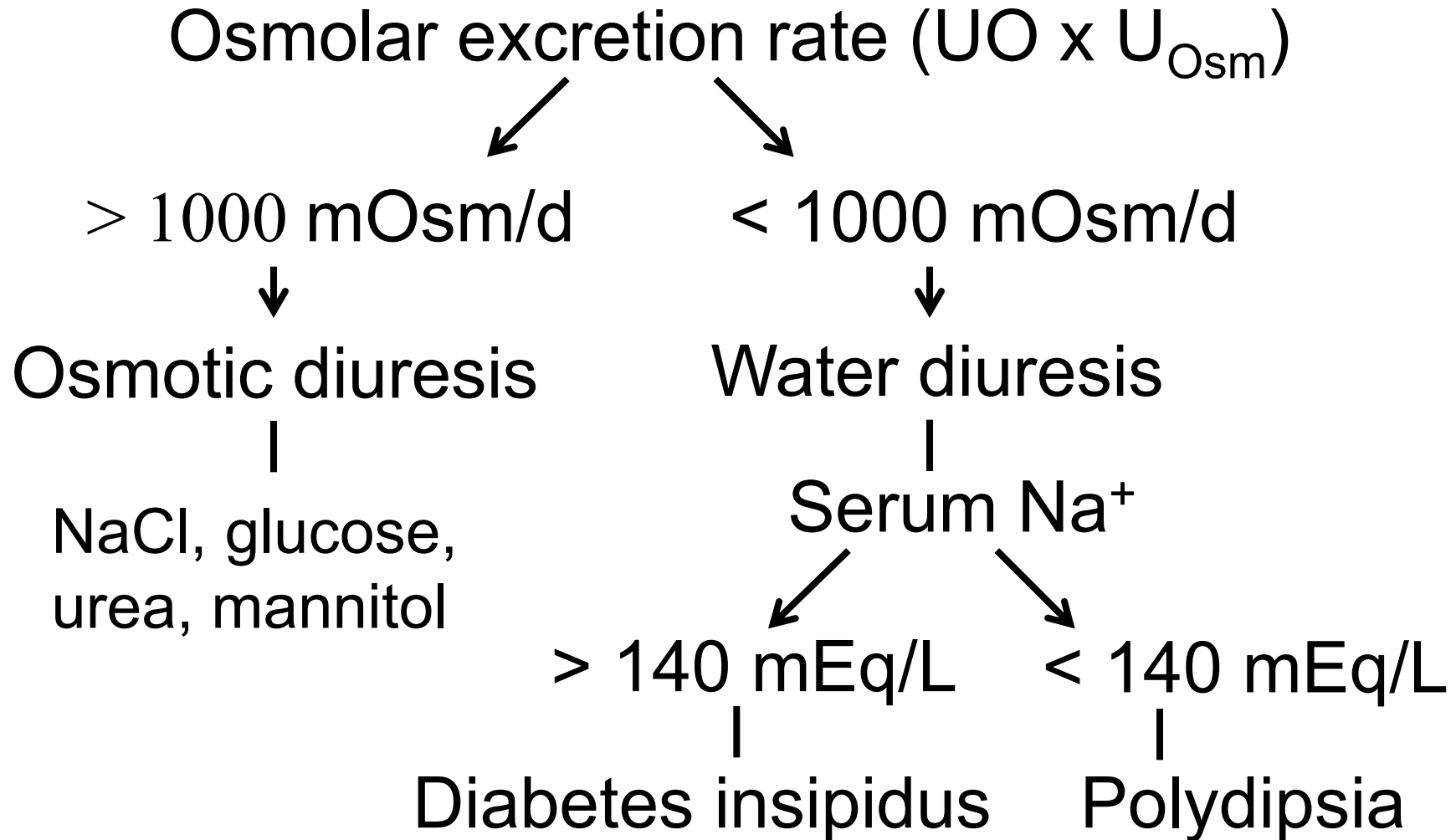
Patterns of Polyuria / Hyponatremia After Pituitary Surgery



Hensen et al,
Clin. Endo., 1999



Polyuria (Urine Output > 3L/d)



Causes of Nephrogenic DI

Genetic

- X-linked – V_2 vasopressin receptor
- Autosomal recessive/dominant – aquaporin-2
- Autosomal recessive – aquaporin-1 (proximal tubule and thin limb)

Drug-induced, e.g. lithium, cisplatin, ifosmamide

Hypokalemia

Hypercalcemia

Infiltrating lesions, e.g. sarcoidosis, amyloidosis

Cellular defect, e.g. after acute tubular necrosis

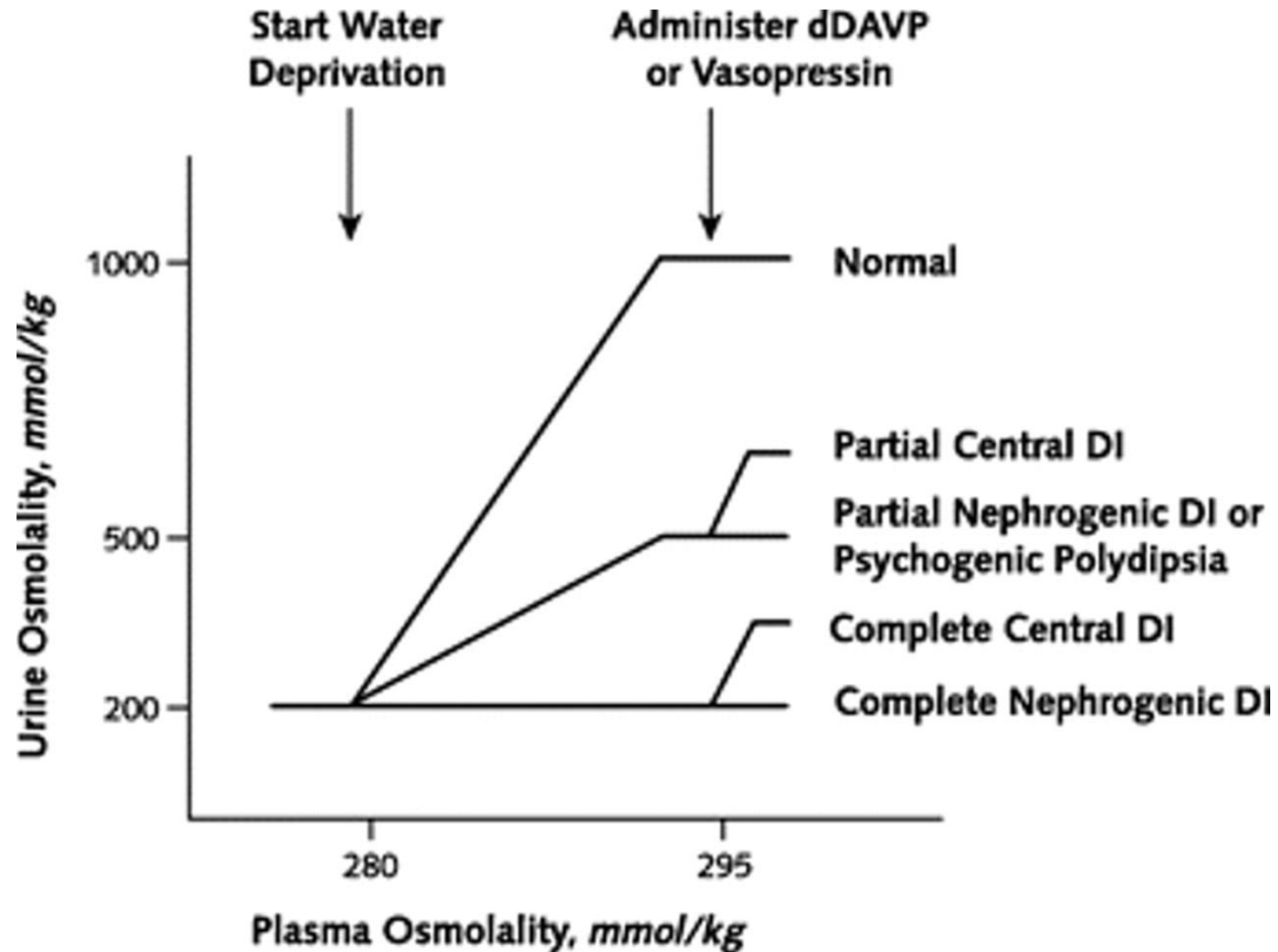


Gestational DI

- 1 in 300,000 pregnancies
- Increased expression/release/activity of vasopressinase, produced by placenta
- May occur in context of pre-eclampsia and/or acute fatty liver of pregnancy
- DDAVP ~ resistant to vasopressinase, hence effective



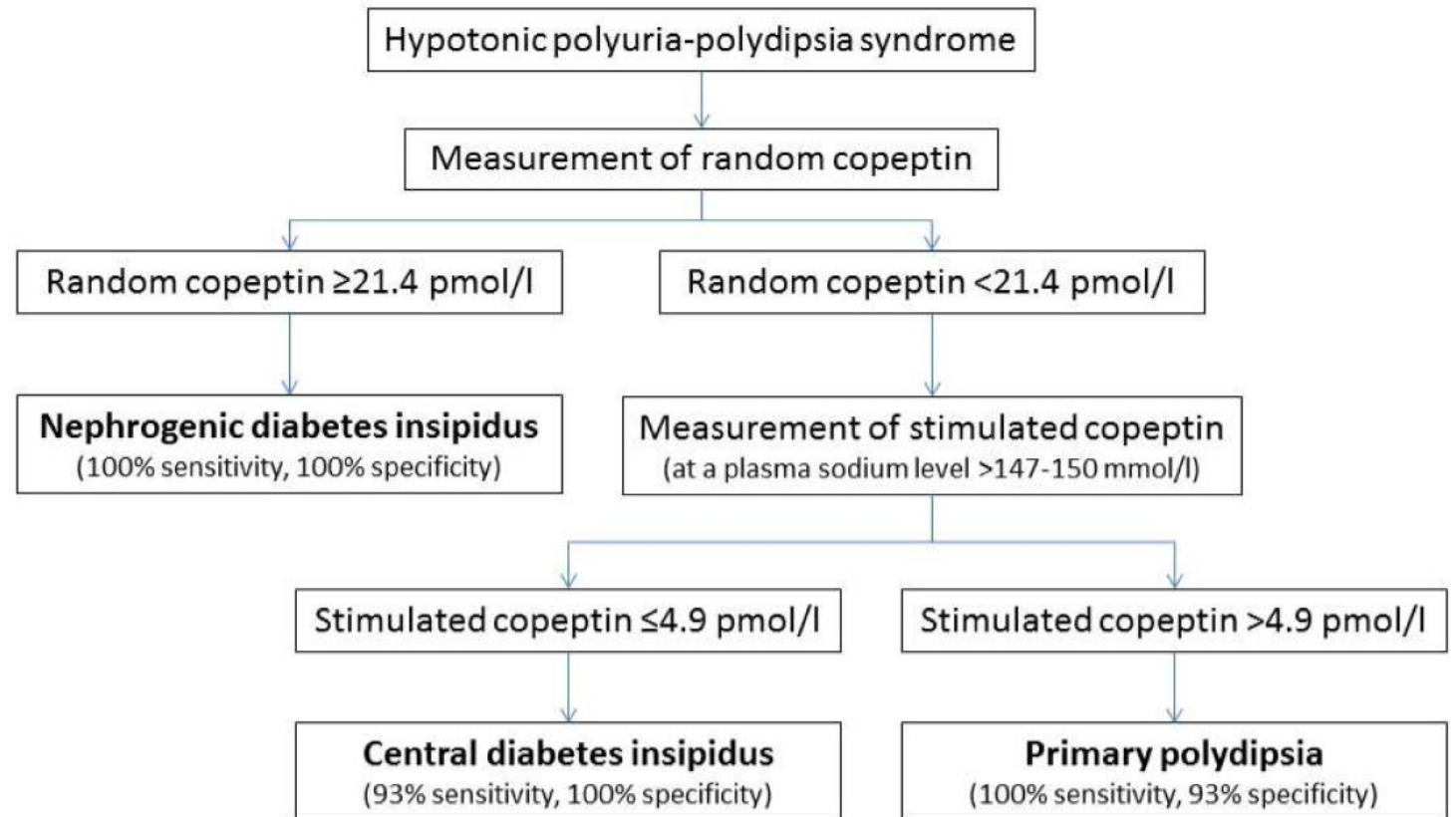
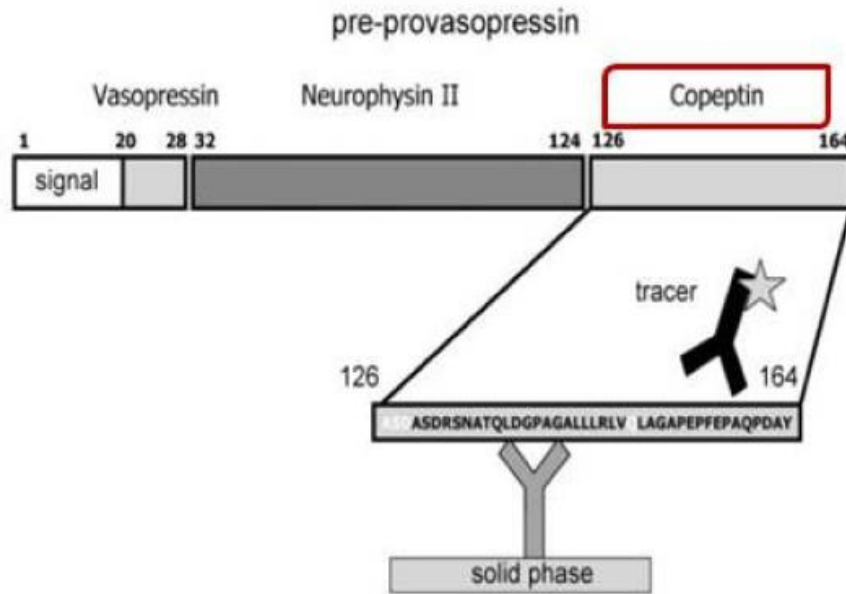
Water Deprivation Testing



Sands and Bichet, Ann. Int. Med., 2006



Copeptin in the DDx of Polyuria



Refardt et al, Clinical Endocrinology, 2019

Treatment of Hypernatremia

Restore water deficit

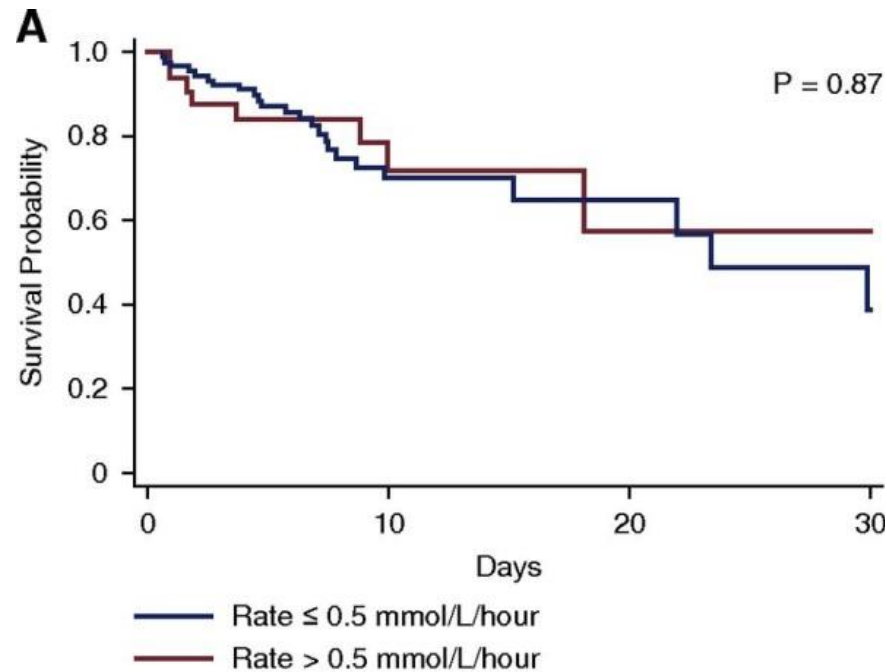
Reduce and/or replace ongoing loss of hypotonic fluids

Treat underlying cause

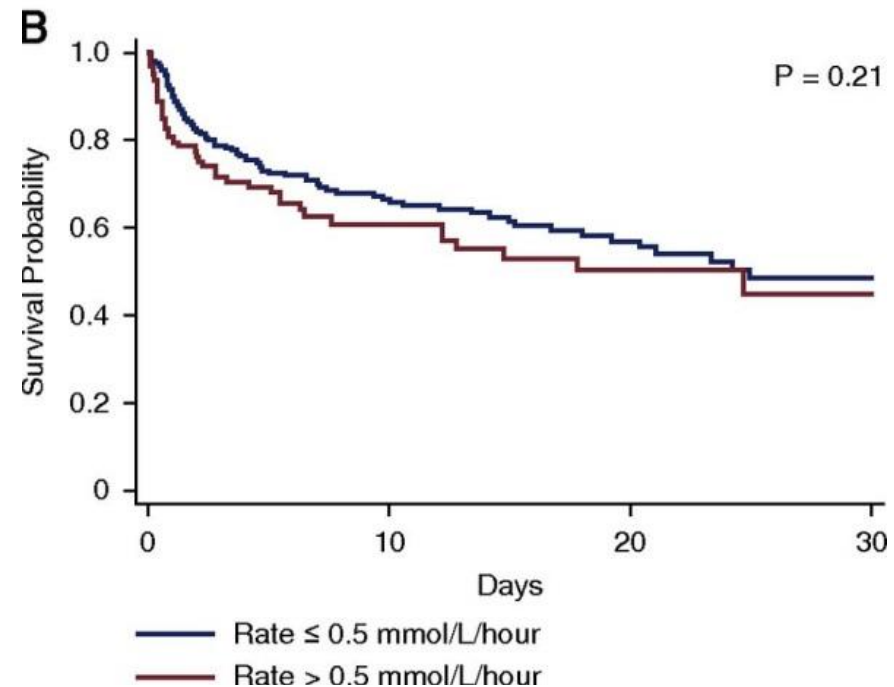
- Central DI – DDAVP
- Nephrogenic DI – HCTZ, NSAID
- Gestational DI - DDAVP



Rate of Correction of Hypernatremia in Critically ill Patients



Admission



Hospital-acquired

CJASN, May 7, 2019



Quantitative Formulas

Free water deficit = $0.6 \times \text{weight}^* \times (1 - 140/\text{Na}^+)$

*premorbid weight

Replace over 48 hours

Electrolyte-free water clearance

$$= \text{urine volume} \times \left[\frac{(U_{\text{Na}} + U_{\text{K}}) - P_{\text{Na}}}{P_{\text{Na}}} - 1 \right]$$

Replace daily losses



TAKE HOME MESSAGES

Central osmoreceptors in hyponatremia.
DDx of acute hyponatremia and
hyponatremia prone to overcorrection.
The role of DDAVP+D5W in patients who
overcorrect.
DDAVP clamp with hypertonic saline to
provide controlled correction.
Use of oral urea in SIADH.
Electrolyte free water clearance in
hypernatremia – estimate ongoing loss.



Suggested References:

“Hyponatremia” (Guest editor D.B. Mount), *Seminars in Nephrology*, May 2009;29(3):175-317

- PDF reprint: dmount@bwh.harvard.edu
- Mount D.B., “Fluid and electrolyte disturbances”, Harrison’s Principles of Internal Medicine, 20th edition, McGraw Hill, 2018, 295-311
- Perianayagam, A, et al : DDAVP is effective in preventing and reversing inadvertent overcorrection of hyponatremia. *CJASN*, 3: 331-6, 2008
- Sood et al: Hypertonic saline and desmopressin: a simple strategy for safe correction of severe hyponatremia. *Am J Kidney Dis* 61:571-8, 2013

