Hyponatremia

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The Kidney in the Olympic News

A Chinese swimmer has tested positive for "diuretic" doping at the Olympics

Very commonly used to dilute the urine and mask the use of PEDs

8% of all WADA positive tests

I personally would use a loop diuretic or vaspressin antagonist

HCTZ could be important in our lecture today !!!

Hyponatremia in the News

Home > Articles > News > Athlete dies after IM Frankfurt

Athlete dies after IM Frankfurt

HERBERT KRABEL — Wed Jul 08 2015

A 30-year old British* age group athlete died in a Frankfurt hospital several days after he collapsed at the finish of the 2015 Ironman European Championships on a very hot day, report various newspapers in Germany.

Fort Benning soldier, 21, dies following medical complication

Published: Wednesday, July 27th 2016, 5:42 pm EDT
Updated: Thursday, July 28th 2016, 11:25 am EDT

By WTVM Web Team CONNECT

FORT BENNING, GA (WTVM) - A Fort Benning Soldier died Wednesday at the Midtown Medical Center, where he was being treated for hyponatremia.

Second Lt. Michael R. Parros, 21, of Walnut Creek, Calif., was in his first day of U.S. Army Ranger School on July 25, when he fell ill and was transported for medical treatment.

"This is a tragic loss," said Lt. Col. Matthew Weber, Commander of the 2nd Battalion, 11th Infantry Regiment. "While 2nd Lt. Parros was only with us for a short time, he showed so much potential and was the epitome of the kind of Soldier you want to serve with. We are truly saddened to lose a member of our Army family."

Parros, who reported to Fort Benning for training on June 27, graduated from the U.S. Army Military Academy in May, as an

"Swelling of the brain is the cause of death and it was likely caused by insufficient salt intake while racing in unusually hot conditions."

"The athlete drank mostly water during the race and did not take in enough minerals. "

Military incidents of hyponatremia increased dramatically, with 125 cases between 1989 and 1996, including at least six deaths, according to a 2006 University of Cape Town study
New fluid guidelines in the military were published July 18, 2016

Football player's death leads to discussion about hyponatremia

Walker Wilbanks died after football game

Drinking too much water and sports drinks may lead to death

The recent deaths of two high school football players illustrate the dangers of drinking too much water and sports drinks, according to Loyola University Medical Center sports medicine physician Dr. James Winger.

Over-hydration by athletes is called exercise-associated hyponatremia. It occurs when athletes drink even when they are not thirsty. Drinking too much during exercise can overwhelm the body's ability to remove water. The sodium content of blood is diluted to abnormally low levels. Cells absorb excess water, which can cause swelling -- most dangerously in the brain.

Georgia football player Zyrees Oliver reportedly drank 2 gallons of water and 2 gallons of a sports drink. He collapsed at home after football practice, and died later at a hospital.

A previous study co-authored by Winger found that almost half of recreational runners in the Chicago area may be drinking too much fluid during races.

And in recent years, there have been more than a dozen documented and suspected runners' deaths from hyponatremia.

Wii radio contest fatality results in $16.5 million verdict

Mother-of-three's surviving family wins lawsuit against organizers of "Hold Your Wee for a Wii" promotion.

by Brendan Sinclair on October 30, 2009

The family of a California woman who died trying to win a Wii in a radio contest has been awarded $16.5 million in its suit against the station, according to the Associated Press.

When the Wii debuted in November of 2006, demand for the system far outstripped supplies, leading some people to go to extremes to get their hands on one. One such person, Jennifer Strange of Rancho Cordova, California, entered a January 2007 "Hold Your Wee for a Wii" radio contest with the system as a grand prize.

After drinking an estimated two gallons of water without urinating or vomiting, the 28-year-old mother of three told a colleague that she felt sick and had a "really bad" headache. She was later found dead in her suburban home, apparently from water intoxication. Drinking excess amounts of water causes the problem of too little sodium in the body (hyponatremia) and can cause swelling of the brain, vomiting, headaches, seizures, coma, and, in extreme cases, death.

Daily Mail

The hiker who died from drinking TOO MUCH water: Excess fluid and lack of food caused her brain to fatally swell

- **Unidentified 47-year-old woman was hiking through the Grand Canyon**
- **Fainted at the end of the hike and then collapsed again en route to hospital**
- **Too much water and exercise caused sodium levels in her blood to fall**
- **Water rushed into her cells, causing her brain to swell and killing her**

By MADLEN DAVIES FOR MAILONLINE

PUBLISHED: 10:49 EST, 5 October 2015 | **UPDATED:** 13:21 EST, 5 October 2015

Doctors said she had suffered a severe brain swelling from 'water intoxication' which led to pressure in the skull, the brain tissues moving, and ultimately 'brain death'.

According to the woman's husband, she 'drank a large amount of water and ate very little' on the hike.

The large amount of water she consumed, along with the strenuous hiking, meant vital salt and mineral levels in the body were diluted.

Montague family awarded $34M in malpractice suit after mother suffers brain damage

Manganiello, then 42, of Montague, went to a Port Jervis, N.Y., hospital for treatment of a low sodium level. She left with a brain injury that took away much of her physical movement and her speech.

The onetime calculus teacher

The jury accepted the Manganiellos' contention the hospital — and specifically, the physician, Moinuddin Ahmed, and a nurse, Rose Aumick — created Diane Manganiello's condition by giving her too much sodium too quickly.

Patients suffering from hyponatremia — or a low sodium level — should have their sodium raised slowly, no more than 10 to 12 units over 24 hours, Winters said. However, Diane Manganiello's level was raised 27 units in 14 hours, causing irreversible brain damage, said Winters, who has an office in Parsippany.

HEALTH

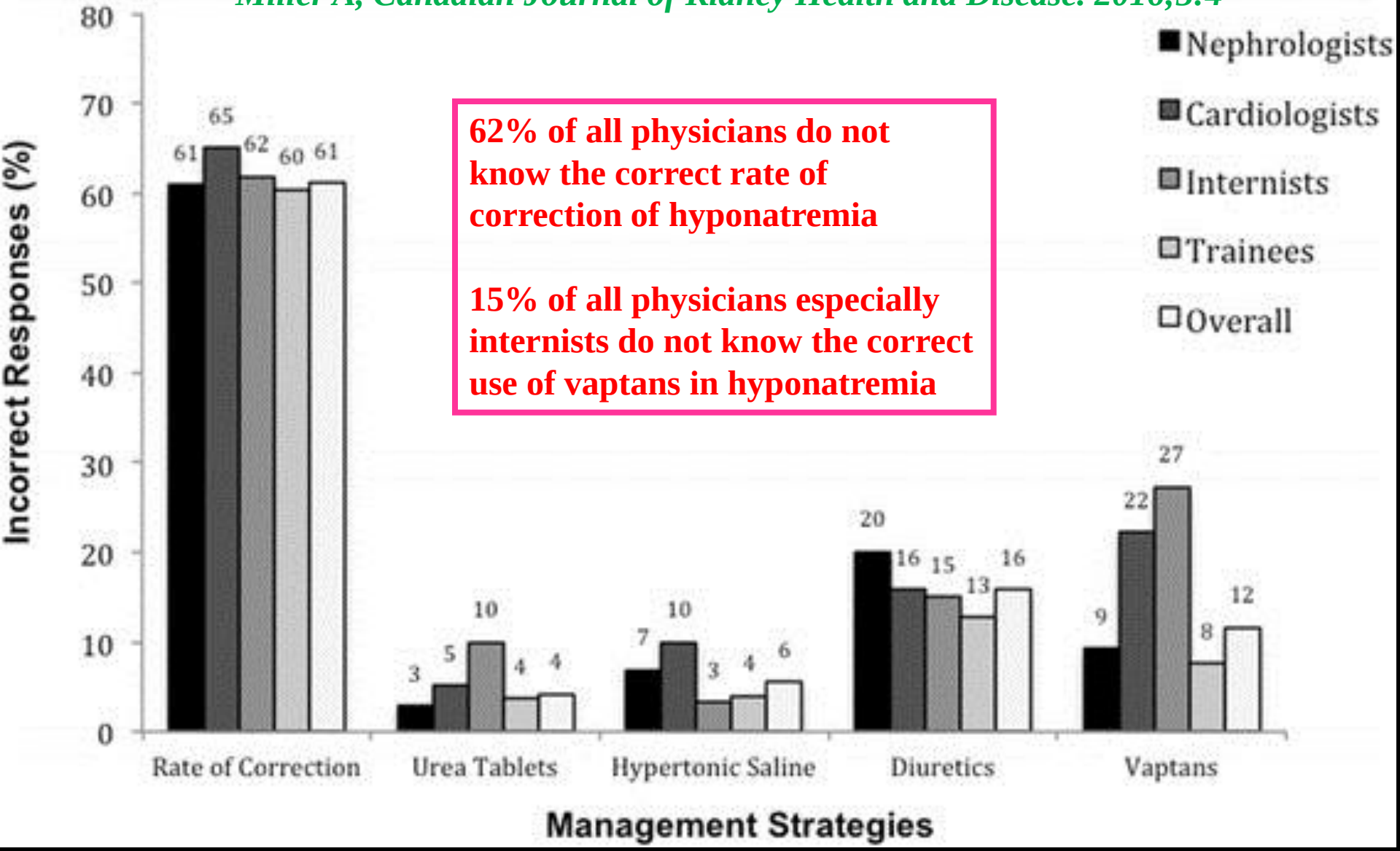
Strange but True: Drinking Too Much Water Can Kill

In a hydration-obsessed culture, people can and do drink themselves to death.

READ THIS NEXT

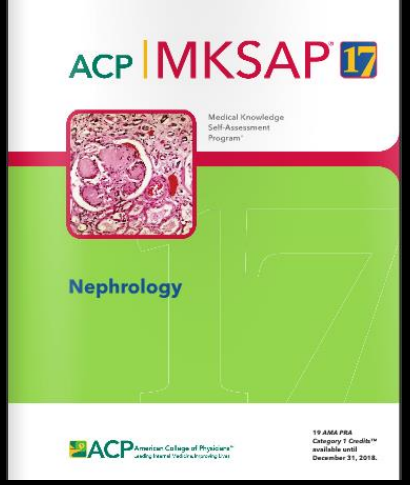
Incorrect Selection of Different Managment Strategies for Hyponatremia in Congestive Heart Failure

Miller A, Canadian Journal of Kidney Health and Disease. 2016;3:4



62% of all physicians do not know the correct rate of correction of hyponatremia

15% of all physicians especially internists do not know the correct use of vaptans in hyponatremia



Lecture Objectives

- **Establish the definition of Hyponatremia**
- **Review the clinical consequences of hyponatremia**
- **Discuss the physiology of ADH production and action**
- **Outline the causes of hyponatremia**
- **Describe the treatment options to acute and chronic hyponatremia**

Case Presentation

- A 25 year old woman with laparoscopic appendectomy 2 days ago
- Moderate postop ileus and generalized abdominal pain
- Now not feeling well with a headache and nausea

- Medication
  - Morphine prn
  - D5 0.45 NS 125 cc/min – total of 6 liters in 2 days

	Na	K	Cl	HCO3	BUN	Cr	Glucose	Osm
Current	125	3.5	90	20	6	0.5	90	257
Pre op	140	4.1	95	25	9	0.7	95	288

	Na	K	Cl	HCO3	BUN	Cr	Glucose	Osm
Current	125	3.5	90	20	6	0.5	90	257
Pre op	140	4.1	95	25	9	0.7	95	288

How would you describe her neurologic condition ?

A. Osmotic Demyelinating Syndrome with cerebral edema

B. Hyponatremic Encephalopathy with cerebral edema

C. Osmotic Demyelinating Syndrome with an acute decrease in cerebral volume

D. Hyponatremic Encephalopathy with an acute decrease in cerebral volume

E. Osmotic Demyelinating Syndrome with no change in brain volume

F. Hyponatremic Encephalopathy with no change in brain volume

G. Subdural hematoma secondary to Hyponatremia

H. Acute CVA secondary to Hyponatremia

How much water can you (normal person) drink before you become hyponatremic ?

A. 3 L
B. 6 L
C. 10 L
D. 18 L
E. 25 L
F. 30 L
G. With normal renal function the sky is the limit ! Drink away ! Last month I bought the unlimited drink package on a cruise ship and I got my money's worth and my brain is fine (I think!)

	Na	K	Cl	HCO3	BUN	Cr	Glucose	Osm
Current	125	3.5	90	20	6	0.5	90	257
Pre op	140	4.1	95	25	9	0.7	95	288

What is your target sodium level and how quickly should you correct symptomatic patients with hyponatremia to avoid seizures ?

A. Correct up to a Na of 135 meq/L within 24 hours

B. Correct up to a Na of 130 meq/L within 24 hours

C. Correct no more than 15 meq/L within 24 hours

D. Correct no more than 12 meq/L within 24 hours

E. Correct no more than 10meq/L within 24 hours

F. Correct no more than 6 meq/L within 24 hours

Definition

- **Hyponatremia is defined as**
  - **Plasma sodium < 135 meq/liter**

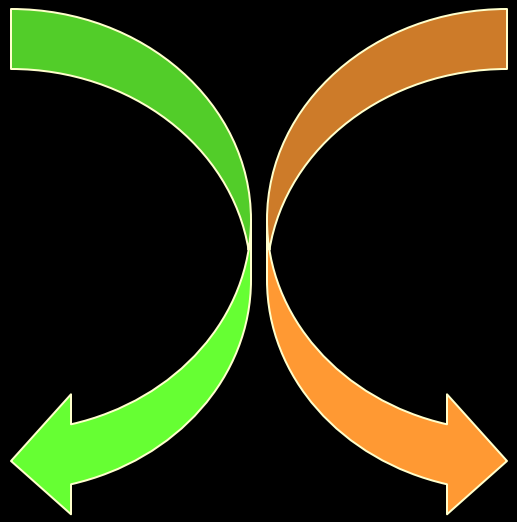
- **Mild Hyponatremia is defined as**
  - **Plasma sodium 130 - 134 meq/liter**
- **Moderate Hyponatremia is defined as**
  - **Plasma sodium 121 – 129 meq/liter**
- **Severe hyponatremia is defined as**
  - **Plasma sodium < 120 meq/liter**

Hyponatremia

- **Most common electrolyte abnormality in hospitalized patients (30%)**
  - **5% with Na < 125 meq/L**

Hyponatremia can be a normal finding
In Pregnancy hyponatremia is a natural and expected result
Normal Na in pregnancy- 130 meq/L
A normal Na in pregnancy is abnormal !!! Nd indicates loss of water i.e. volume depletion or pre-eclampsia (third spacing of fluid)

Hyponatremia



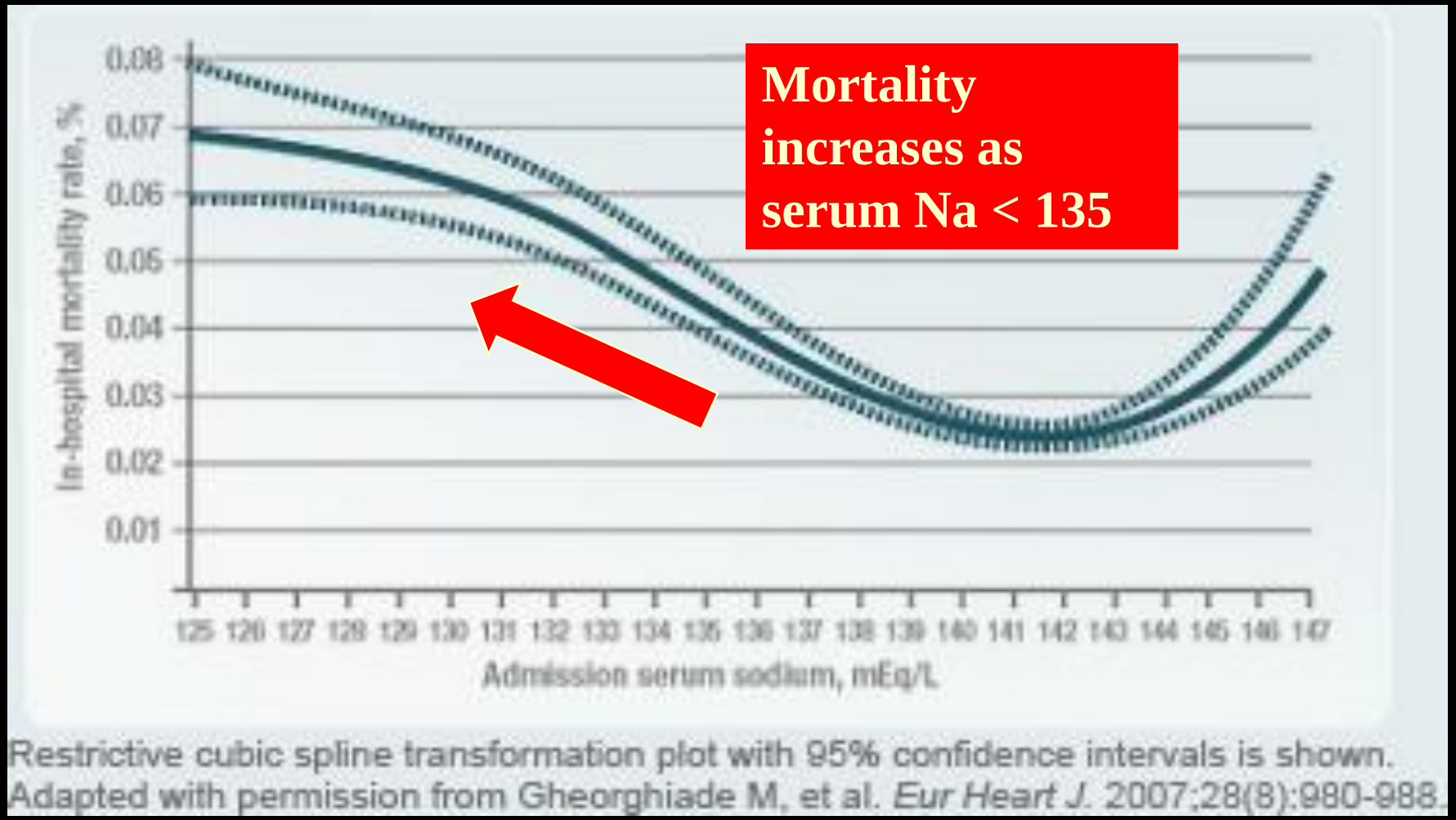
Direct CNS Neurotoxicity

Cerebral Edema

Marker for Increased Mortality

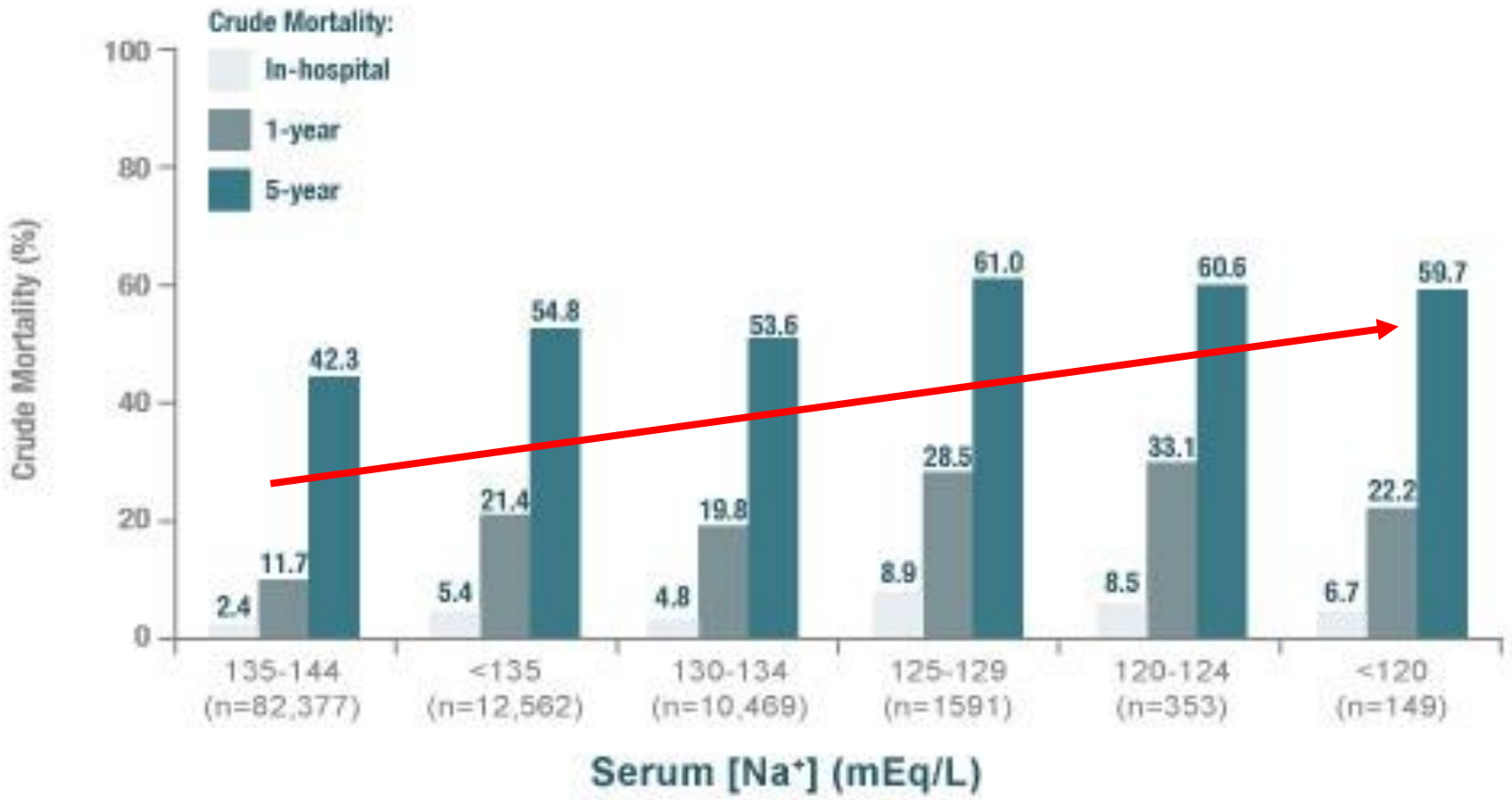
CHF Cirrhosis Cancer

Hospital Mortality and Hyponatremia



Restrictive cubic spline transformation plot with 95% confidence intervals is shown.
Adapted with permission from Gheorghiade M, et al. *Eur Heart J.* 2007;28(8):980-988.

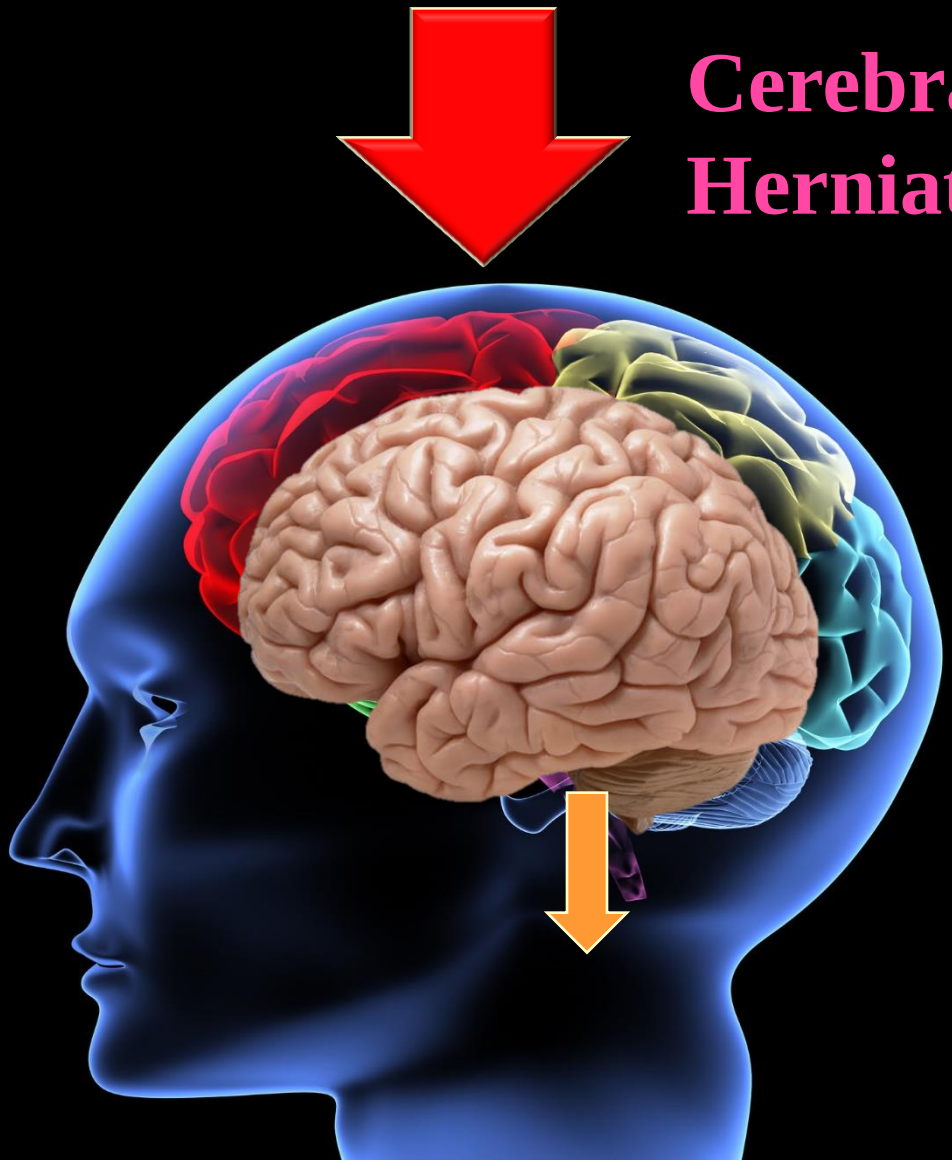
Hyponatremia is associated with a Graded Increase in Short and Long Term All Cause Mortality



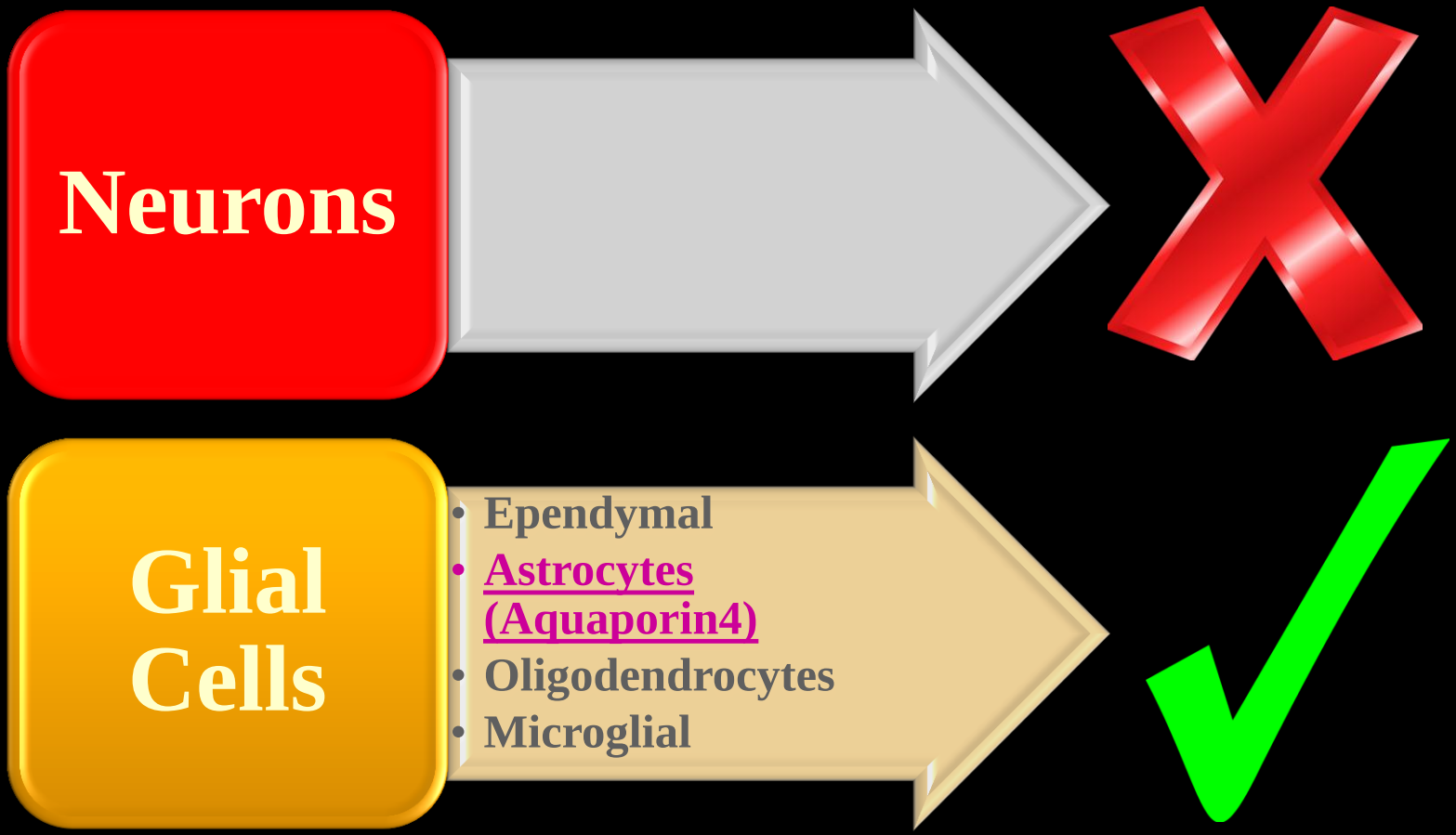
Adapted from Waikar SS, et al. *Am J Med.* 2009;122(9):857-865.

Clinical Consequences of Hyponatremia

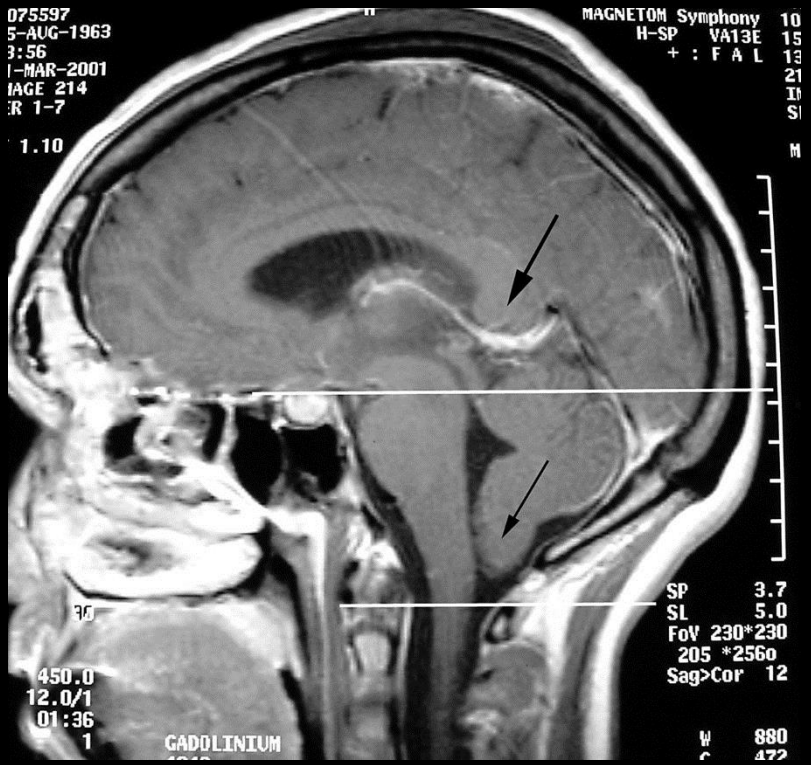
Cerebral edema
Herniation



Which Cells Swell in the Brain ?



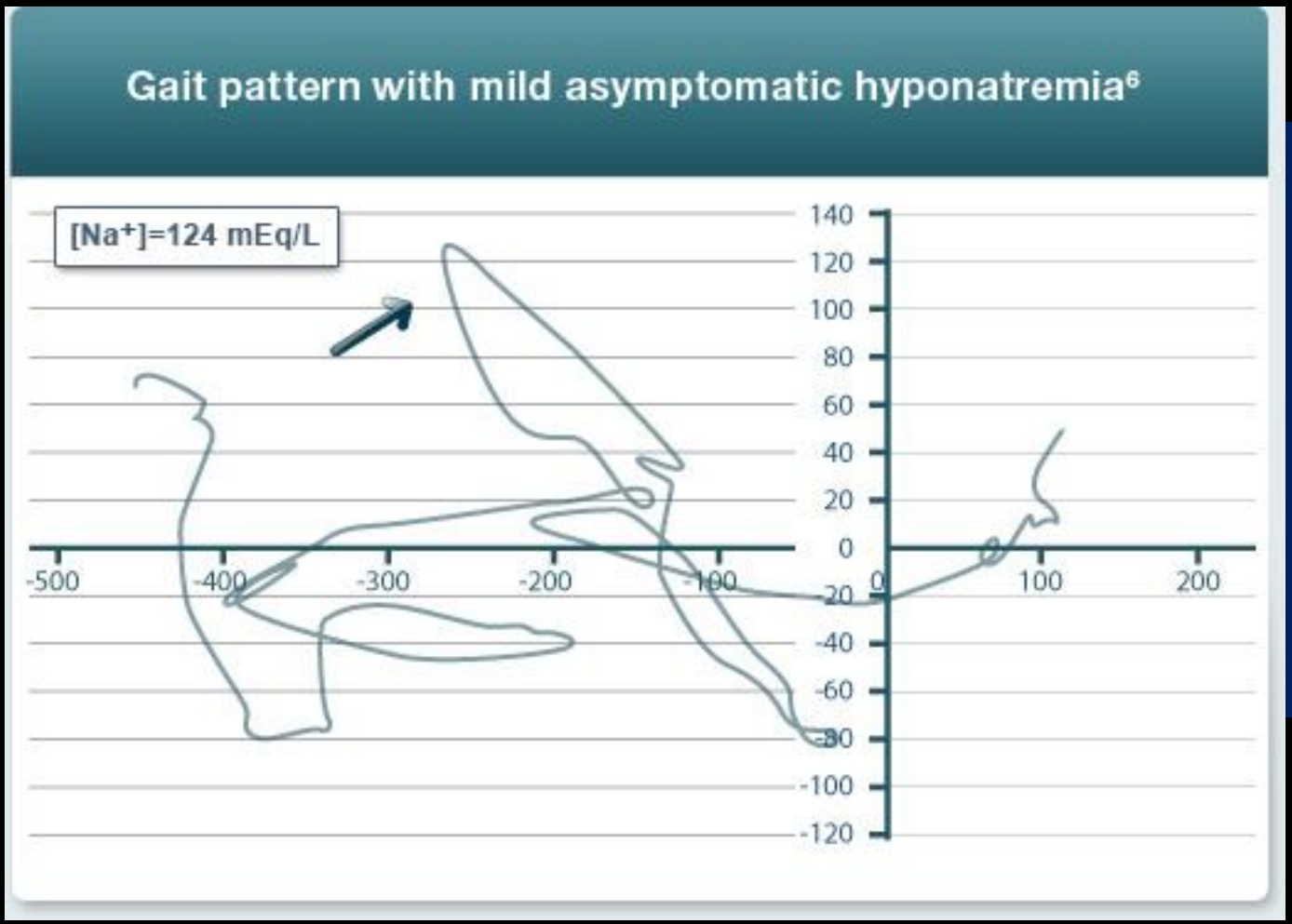
Brain Herniation in Hyponatremic Encephalopathy (HE)



Normal

Cerebellar Herniation

Hyponatremia and Gait

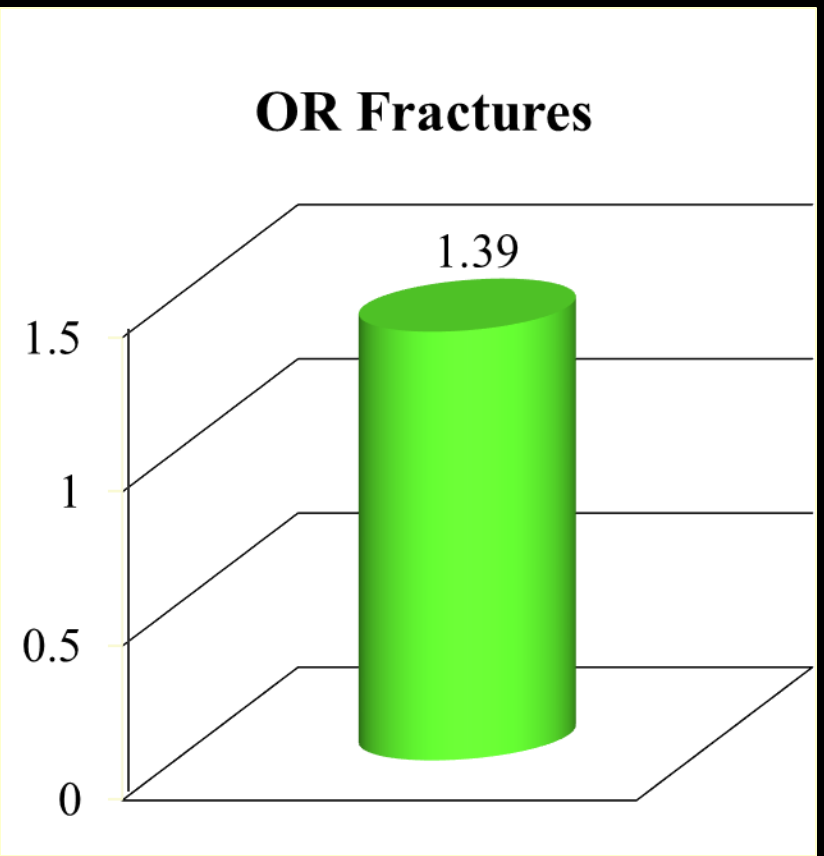


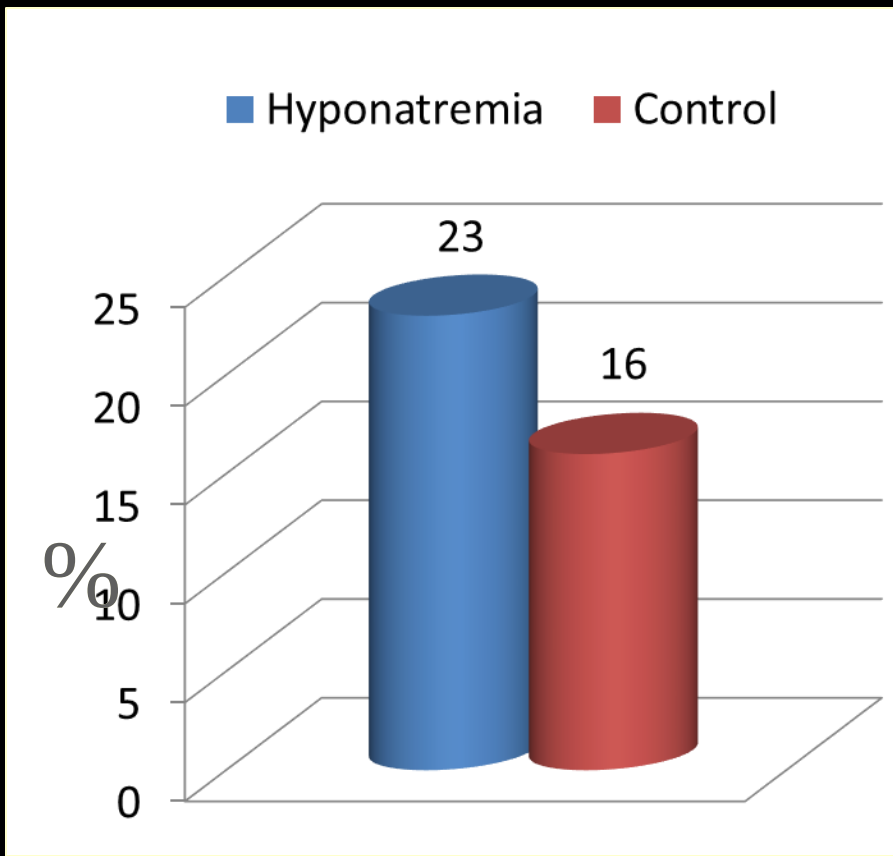
It is suggested that one of the most common unsuspected contributing factors causing falls in the elderly is hyponatremia !

Renneboog B, Musch W, Vandemergel X, Manto MU, Decaux G. *Am J Med*. 2006;119:71

Hyponatremia and Fractures

- Hoorn EJ, Mild Hyponatremia as a risk factor for Fractures: The Rotterdam Study.J Bone Miner Res. 2011 Mar 4





Complications of Hyponatremia

Acute

- Dizziness/ataxia
- Confusion
- Disorientation
- Seizures
- Increased Mortality

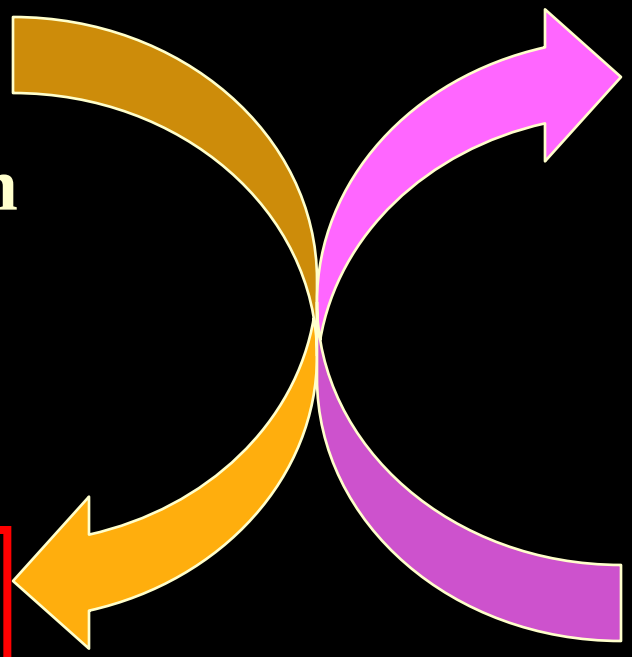
Chronic

- Dizziness/ataxia
- Confusion
- Fractures
- Osteoporosis
- Increased mortality

Total cost 1.6 – 3.6 billion dollars / year

Hyponatremia and CNS Disease

Consequence of the actual serum Na concentration

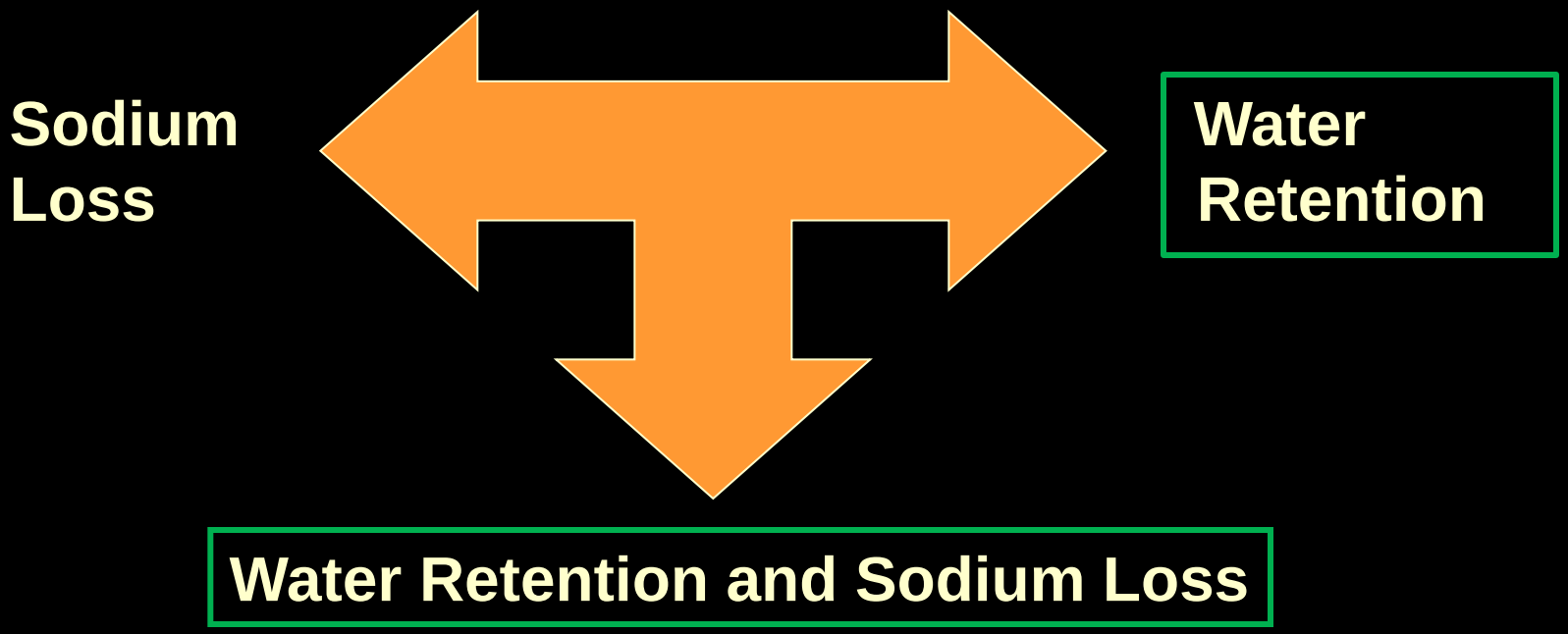


Osmotic Demyelinating Syndrome (ODS)

Hyponatremic Encephalopathy (HE)

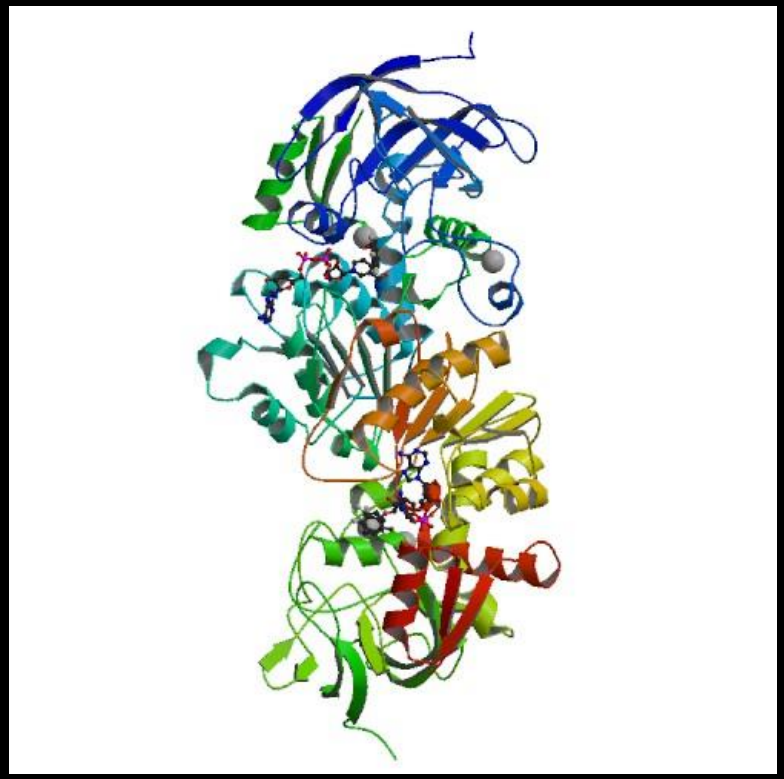
Consequence of the treatment of the serum Na concentration

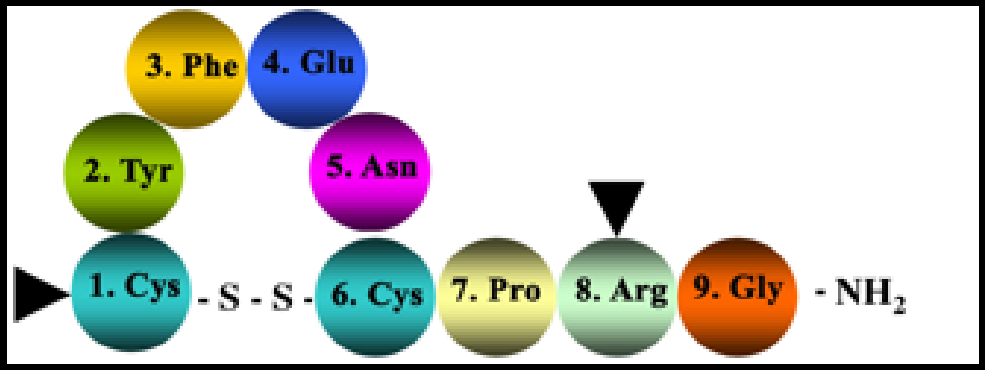
Etiologies of Hyponatremia



The majority of cases of Hyponatremia are due to excessive water retention with or without a lesser component of Na (solute) loss

To Understand Hyponatremia We Must Understand Water Balance

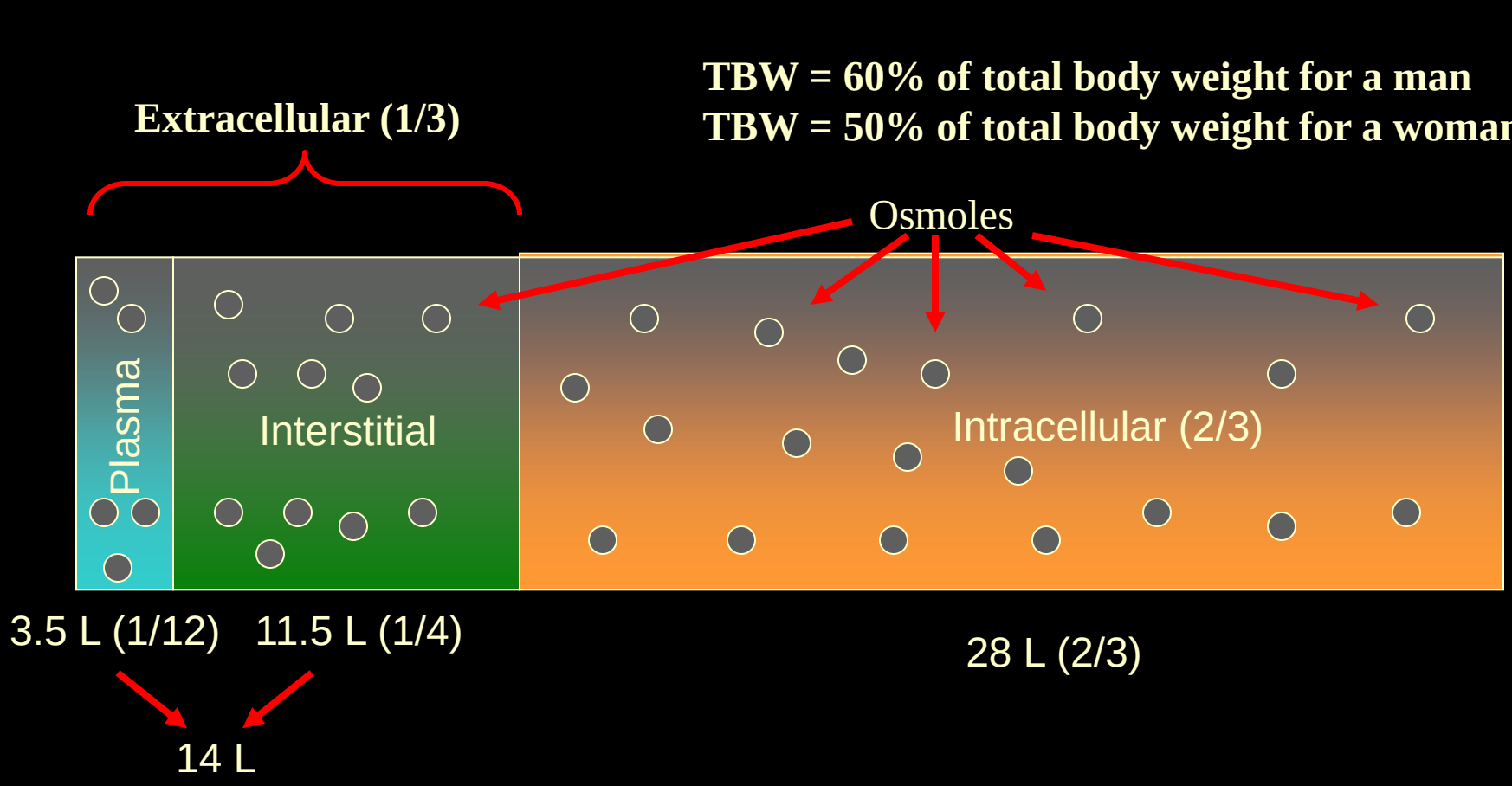




Arginine Vasopressin (ADH)

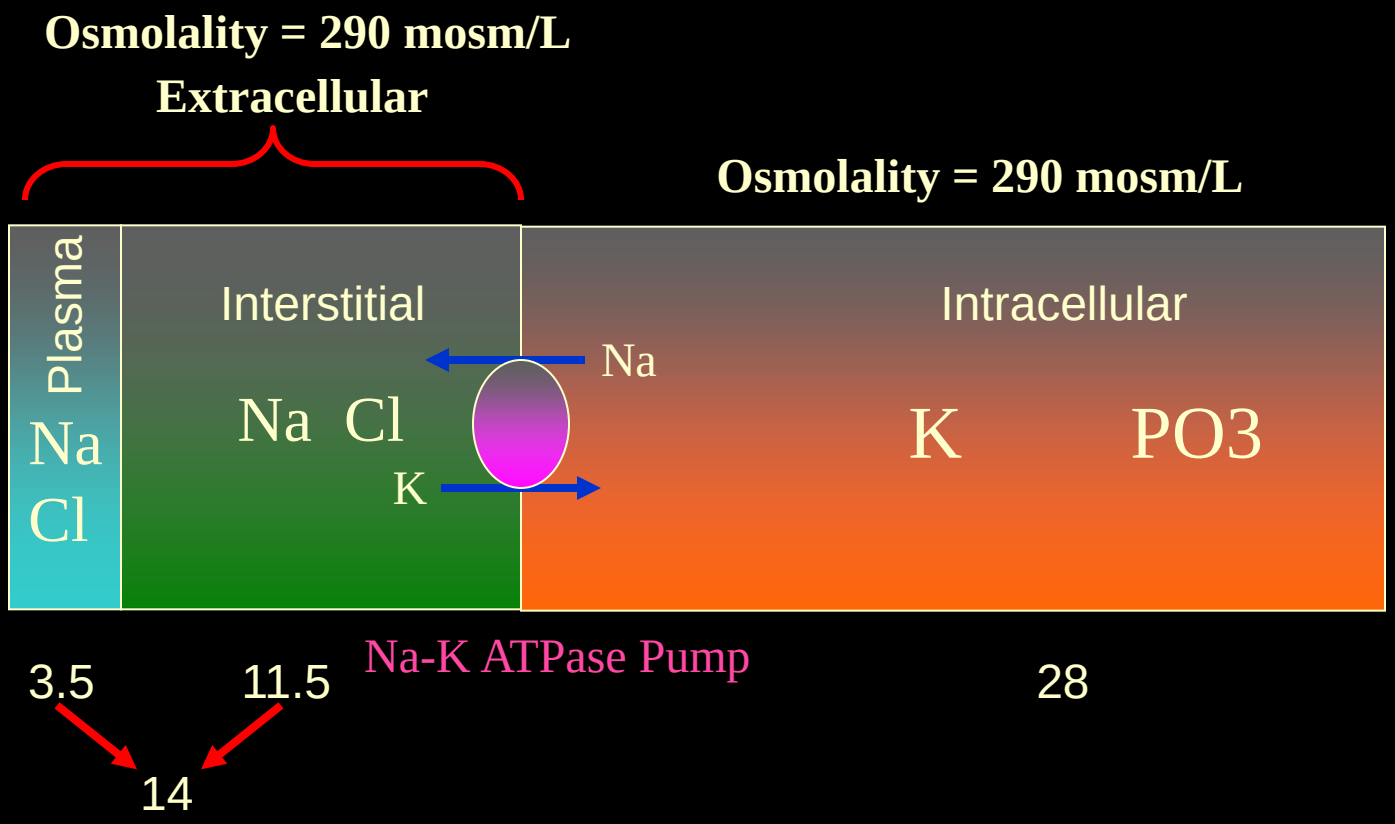
Total Body Water

TBW = 60% of total body weight for a man
TBW = 50% of total body weight for a woman



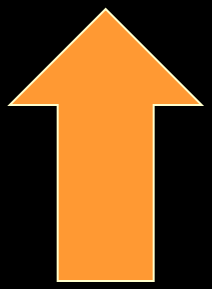
Osmolality of Plasma = Osmolality of Interstitial Fluid = Osmolality of Intracellular Fluid

Total Body Water

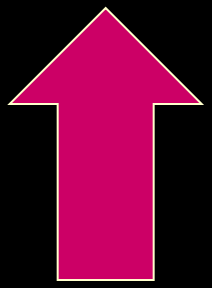


Changes in the Na concentration in the plasma are related predominately to <u>changes in total body water</u> resulting in a dilution of the number of osmoles

Plasma Na concentration



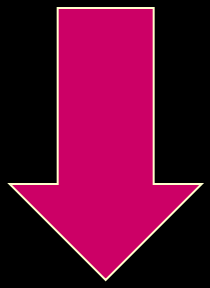
Water Balance (Intake / Output)



Anti-Diuretic Hormone (ADH / Vasopressin)

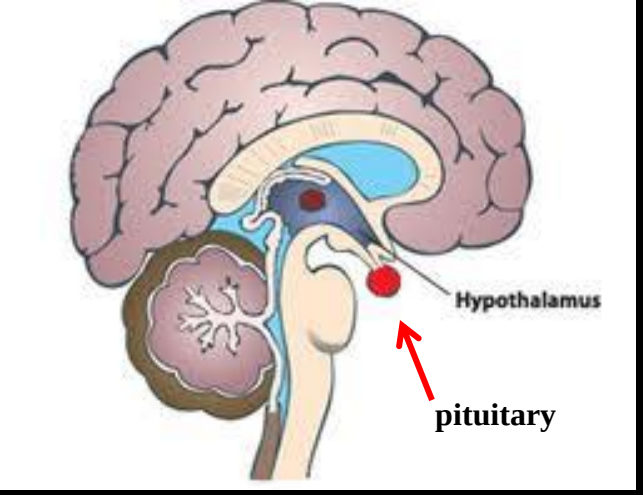
Plasma Na concentration

Na Balance (Intake/Output)

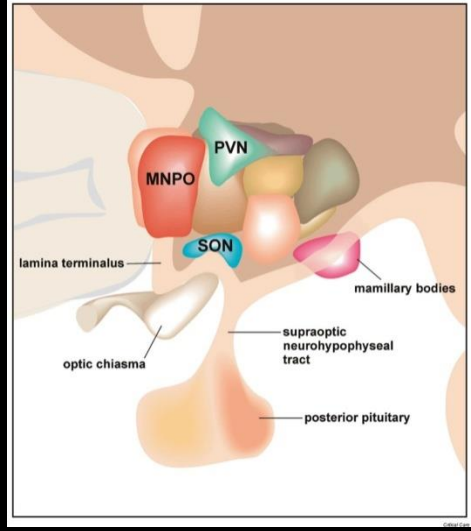


Extracellular Fluid Balance

Edema (pulmonary / lower extremity)



Physiologic ADH Stimuli



Volume — **Hypothalamus** — **Tonicity**

Indirect Stimulation

Baroreceptor Stimulation of Angiotensin II And Sympathetic Nervous System

Direct Stimulation

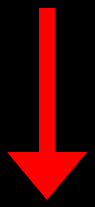
Paraventricular nucleus

Supraoptic nucleus

Sensors of ECF Volume

- **Cardiopulmonary**
  - **Atria (distension)**
  - **Ventricles (distension)**
- **Arterial**
  - **Aortic Arch (pressure)**
  - **Carotid sinus (pressure)**
- **Renal**
  - **Afferent arteriole (pressure)**
  - **Macula Densa (NaCl delivery)**

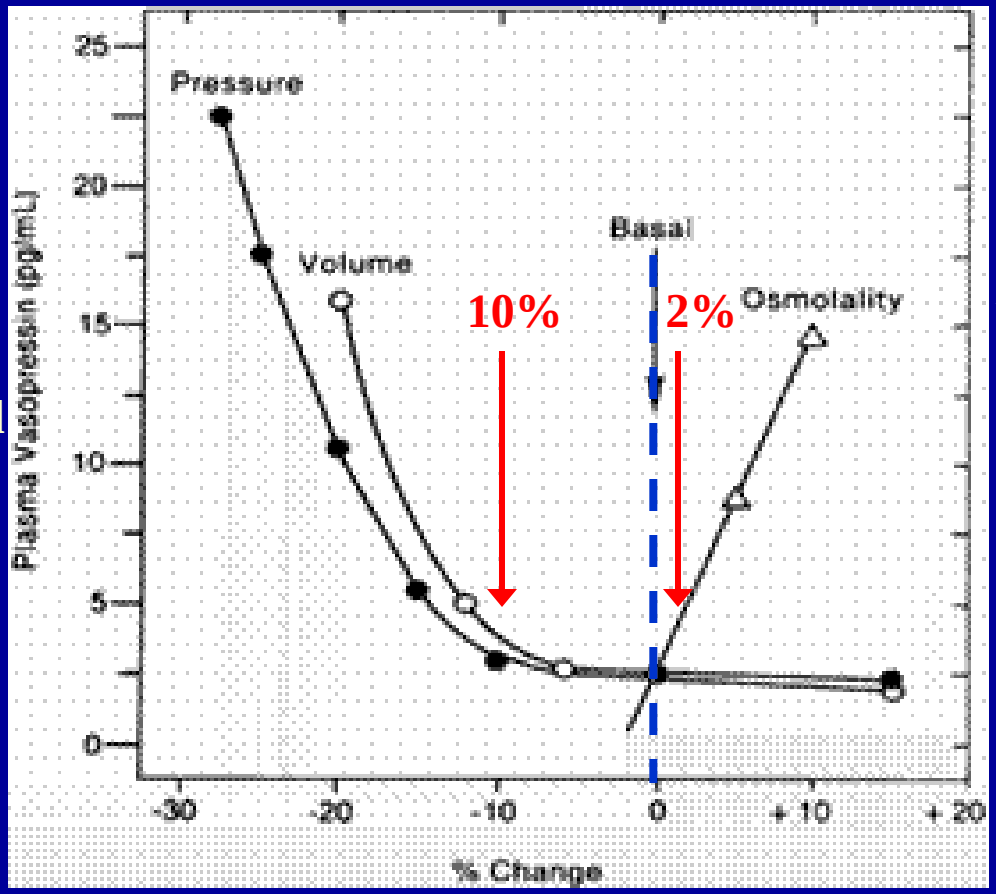
Signals via cranial nerves IX and X to the nucleus tractus solitarius (NTS) in the brain stem



Hypothalamus

Stimuli for Vasopressin Secretion

Volume results in an exponential increase in ADH



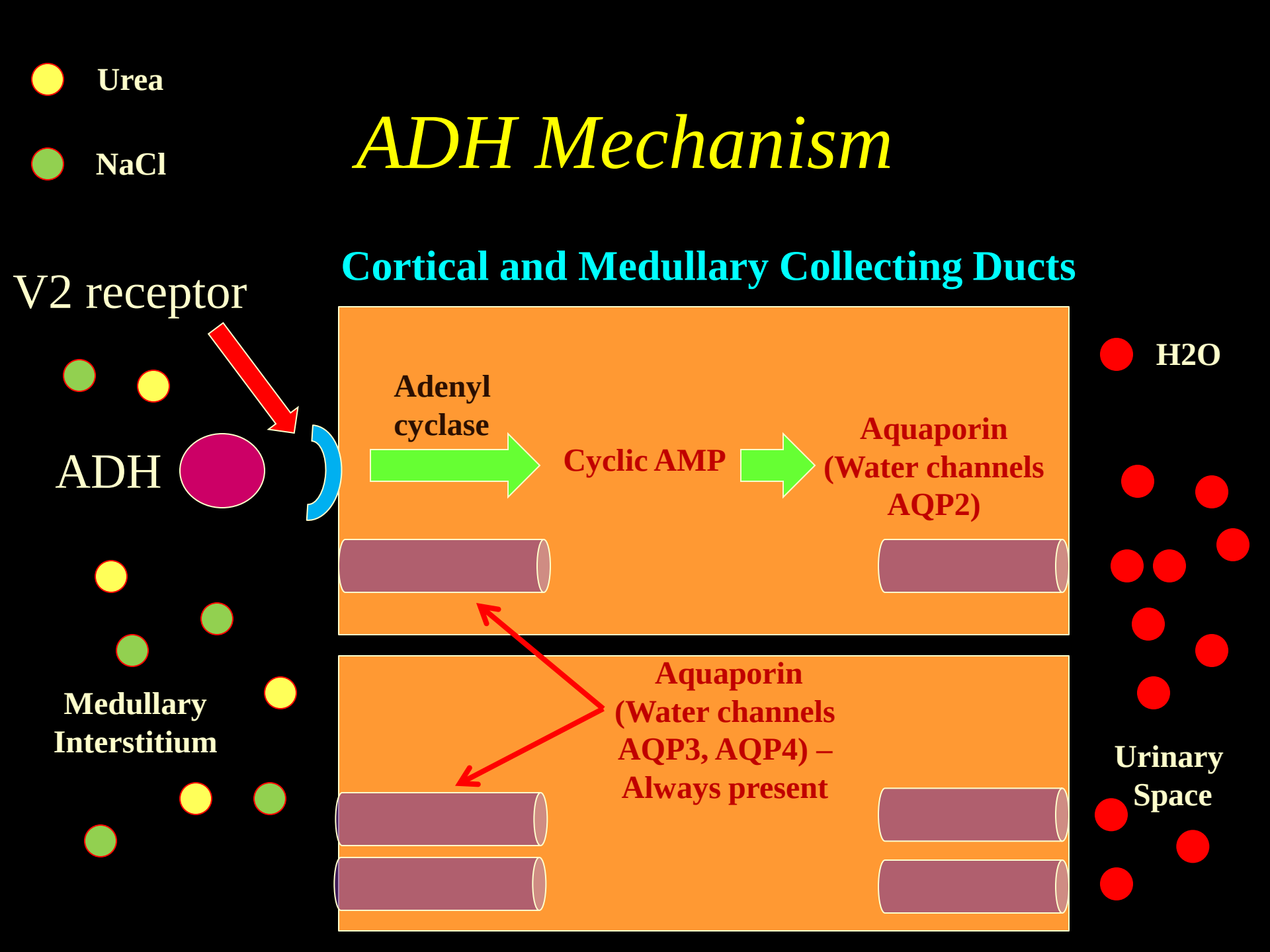
Osmolality results in A linear increase in ADH secretion

Volume Control of ADH >>> Osmolality

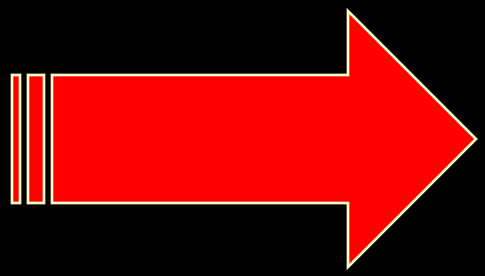
Key Principle

The Body Protects Volume over Tonicity

When the Change in Volume is > 10%


Urea
NaCl
ADH Mechanism
Cortical and Medullary Collecting Ducts
V2 receptor
ADH
Adenyl cyclase
Cyclic AMP
Aquaporin (Water channels AQP2)
H2O
Medullary Interstitium
Aquaporin (Water channels AQP3, AQP4) – Always present
Urinary Space

Hyponatremia
Rule #1



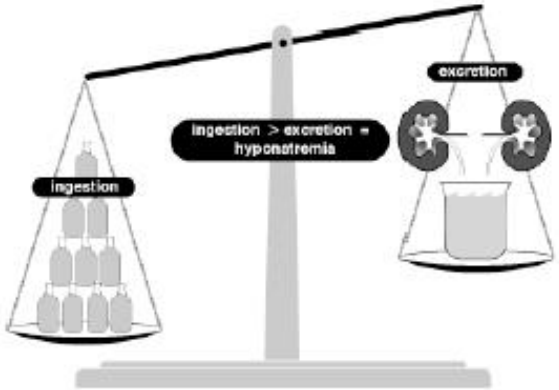
Almost all cases of Hyponatremia are associated with inappropriate ADH stimulation AND limited dietary intake that limits the degree of water diuresis

Your Diet Affects How much Water You can Drink

ADH	Urine Specific Gravity	Maximum Fluid intake Before Hyponatremia (Normal Diet 900 mosm)	Maximum Fluid intake Before Hyponatremia (Reduced Diet 450 mosm)
None	1.003	18 L	9 L
+	1.010	3 L	1.5 L
++	1.015	2 L	1 L
+++	1.020	1.5 L	0.75 L

Dietary oral intake is just as important as ADH regulation in controlling water balance Simply feeding a patient can markedly improve hyponatremia

How much Water can you drink before you will get Hyponatremia ?



- So how much water intake is too much?

With a normal diet of 900 mosm / day

Hyponatremia in Heart and Kidney Failure : It is All about the Underfilled Circulation and ADH

Low Cardiac Output –
Decreased Effective Circulation Volume

ADH

Serum Na Concentration

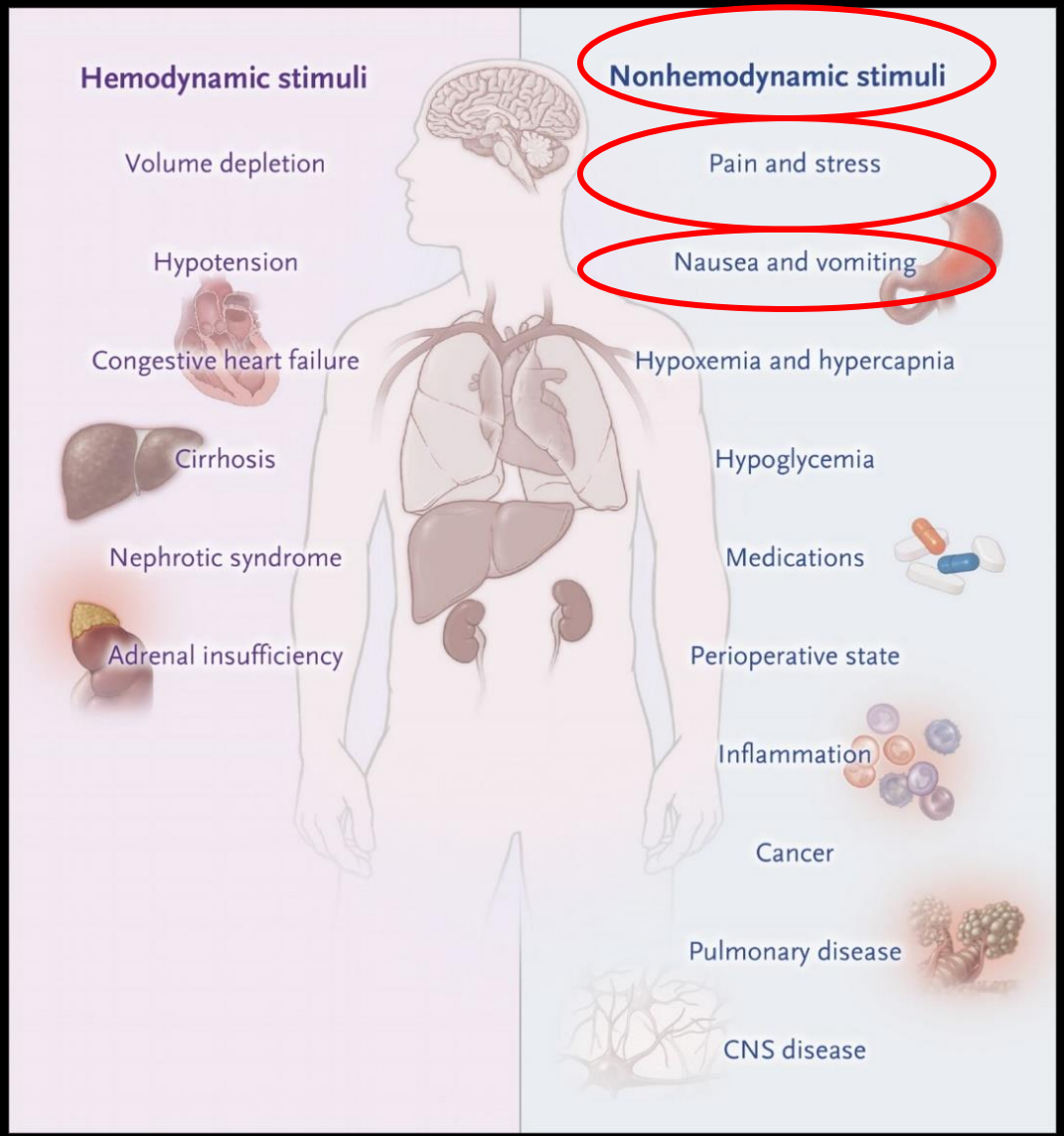
Portal HTN - Ascites
Decreased Effective Circulation Volume

ADH

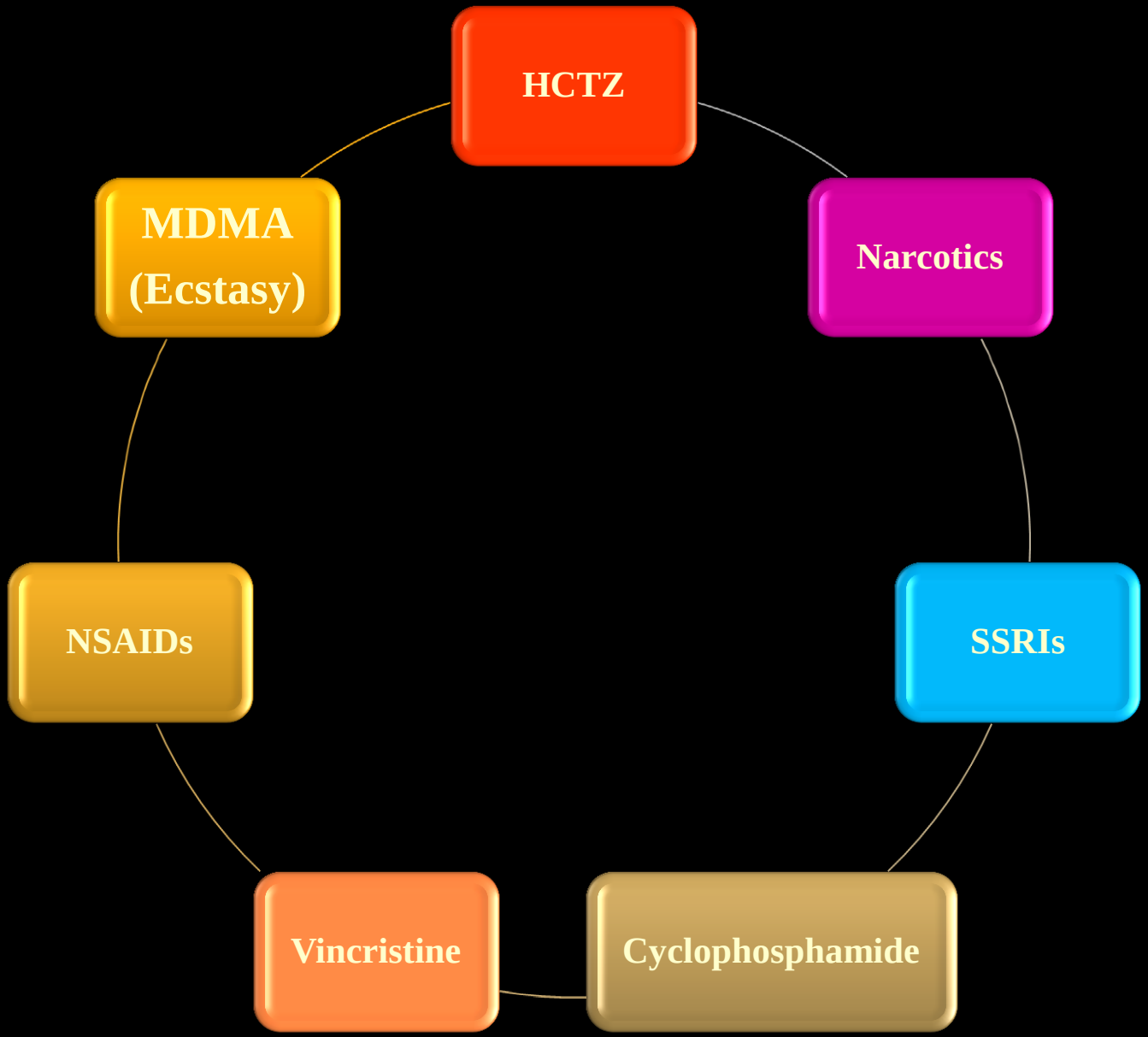
Serum Na Concentration

Moritz ML, Ayus JC. N Engl J Med 2015;373:1350-1360.

Nonosmotic States of Arginine Vasopressin Release



Drug Induced SIADH



Hospital Acquired Hyponatremia

Osmotic or Non Osmotic Release of ADH + **Hypotonic IV Fluid** = **Hyponatremia**

Moritz M. N Engl J Med 2015;373:1350-60.

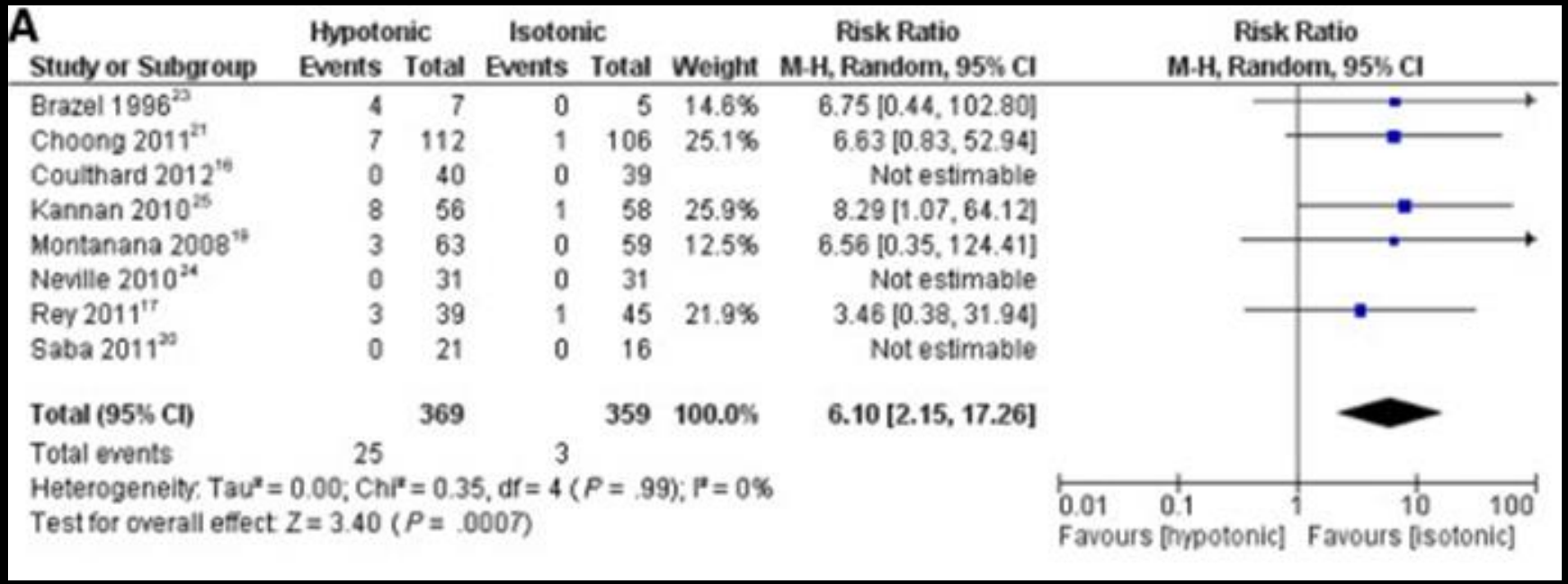
Iatrogenic Hyponatremia in the Hospital

- **Avoid the use of …..**
  - **0.45 NS**
  - **D_5W**

Conclusion

- **The routine use of hypotonic solutions for hospitalized patients is not justified**
- **Most inpatients have non osmotic release of ADH and are at risk of hyponatremia**
- **Isotonic IV fluids should be the standard of care**

Prevention of Hyponatremia Based on IV Solution



A

Study or Subgroup	Hypotonic Events	Hypotonic Total	Isotonic Events	Isotonic Total	Weight	Risk Ratio M-H, Random, 95% CI
Brazel 1996[23]	4	7	0	5	14.6%	6.75 [0.44, 102.80]
Choong 2011[21]	7	112	1	106	25.1%	6.63 [0.83, 52.94]
Coulthard 2012[16]	0	40	0	39		Not estimable
Kannan 2010[25]	8	56	1	58	25.9%	8.29 [1.07, 64.12]
Montanana 2008[19]	3	63	0	59	12.5%	6.56 [0.35, 124.41]
Neville 2010[24]	0	31	0	31		Not estimable
Rey 2011[17]	3	39	1	45	21.9%	3.46 [0.38, 31.94]
Saba 2011[20]	0	21	0	16		Not estimable
Total (95% CI)		**369**		**359**	**100.0%**	**6.10 [2.15, 17.26]**
Total events	25		3			

Heterogeneity: Tau² = 0.00; Chi² = 0.35, df = 4 (*P* = .99); I² = 0%

Test for overall effect: Z = 3.40 (*P* = .0007)

Risk Ratio M-H, Random, 95% CI

0.01 0.1 1 10 100

Favours [hypotonic] Favours [isotonic]

The use of an isotonic IV solution is effective to reduce to reduce the risk of hyponatremia

Foster BA.J Pediatr 2014 Jul;165(1):163-169

Exercise Associated Hyponatremia (EAH)

- **Combination of solute loss (sweating) and hypotonic fluid intake (sports drinks)**
- **Common in Endurance Sports activities**
  - **Marathon**
  - **Triathlon**
  - **Hiking**
  - **Cycling**
  - **Football training camps**
  - **Military training camp**
  - **Police training**

ADH

~ 80 mosm/L

0 mosm/L

Hyponatremia : YES or NO

Thiazides
Distal tubule
Na-Cl channel

Loop Diuretics
TALH
Na-K - 2Cl channel

Diuretics and Hyponatremia

- **Facts**
  - **Diuretics DO NOT cause hyponatremia because they lead to increased urinary sodium losses (Natriuresis)**
    - **They can not cause more Na loss than water !!!**
  - **Only Thiazides (weaker diuretic) cause Hyponatremia while Loop Diuretics (more potent) DO NOT**
- **Thiazides do not interfere with the urine concentrating mechanism**
- **Loop diuretics inhibit the development of a medullary hyperosmolar state by preventing the movement of NaCl into the interstitium at the TALH**

Non Osmotic / Non Volumetric Causes of SIADH

- **Malignancies**
  - **Small Cell carcinoma (oat cell) of the lung**
    - **10-15% incidence**
    - **m-RNA for AVP**
  - **Head and Neck squamous cell carcinomas**
    - **7% incidence**
  - **Non-small cell carcinoma of the lung**

Hyponatremia
Rule #2

Always check serum osmolality
If < 270 mosm/L : you have
true **Hypotonic Hyponatremia**

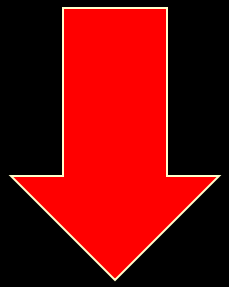
Cerebral edema

Hyponatremia

- **Only clinically dangerous if it is associated with**
  - **Hypotonicity**
    - **Serum Osmolality / Tonicity < 270 mosm/L**
- **Do not get tricked by hyponatremia associated with a normal or high serum osmolality / tonicity**
  - **This condition is called Pseudohyponatremia**
  - **These patients will NOT develop cerebral edema**

Pseudohyponatremia

Hyperglycemia or Mannitol



Hypertonicity pulls Na free water out of the intracellular compartment leading to dilutional hyponatremia

No brain swelling will occur because the patient is not hypotonic (< 270 mosm/L) !!!

They are Hypertonic (>300 mosm/L)

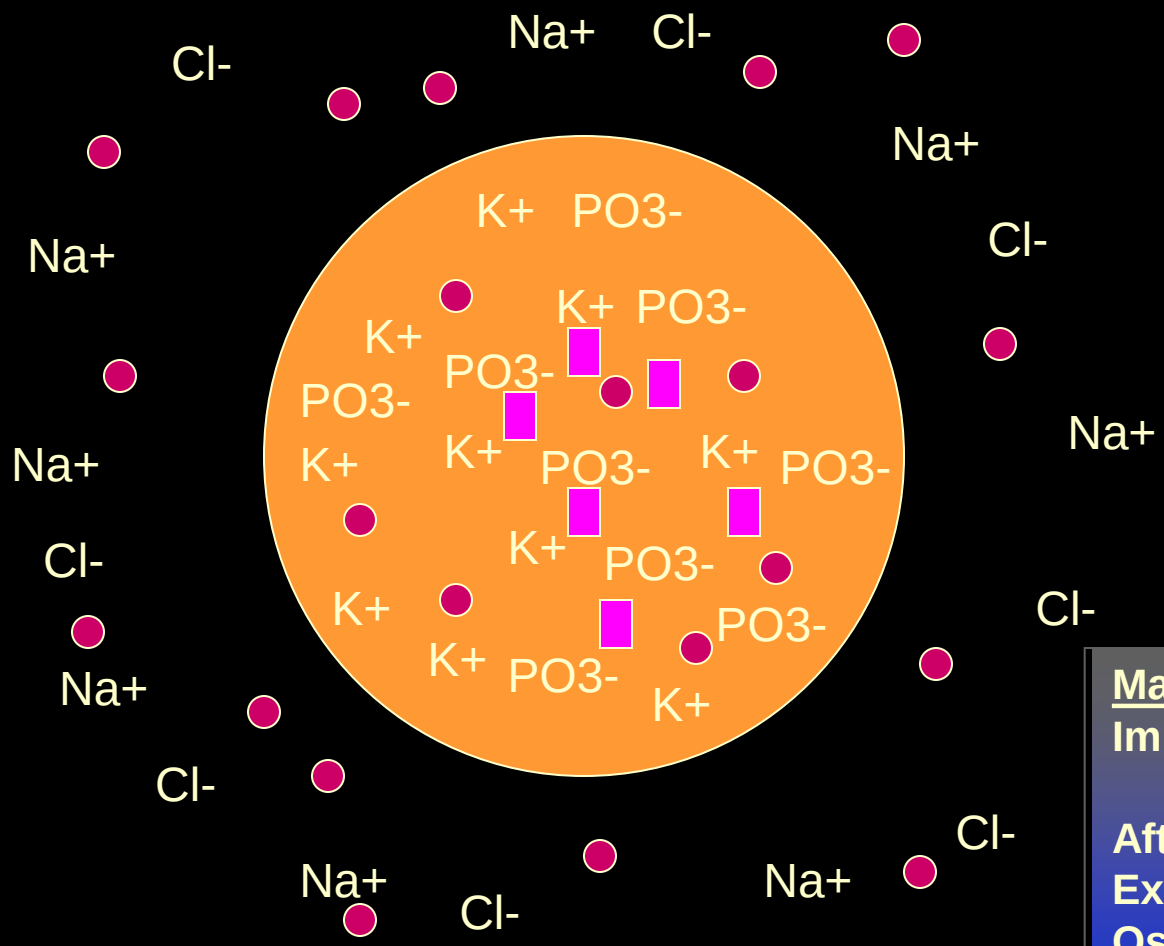
Pseudo-Hyonatremia

- **A machine analyzer error produced by excess**
  - **Protein (Multiple Myeloma)**
  - **Lipids (Hypertriglyceridemia- > 1000 mg/L)**
- **Etiology**
  - **Displacement of the plasma by an increase in the semi-solid phase –**
- **Complete Artifact ! No actual hypotonicity – No treatment needed**

PREVENTION WORKS!

Hyponatremia : Cellular Response Regulatory Volume Decrease

= organic osmoles



= water molecule

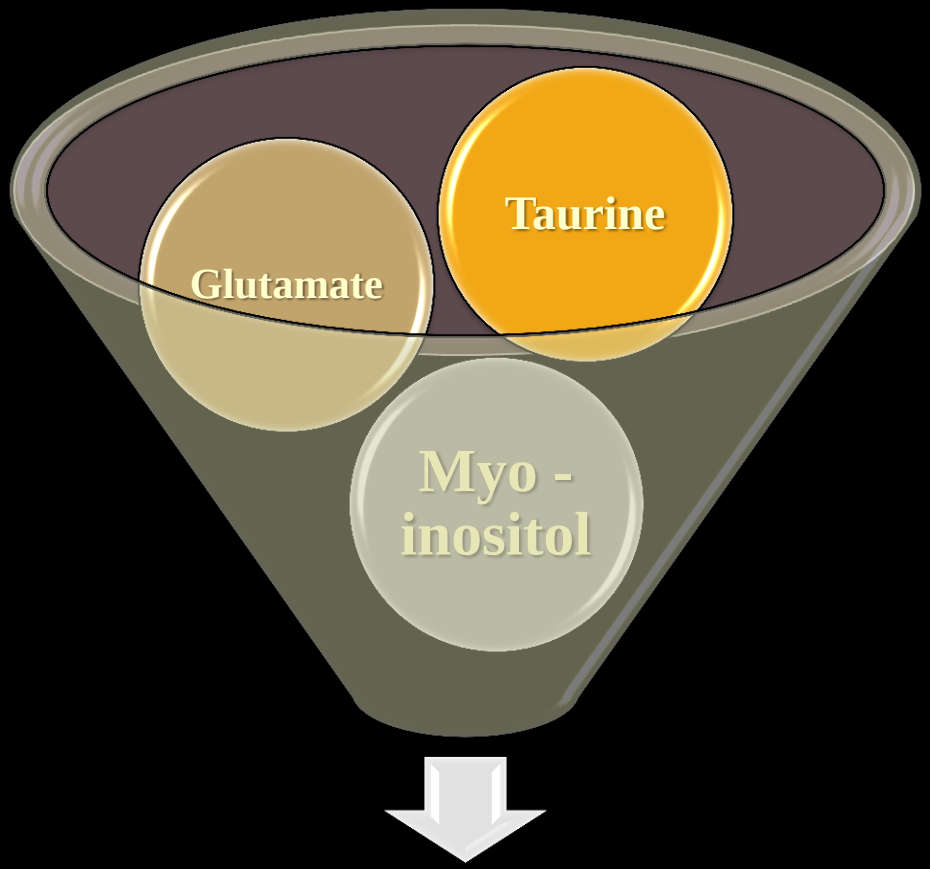
Full adaptation requires a minimum of 48 hours

Major Pathways

Immediate :K efflux

After 48 hours: Extrusion of organic Osmolytes (solutes) such as inositol

Organic Osmolytes



Maintenance of Intracellular Fluid Volume

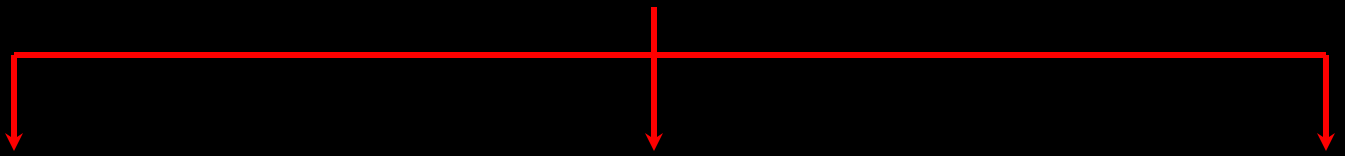
Risk Factors for Hyponatremic Encephalopathy

Rate of onset < 48 hrs	• Decreased time for brain adaptation
Age < 16 yrs	• Increased ration of brain mass to intracranial volume (space)
Pre-Menopausal	• Estrogen limits brain adaptation • Increases ADH • Vasoconstriction
Hypoxemia	• Impaired adaptation

Hyponatremia

- Step I : Is it real Hypotonic Hyponatremia ??
  - Yes it is !!
- Step II : Classification
  - Establish Volume status

Classification of Hyponatremia



Hypovolemic Hypotonic hyponatremia

1. GI losses
2. Skin losses
3. Lung losses
4. Third-space losses
5. Renal losses-diuretics
6. Cerebral salt wasting

Hypervolemic Hypotonic hyponatremia

1. CHF
2. Cirrhosis
3. Nephrosis
4. Kidney Failure

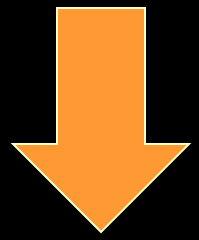
Isovolemic Hypotonic hyponatremia

1. Water intoxication
2. K+ losses
3. Reset osmostat
4. SIADH
5. Impaired Adrenal or Thyroid function
6. Drugs
   - **sulfonylureas**
   - **carbamazepine**
   - **phenothiazines**
   - **antidepressants**

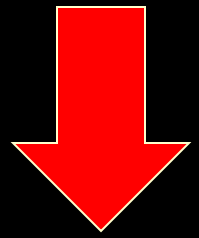
Workup of Hyponatremia to Confirm Excess ADH The 3 Essential Components !

Serum Osmolality	Urine Osmolality	Urine Sodium
• Need to demonstrate true hypotonicity • < 270 mosm/L	• > 100 mosm/L • Specific Gravity can also be used (> 1.005)	• SIADH > 30 meq/L • Hypovolemic or Hypervolemic < 20 meq/L

Appropriate Response to Hypotonicity

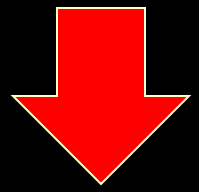


Supraoptic / Paraventricular Nuclei

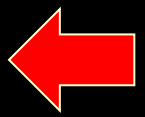


Inhibit

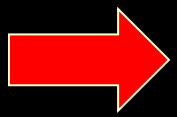
ADH



Specific Gravity < 1.003



Dilute urine



Osmolality < 100 mosm/L

Treatment of Hyponatremia

- **Key Questions**
  - **Does the patient have symptoms ?**
    - **Yes**
    - **No**
  - **How long has the hyponatremia been present ?**
    - **Acute < 48 hours**
    - **Chronic > 48 hours**

Correction of Hyponatremia

- **Cellular Process of recovery from hyponatremia**
  - **Re-uptake of electrolytes (K, Phos)**
  - **Re-synthesis of organic osmolytes**
  - ***If the rate of correction exceeds the rate of re-accumulation of intracellular osmoles the cell will acutely shrink***
    - **Astrocytes / Oligodentrocytes are particularly sensitive to volume changes**
    - **Acute volume contraction of the cell causes it to stop producing myelin - Apoptosis**

Myelinolysis Syndromes

Central Pontine Myelinolysis (CPM)

Extra Pontine Myelinolysis (EPM)

Osmotic Demyelinating Syndrome(ODS)

Osmotic Demyelinating Syndrome

- **Clinical Sequence**
  - **Almost Always associated with severe hyponatremia (Na < 120 meq/L)**
  - **Rapid correction of serum Na**
    - **> 10 meq/24 hours**
  - **Improvement of neurological symptoms for 2 – 6 days followed by the rapid development of**
    - **Confusion**
    - **Quadriplegia**
    - **pseudobulbar palsy**
    - **pseudo coma ('locked-in syndrome')**

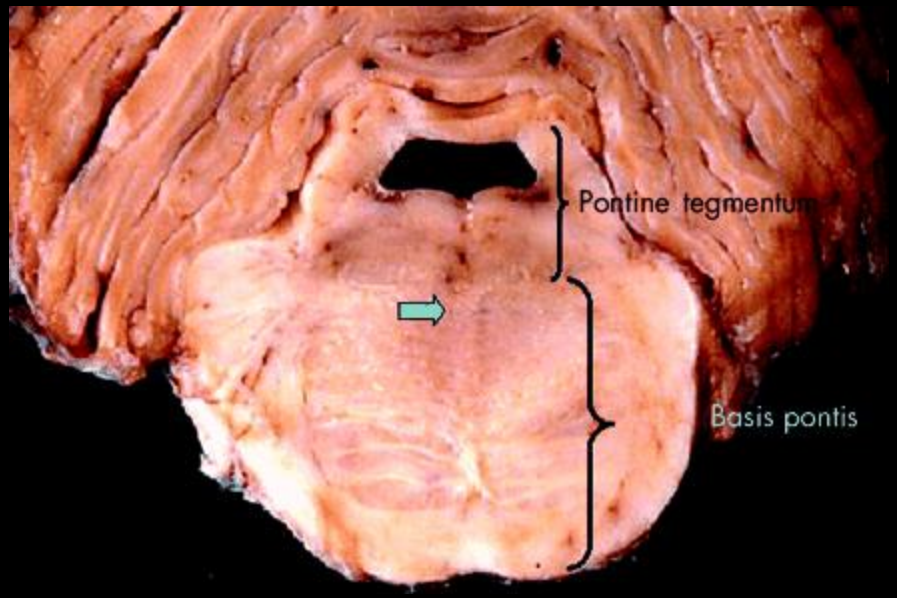
Osmotic Demyelinating Syndrome

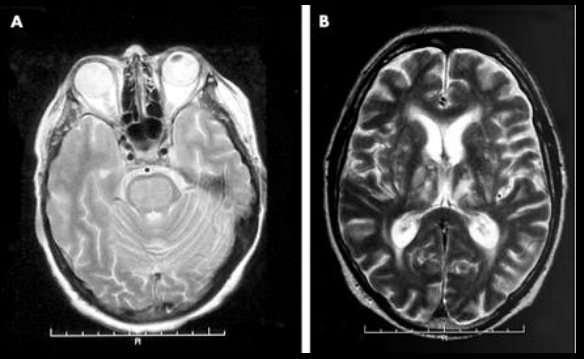
Most common sites in order of frequency of involvement

- **Pons**
- **Cerebellum**
- **Lateral geniculate body**
- **External capsule**
- **Extreme capsule**
- **Hippocampus**
- **Putamen**
- **Cerebral cortex/subcortex**
- **Thalamus**
- **Caudate nucleus**

The following 10% or less:
• Claustrum
• Internal capsule
• Midbrain
• Internal medullary lamella
• Mamillary body
• Medulla oblongata

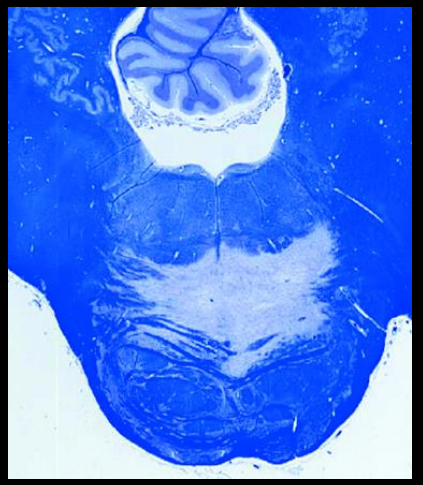
Osmotic Demyelinating Syndrome



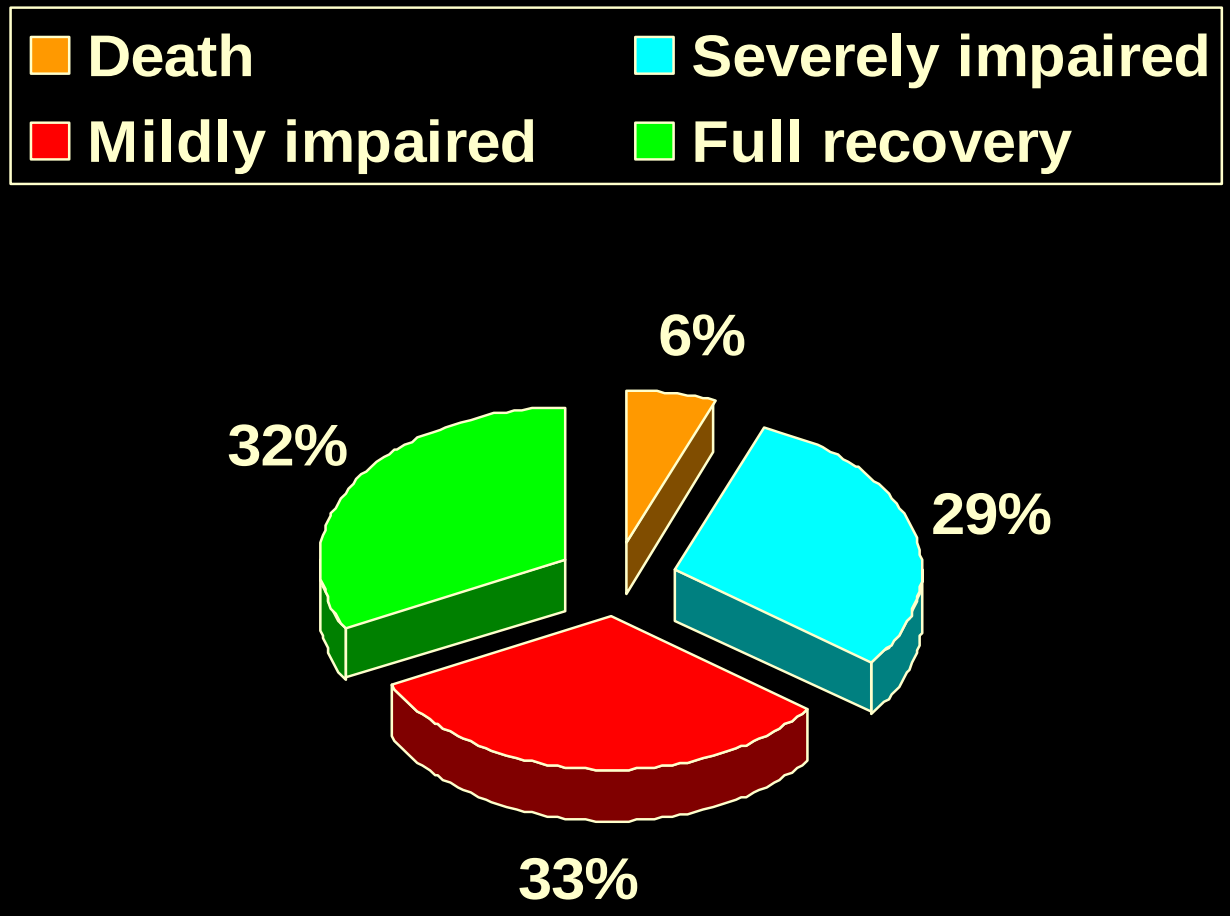


CAT scan and/or MRI may not be Positive for Myelinolysis for up to 4 weeks after the event

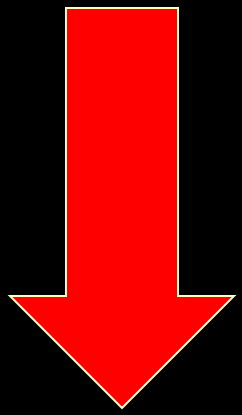
Followup studies if the initial test is negative are mandatory



Osmotic Demyelinating Syndrome : Outcome



Treatment of Hyponatremia



Avoid the
Osmotic Demyelinating Syndrome

Hyponatremia : Treatment

Do not aggressively treat <u>Chronic Hyponatremia</u>

< 48 hours

Acute

Cerebral Edema ?

Symptomatic (Na < 130 meq/L)

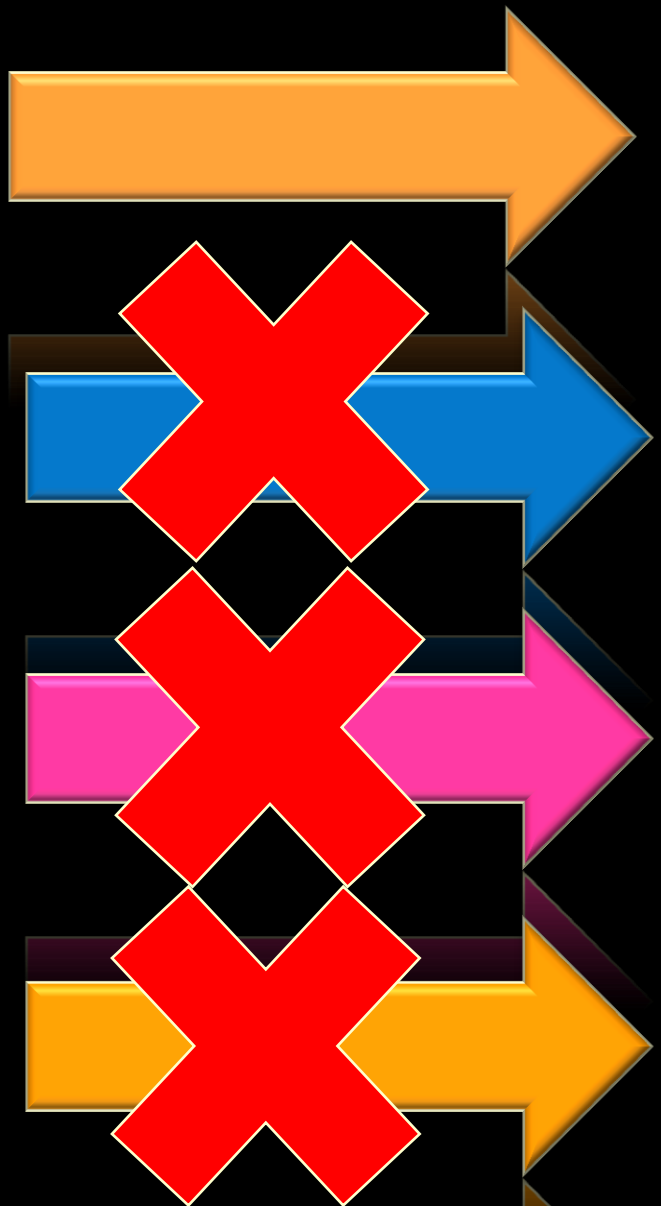
Asymptomatic (Na < 120 meq/L)

3% Saline

Asymptomatic (Na 121 – 134 meq/L)

Water restriction
Oral Solute

Treatment of Symptomatic Hyponatremic Encephalopathy



3% Saline

0.9 Normal Saline

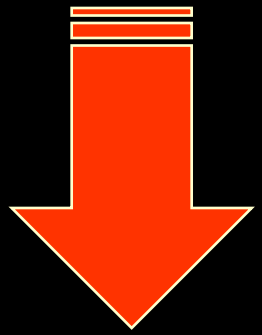
Vaptan

Water Restriction

Hypertonic Saline (3%) and the Treatment of Hyponatremic Encephalopathy

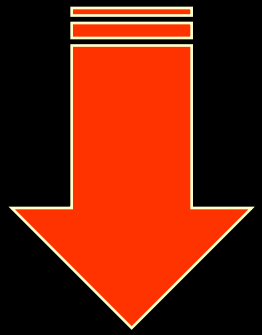
- **Na concentration of 513 meq/L**
  - **Compared to 154 meq/L in NS**
- **Two options for administration**

IV Bolus



100-150 cc over 10-20 minutes
Repeat x 3 until symptoms resolve

IV Infusion



125 cc/hr for 4 hrs
or less if symptoms resolve

Osmotic Demyelinating Syndrome

- **Correction rate of 1-2 meq/L/hr is acceptable in a patient with severe symptoms up to a total of 4 – 6 meq/L /day !**

- **Do not exceed > 8 meq/L increase in Na within a 24 hour period**

Medical Options for Chronic Hyponatremia

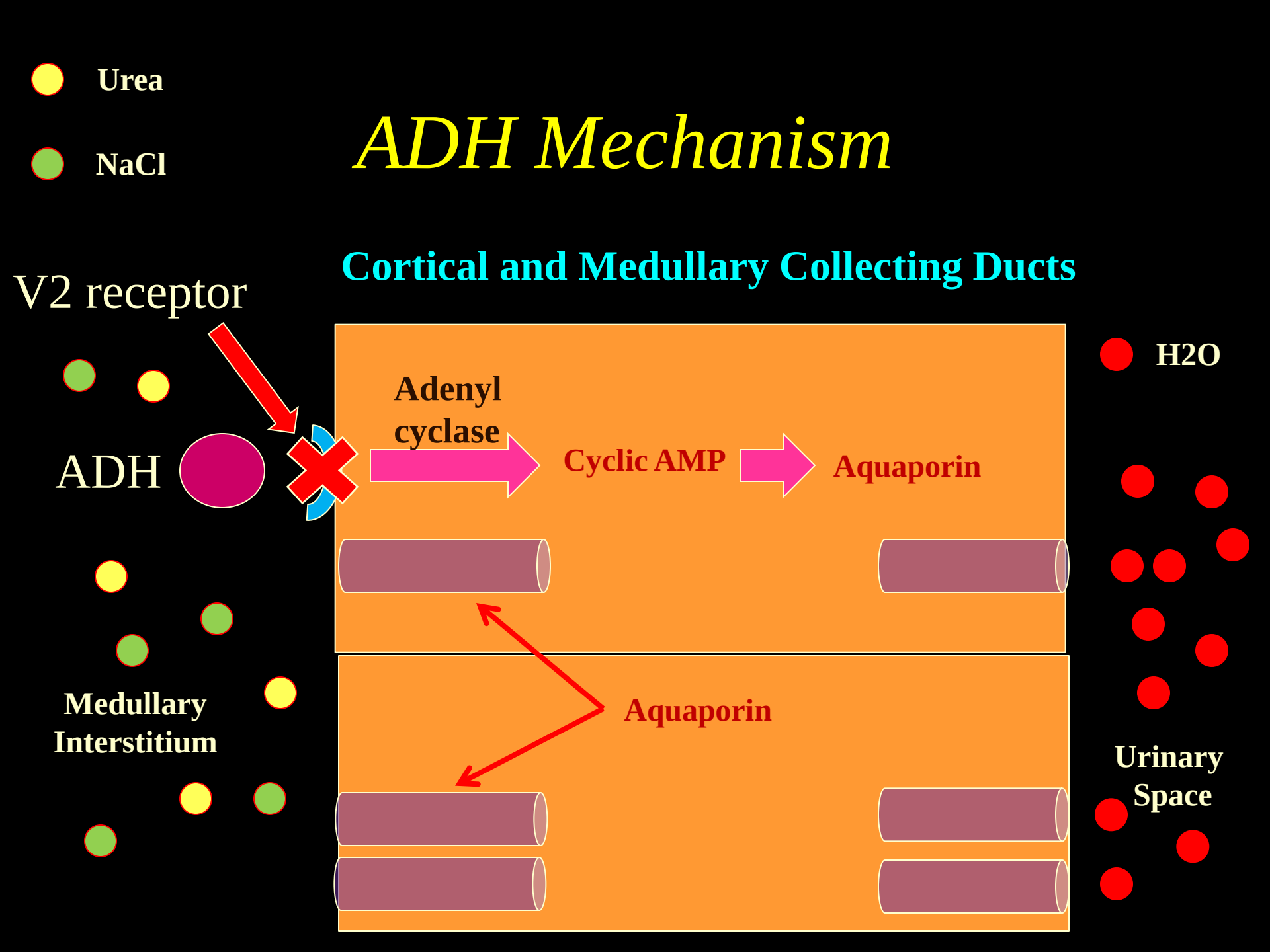
- Water Restriction < 0.8 L /Day
- Increase Solute Intake
- Tolvaptan
- Avoid Thiazides / NSAIDs
- Urea
- Demeclocycline 300 mg BID

Vasopressin Receptors

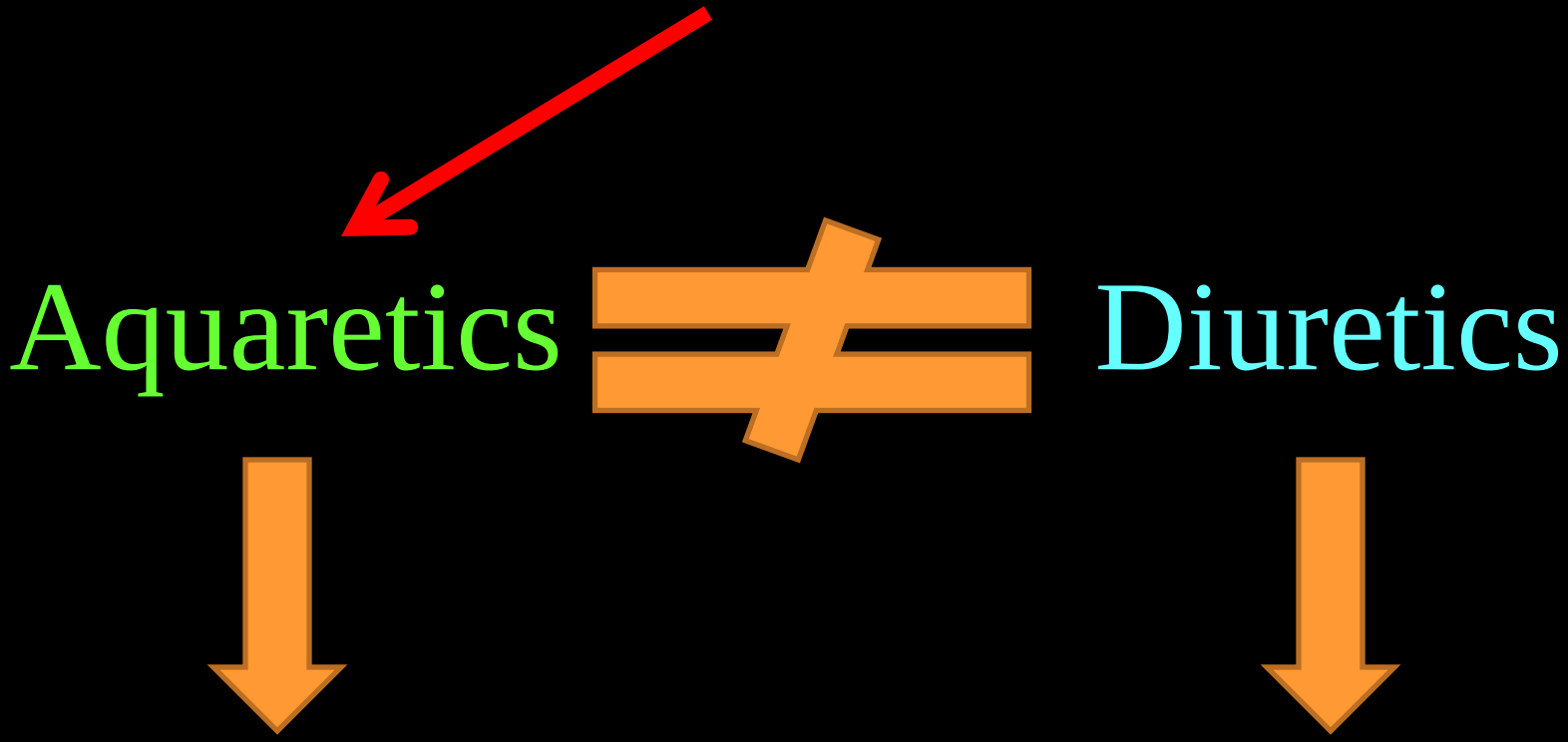
V1a	**vascular smooth muscle**	**vasoconstriction**
	platelets	**aggregation**
	myometrium	**contraction**
	hepatocytes	**glycogenolysis**
V1b	**anterior pituitary**	**ACTH release**
V2	**basolateral membrane collecting tubule**	**AQP2 channel insertion and induction of AQP2 synthesis**
	vascular endothelium	**vWF and factor 8 release**
	vacular smooth muscle	**vasodilation**

Vasopressin Antagonists- The Vaptans

Agent	Receptor	Route
Conivaptan	V1a + V2	IV
Lixivaptan	V2	oral
Tolvaptan	V2	oral
Satavaptan	V2	oral

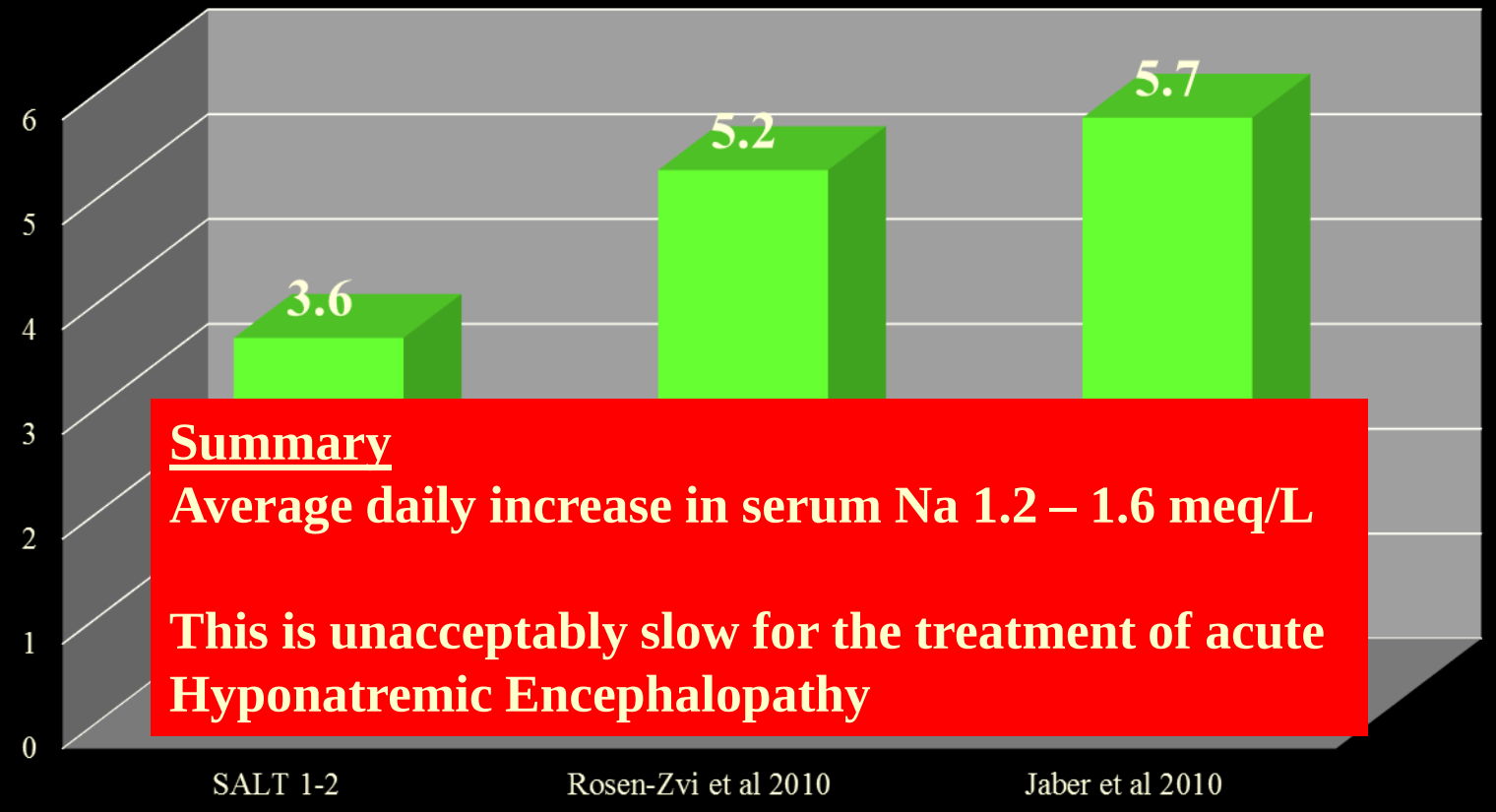

Urea
NaCl
ADH Mechanism
Cortical and Medullary Collecting Ducts
V2 receptor
ADH
Adenyl cyclase
Cyclic AMP
Aquaporin
H2O
Aquaporin
Medullary Interstitium
Urinary Space

Vaptans



Berl T. N Engl J Med 2015;372:2207-16.

Response Rate of Serum Na to Tolvaptan



Summary

Average daily increase in serum Na 1.2 – 1.6 meq/L

This is unacceptably slow for the treatment of acute Hyponatremic Encephalopathy

Battle of the Guidelines for Acute Hyponatremia

European Guidelines

Vaptans are contraindicated
3% saline is the foundation of therapy

American Guidelines

Vaptans are permitted based on discretion of the physician
3% saline is the foundation of therapy

Tolvaptan for Chronic Hyponatremia

AJKD

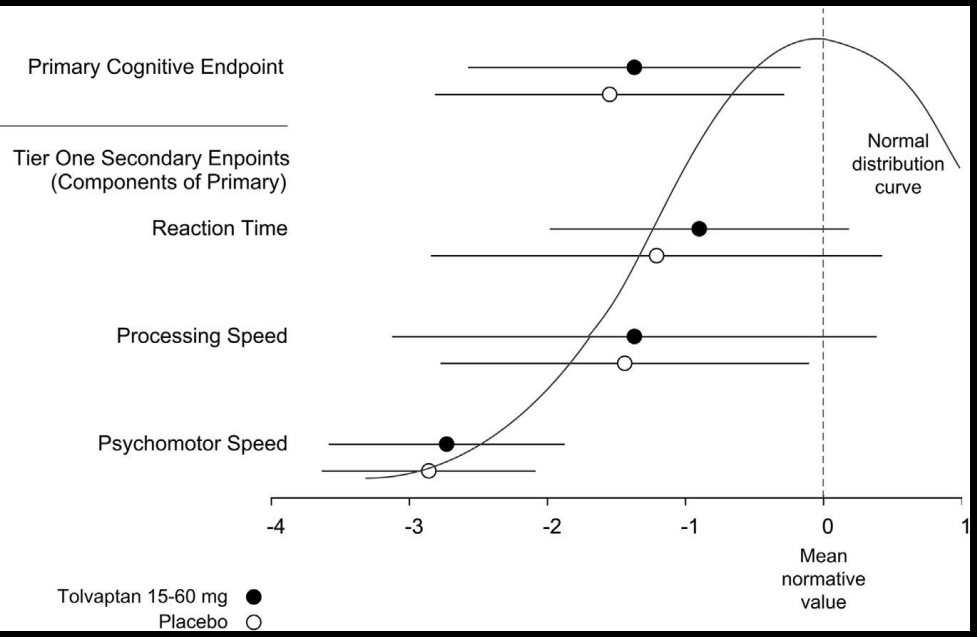
Original Investigation

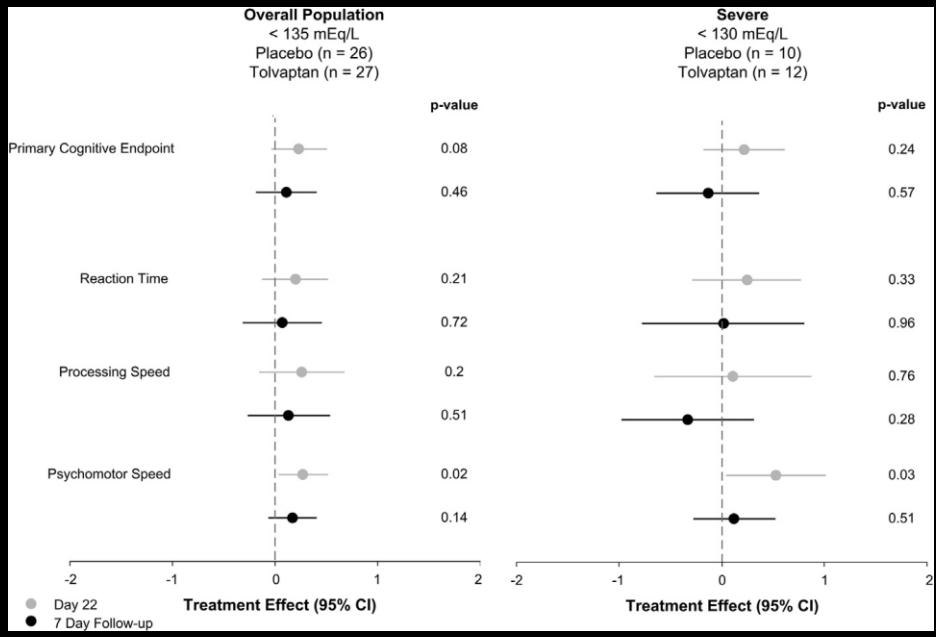
Tolvaptan and Neurocognitive Function in Mild to Moderate Chronic Hyponatremia: A Randomized Trial (INSIGHT)

*Joseph G. Verbalis, MD,[1] Howard Ellison, MD,[2] Mary Hobart, PhD,[3] Holly Krasa, MS,[3] John Ouyang, PhD,[3] and Frank S. Czerwiec, MD, PhD,[3] on behalf of the Investigation of the Neurocognitive Impact of Sodium Improvement in Geriatric Hyponatremia: Efficacy and Safety of Tolvaptan (INSIGHT) Investigators**

- **Phase 3b, multicenter, randomized, double-blind, placebo-controlled, parallel-group pilot study**
- **16 U.S. centers**
- **Titrated Tolvaptan to achieve a serum Na > 138 meq/L**
- **3 week duration**

Verbalis J. Am J Kid Dis 2016 February



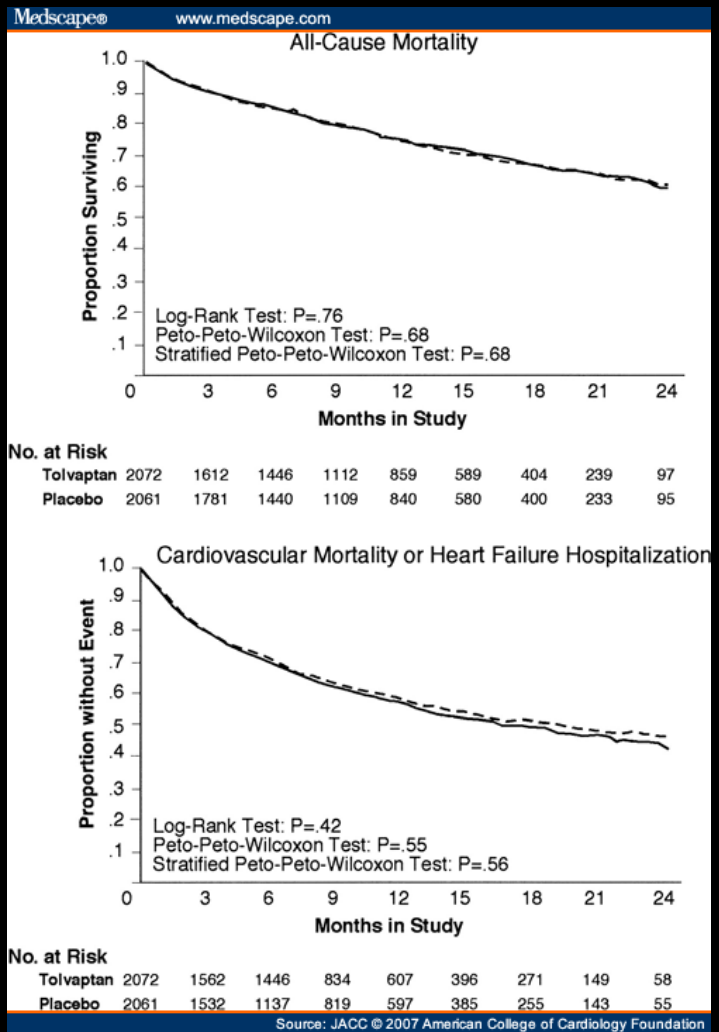


- **Na endpoint of 138 meq/L could only be achieved in 50%**
- **Slight improvement in neurocognitive scores but not statistically significant**
- **Improved bone mineralization**
- **More long term data is required to support the use of Tolvaptan for chronic Hyponatremia**

Konstam MA, Gheorghiade M, Burnett Jr. JC, et al. Effects of oral tolvaptan in patients hospitalized for worsening heart failure: the EVEREST outcome trial JAMA 2007;297:1319-1331

Tolvaptan in CHF

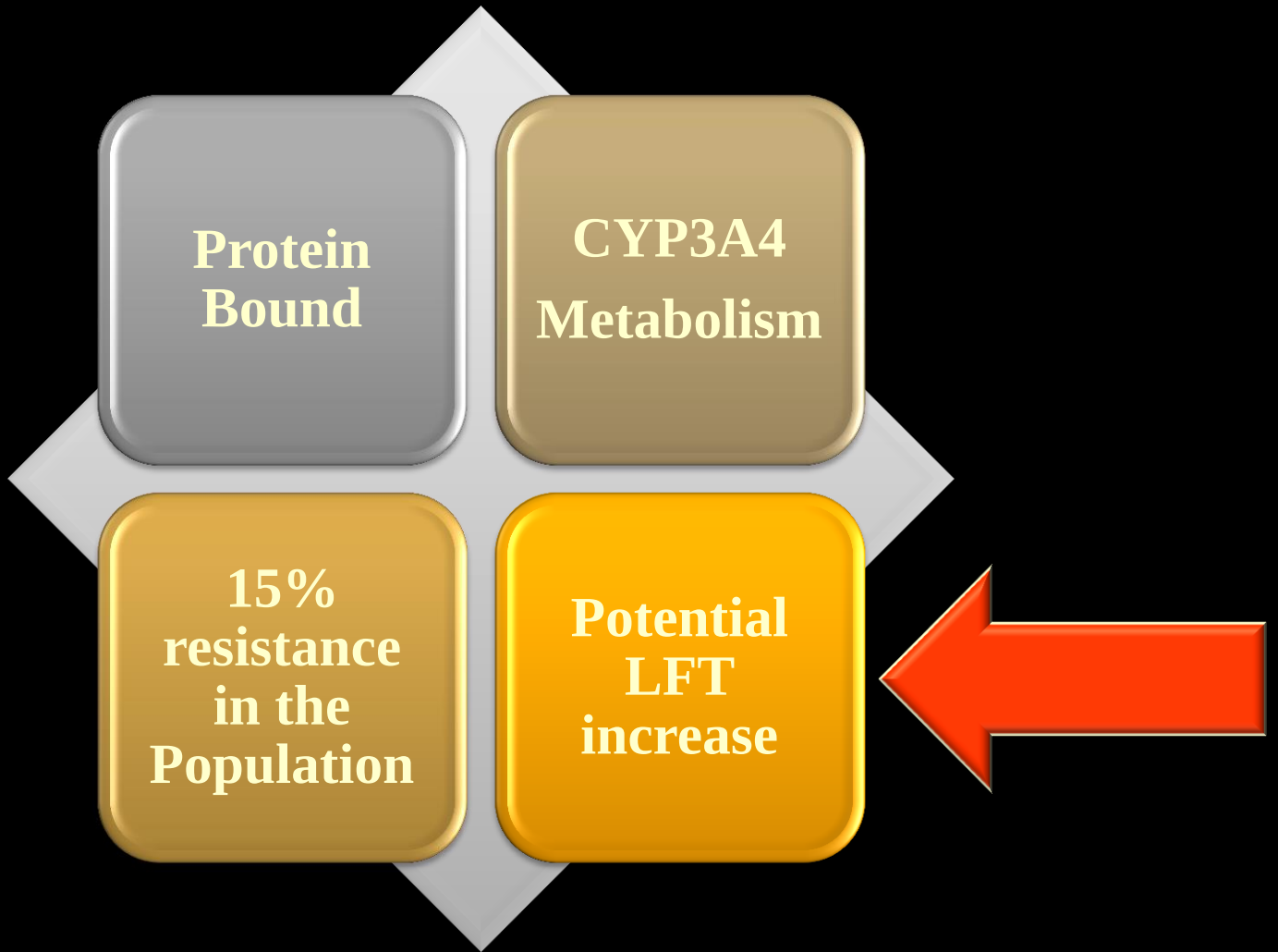
No Improvement in Outcomes



Hyponatremia : Treatment

- **Inhibition of Vasopressin**
  - **V2 receptor antagonists are now routinely available for the short term treatment of symptomatic chronic hyponatremia in the setting of hypervolemic or isovolemic Hyponatremia**
    - **Contraindicated in patients with hypovolemic hyponatremia**
      - **Will make the fluid deficit greater**

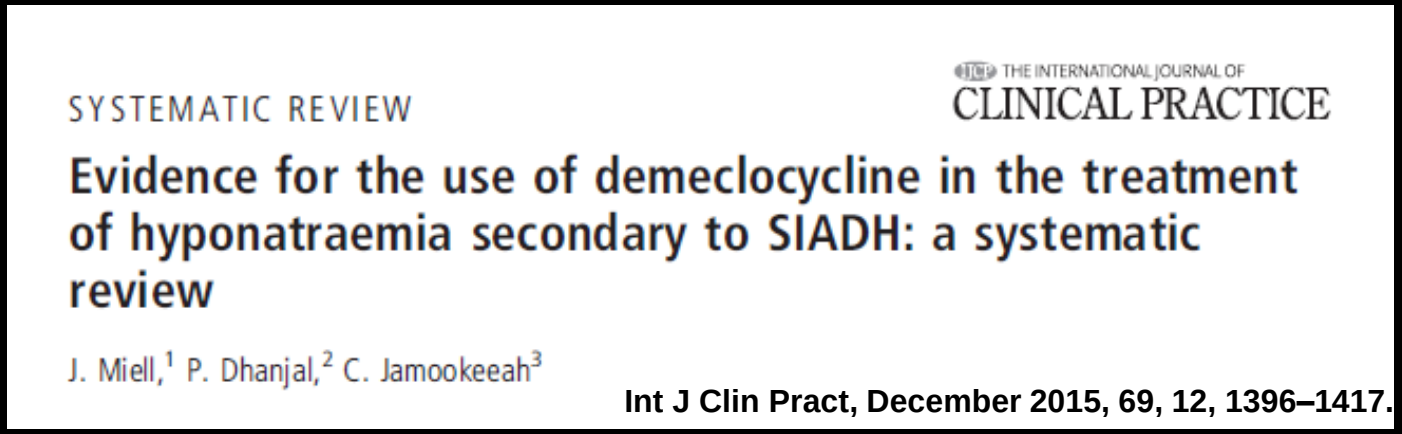
Tolvaptan


Protein Bound
CYP3A4 Metabolism
15% resistance in the Population
Potential LFT increase

FDA

Tolvaptan is not approved beyond 30 days of continuous therapy due to potential hepatotoxicity

Don't forget about …..Demeclocylcine



SYSTEMATIC REVIEW

THE INTERNATIONAL JOURNAL OF CLINICAL PRACTICE

Evidence for the use of demeclocycline in the treatment of hyponatraemia secondary to SIADH: a systematic review

J. Miell,[1] P. Dhanjal,[2] C. Jamookeeah[3]

Int J Clin Pract, December 2015, 69, 12, 1396–1417.

- Tetracylcine derivative
- Results in ADH antagonism
- Dosed at 300mg BID to 600 mg BID
- Slow onset 3-5 days
- Adverse reactions
  - GI upset

Due to lack of data European Guidelines do not recommend Demeclocycline but if water restriction fails this remains a viable option

And Don't forget about …..Urea

- **Provides an osmotic diuretic that will improve water loss**
- **Oral solution to be used for chronic hyponatremia**

	Na	K	Cl	HCO3	BUN	Cr	Glucose	Osm
Current	125	3.5	90	20	6	0.5	90	257
Pre op	140	4.1	95	25	9	0.7	95	288

Question

- How would you describe her neurologic condition ?

A. Osmotic Demyelinating Syndrome with cerebral edema

B. Hyponatremic Encephalopathy with cerebral edema

C. Osmotic Demyelinating Syndrome with an acute decrease in cerebral volume

D. Hyponatremic Encephalopathy with an acute decrease in cerebral volume

E. Osmotic Demyelinating Syndrome wit hno change in brain volume

F. Hyponatremic Encephalopathy with no change in brain volume

G. Subdural hematoma secondary to Hyponatremia

H. Acute CVA secondary to Hyponatremia

Question

- **How much water can you (normal person) drink before you become hyponatremic ?**

A. **3 L**

B. **6 L**

C. **12 L**

D. **18 L**

E. **25 L**

F. **30 L**

G. **With normal renal function the sky is the limit ! Drink away ! Last month I bought the unlimited drink package on a cruise ship and I got my money's worth and my brain is fine (I think!)**

	Na	K	Cl	HCO3	BUN	Cr	Glucose	Osm
Current	125	3.5	90	20	6	0.5	90	257
Pre op	140	4.1	95	25	9	0.7	95	288

Question

- **What is your target sodium level and how quickly should you correct symptomatic patients with hyponatremia to avoid seizures ?**

A. Correct up to a Na of 135 meq/L within 24 hours

B. Correct up to a Na of 130 meq/L within 24 hours

C. Correct no more than 15 meq/L within 24 hours

D. Correct no more than 12 meq/L within 24 hours

E. Correct no more than 10meq/L within 24 hours

F. Correct no more than 8 meq/L within 24 hours

Final Hypotonic Hyponatremia Rule # 3

Never correct Hyponatremia

- **4 – 6 meq/l in 24 hours**
- **(Maximum 8 meq/L)**

ODS does not result from Hyponatremia

ODS results from the treatment of Hyponatremia

Hyponatremia is not a sodium problem

Hyponatremia is a water problem

Thank you !