The challenges of hyponatremia

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"Treating hyponatremia: damned if we do and damned if we don't"

Thomas Berl

"Hyponatremia places the treating physician between a rock and a hard place"

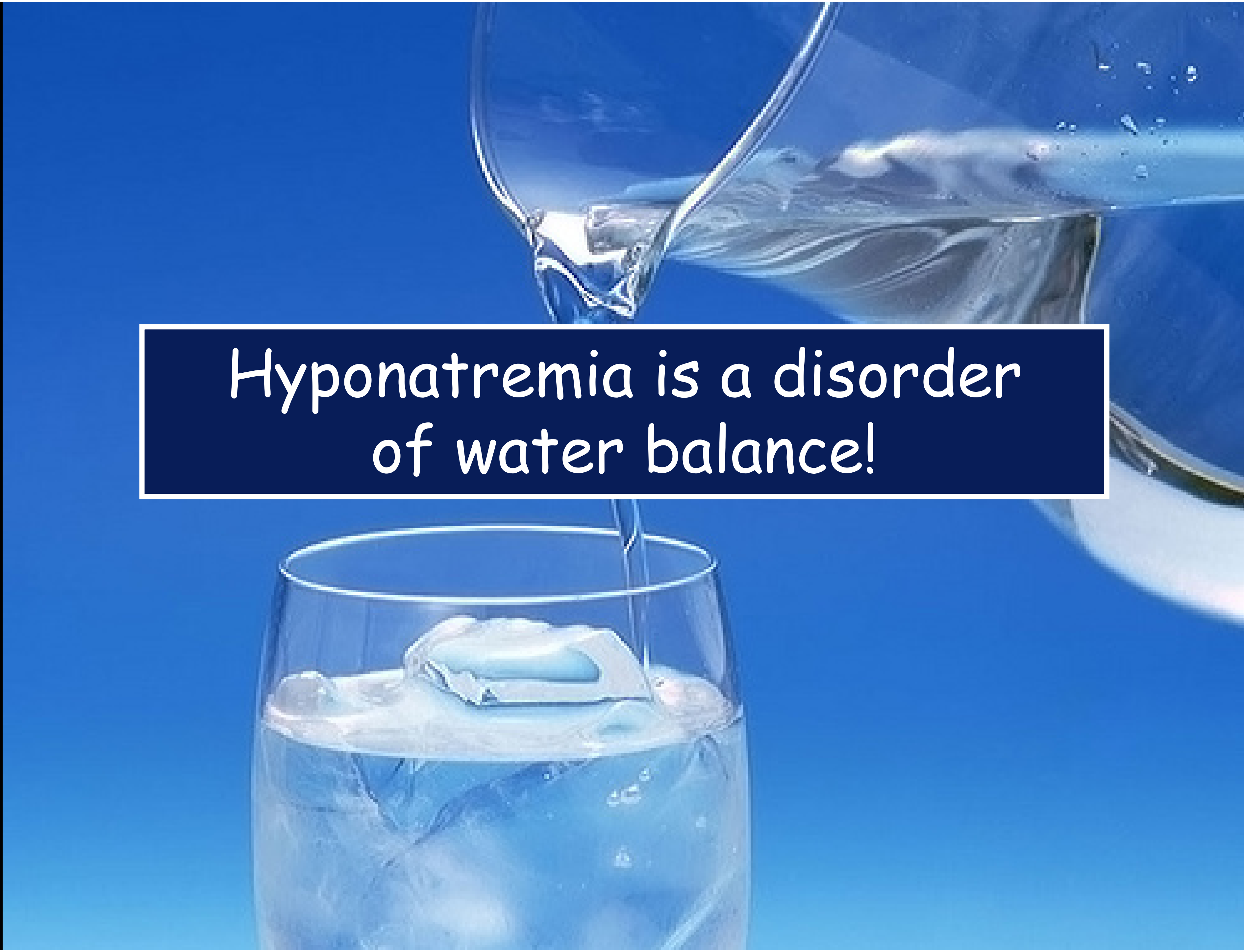
Richard Sterns

Learning objectives

- Recognize how understanding of the physiology of water homeostasis and cell volume regulation provides a foundation for prudent treatment of hyponatremia
- Be able to distinguish between acute and chronic hyponatremia
- Understand how the choice of treatment for hyponatremia depends on severity, rate of onset and the clinical features
- Be able to diagnose and aggressively manage life-threatening hyponatremic emergencies
- Be able to administer therapies that reliably correct hyponatremia at an appropriate rate

Epidemiology of hyponatremia

- Hyponatremia is defined as serum Na <135 mmol/L
- It is common in both the inpatient and outpatient setting, particularly among the elderly
  - Studies have shown that 15-30% of hospitalized patients have hyponatremia
    - Two thirds have hyponatremia on admission to hospital
    - 80-90% have mild hyponatremia (serum Na 125-134 mmol/L)
  - Hyponatremia is common among elderly nursing home residents, with reported prevalence ranging from 11-22%
- Hyponatremia is associated with increased mortality rates


Hyponatremia is a disorder of water balance!

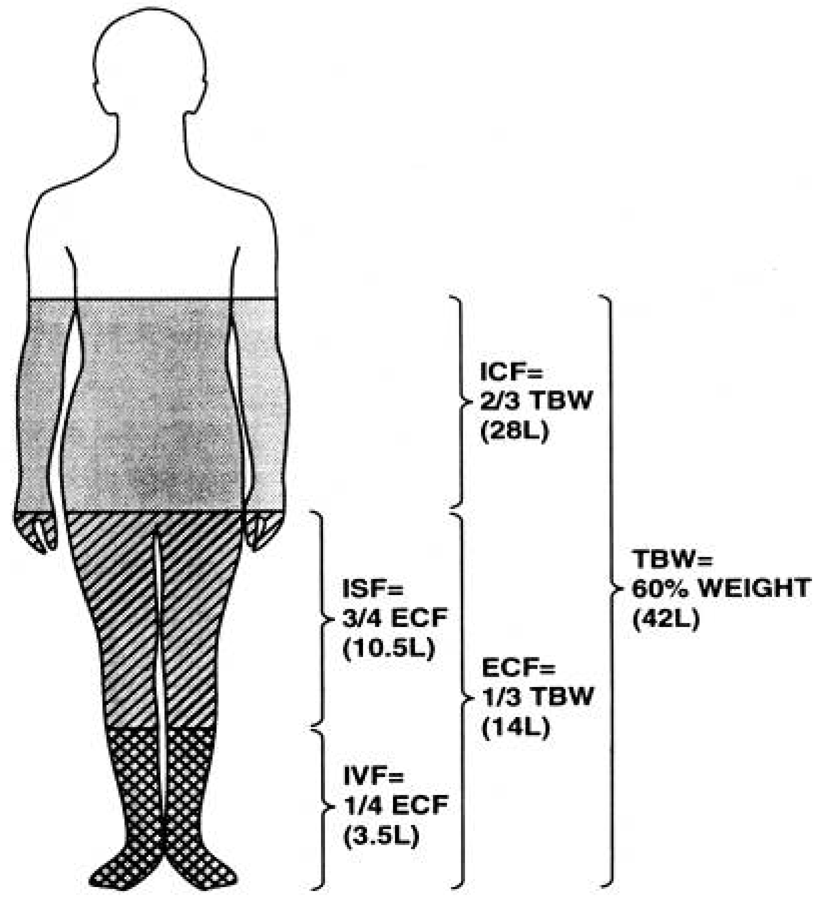
Water homeostasis: key concepts

- Difference between intake and excretion of water results in alteration of body fluid tonicity
- The body senses and regulates serum osmolality (not serum Na) which is kept constant at ~285 mOsm/kg by matching water excretion and intake
- Serum Na is a surrogate marker for serum osmolality
- Serum osmolality is regulated by water balance (not sodium balance)

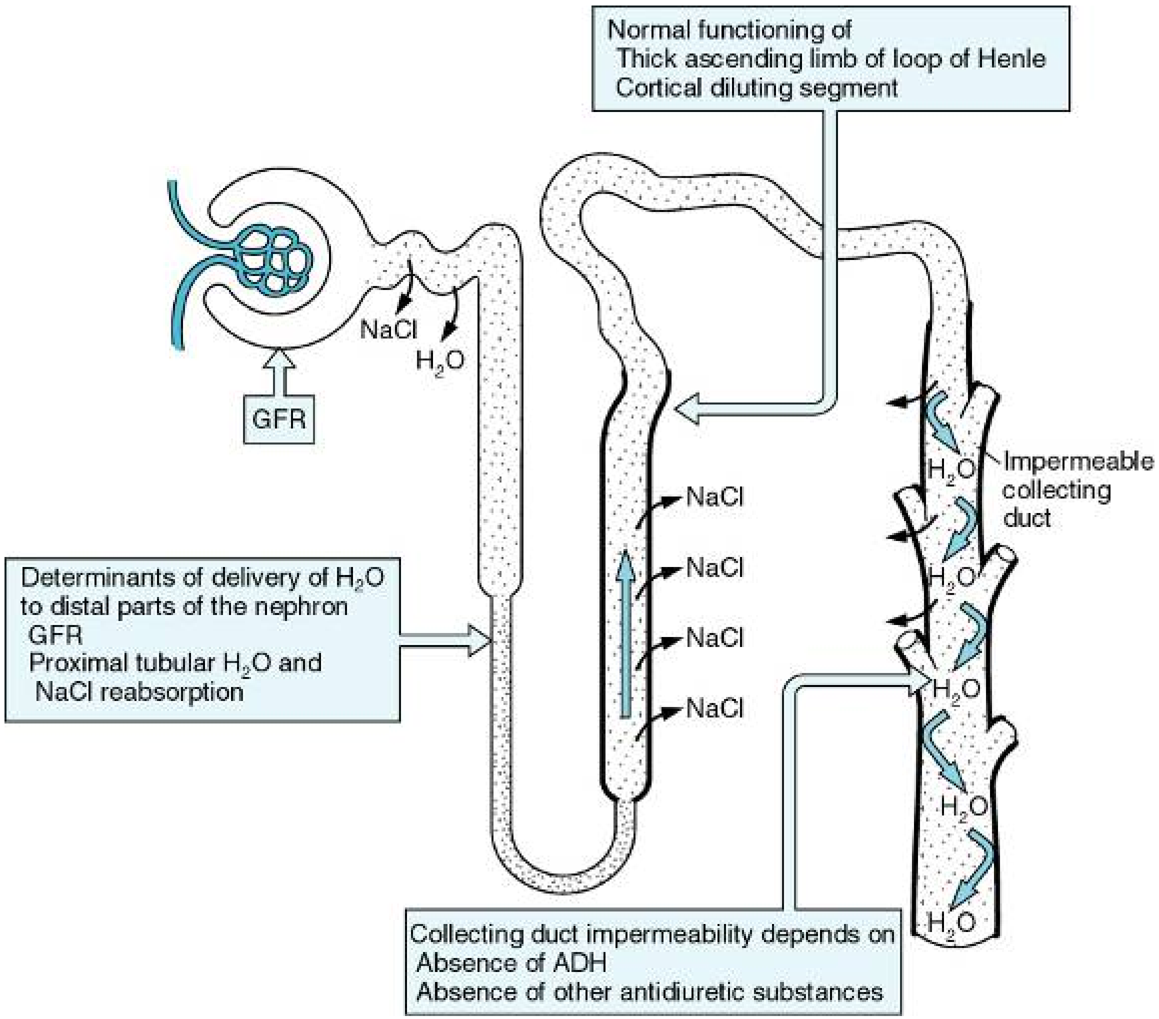
Osmolality of the body fluids

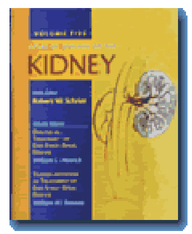
- Osmolality is equal in all body fluid compartments
- Serum osmolality can be calculated:

  Osmolality = 2 x serum Na + glucose + urea
- Effective osmolality = 2 x serum Na



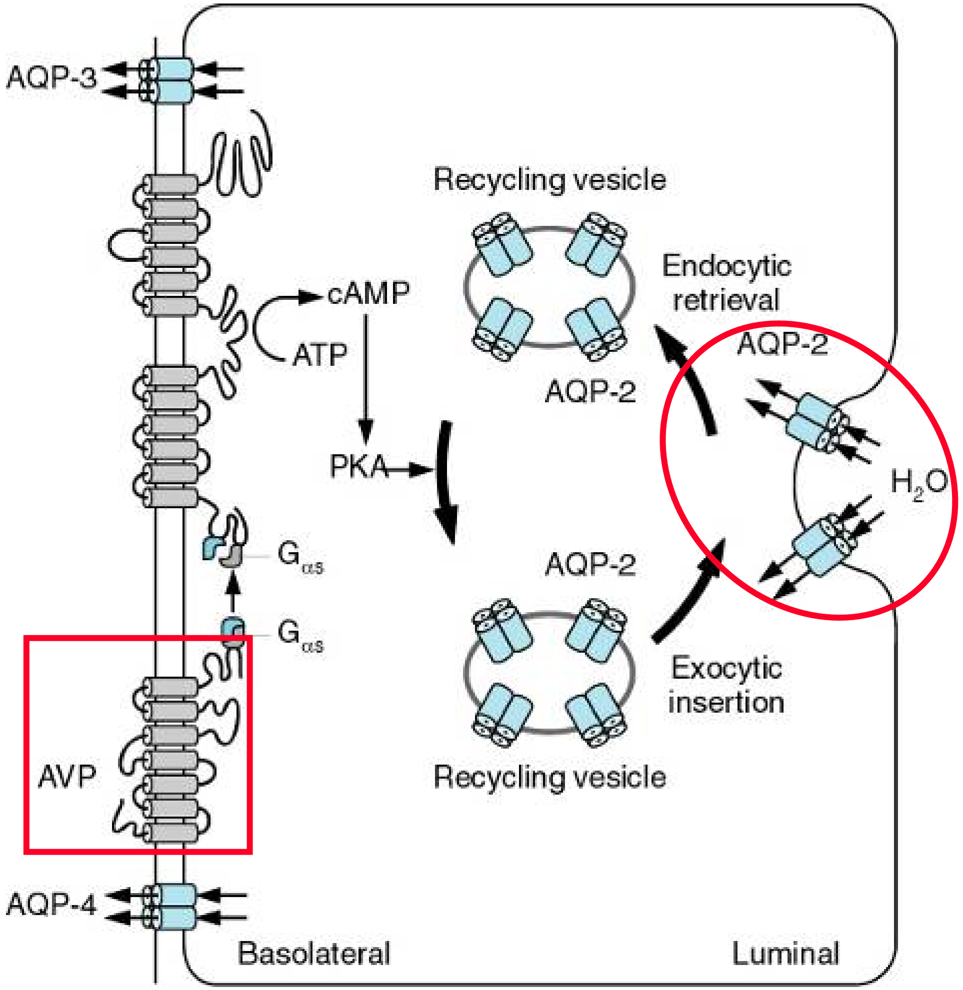
Excretion of free water by the kidney

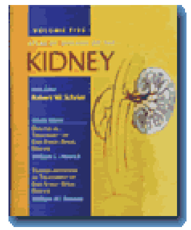




Sumit Kumar & Tomas Berl

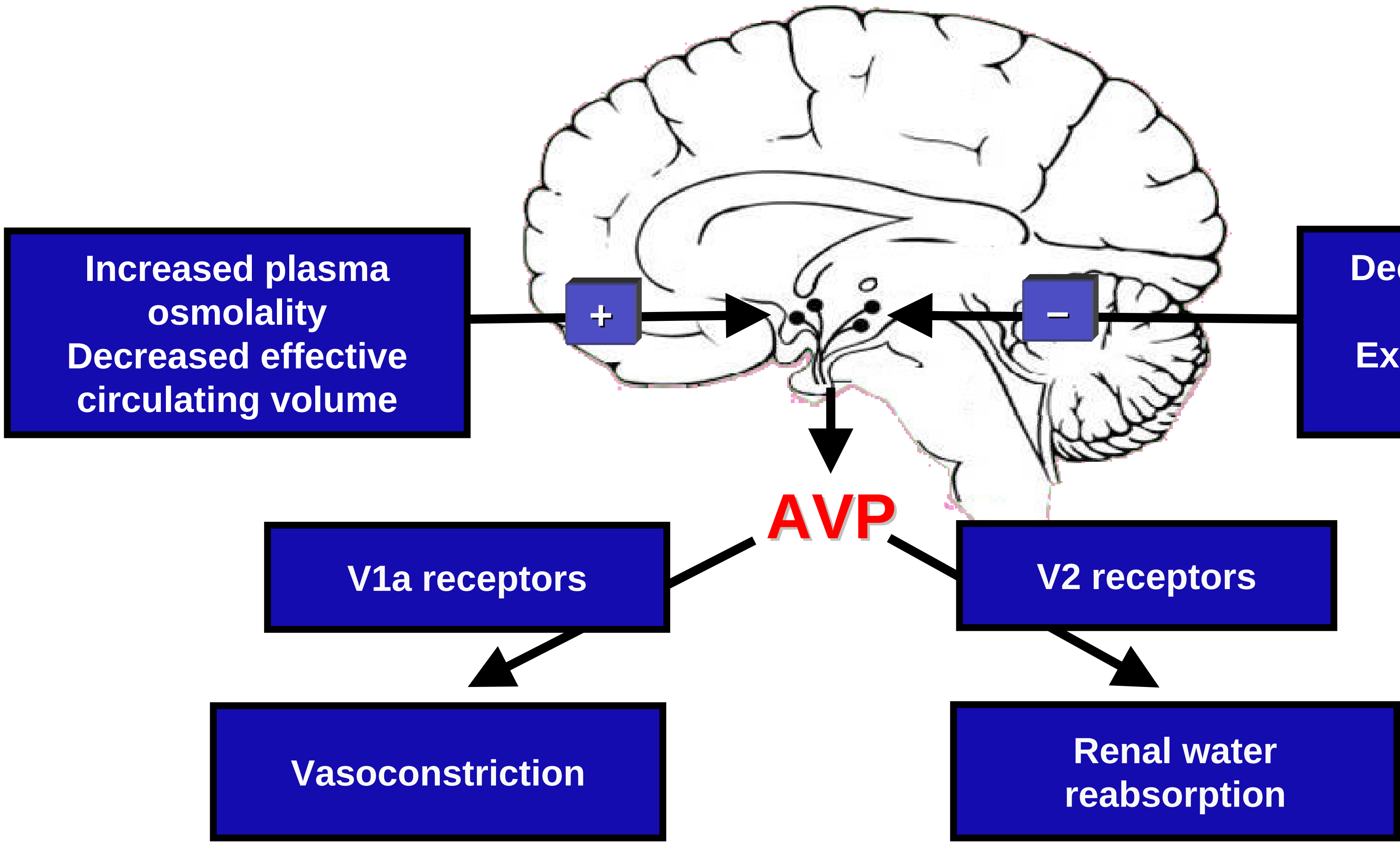
Action of arginine vasopressin on the renal principal cell



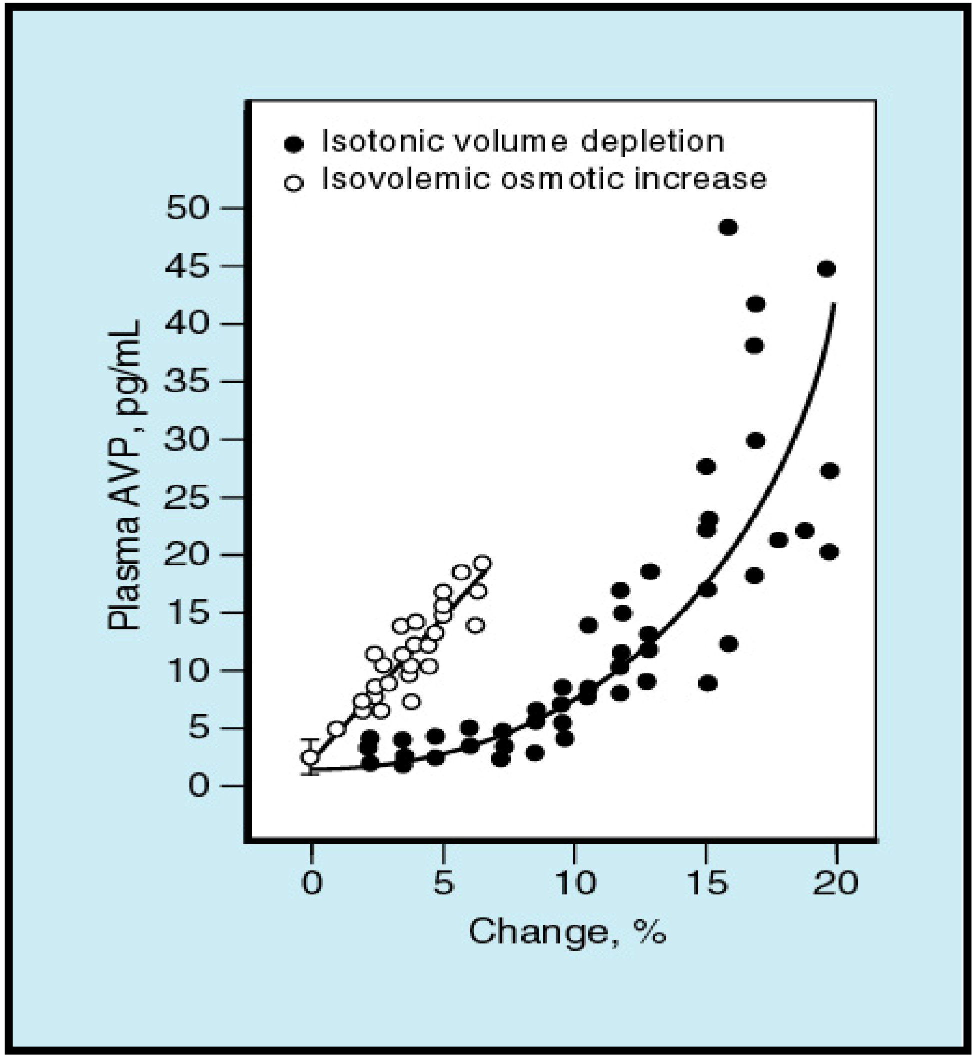


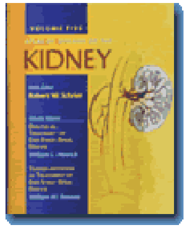
Sumit Kumar & Tomas Berl

Regulation of vasopressin secretion



Osmotic and nonosmotic regulation of vasopressin secretion





Sumit Kumar & Tomas Berl

How does hyponatremia develop?

- Accumulation of water rarely occurs unless the ability to excrete water is impaired
- The capacity of the kidneys to excrete water is normally very large or up to 15-20 L/day
- Thus, enormous water intake is required to cause hypotonic hyponatremia under normal conditions
- If renal water handling is impaired, then modest water intake can cause hypotonicity
- Impaired water excretion leading to hyponatremia, almost invariably results from the inability to suppress the secretion of vasopressin

Classification of hyponatremia

- **Isotonic hyponatremia (pseudohyponatremia)**

  A laboratory artifact caused by severe hypertriglyceridemia or paraproteinemia that is rarely encountered today due to widespread use of ion-specific electrode for serum Na measurement
- **Hypertonic hyponatremia (translocational)**
  - Caused by hyperglycemia or hypertonic mannitol therapy resulting in osmotic shift of water from ICF to ECF, thereby diluting serum Na
  - Serum Na tends to decrease ~1.7 mmol/L for every 5.6 mmol/L (100 mg/dL) serum glucose is above its normal value
- **Hypotonic hyponatremia (dilutional)**

  By far the most common type and is caused by water retention resulting in water excess in relation to sodium stores, which can be decreased, normal or increased

Causes of hyponatremia

- Impaired renal water excretion
  - Decreased extracellular fluid volume
  - Increased extracellular fluid volume
    - Heart failure
    - Cirrhosis
    - Advanced renal failure
  - Normal extracellular fluid volume
    - Thiazide diuretics
    - Syndrome of inappropriate secretion of antidiuretic hormone (SIADH)
    - Adrenal insufficiency
    - Hypothyroidism
    - Low dietary solute intake
- Excessive water intake
  - Psychogenic polydipsia
  - Associated with prolonged exercise

SIADH:

- CNS disorders (including acute psychosis)
- Cancer
- Medications
  - SSRI's
  - Tricyclic antidepressants
  - NSAID's
- Pulmonary disease
- Miscellaneous
  - Postoperative state
  - Pain
  - Severe nausea

Low dietary solute intake

- Healthy individuals on a normal diet excrete 600-900 mosmoles of solute in the urine daily
- If minimum urine osmolality is 60 mOsm/kg, then maximum urine output will be 10-15 L
- Poor dietary intake can lower the daily urinary solute excretion to below 250 mosmoles, resulting in significant reduction in urine volume
- Examples:
  - Beer drinker's potomania - high water intake, low dietary protein
  - Tea and toast hyponatremia - a diet that is deficient in salt and protein
- Hyponatremia develops if fluid intake is greater than the maximum amount of urine output that can be generated

Low dietary solute intake

- Healthy individuals on a normal diet excrete 600-900 mosmoles of solute in the urine daily
- If minimu … maximum urine out …

600 mosmoles ÷ 60 mOsm/kg = 10 L

900 mosmoles ÷ 60 mOsm/kg = 15 L

- Poor diet … lute excretion to below 250 mosmoles, resulting in significant reduction in urine volume
- Examples:
  - Beer drinker’s potomania - high water intake, low dietary protein
  - Tea and toast hyponatremia - a diet that is deficient in salt and protein
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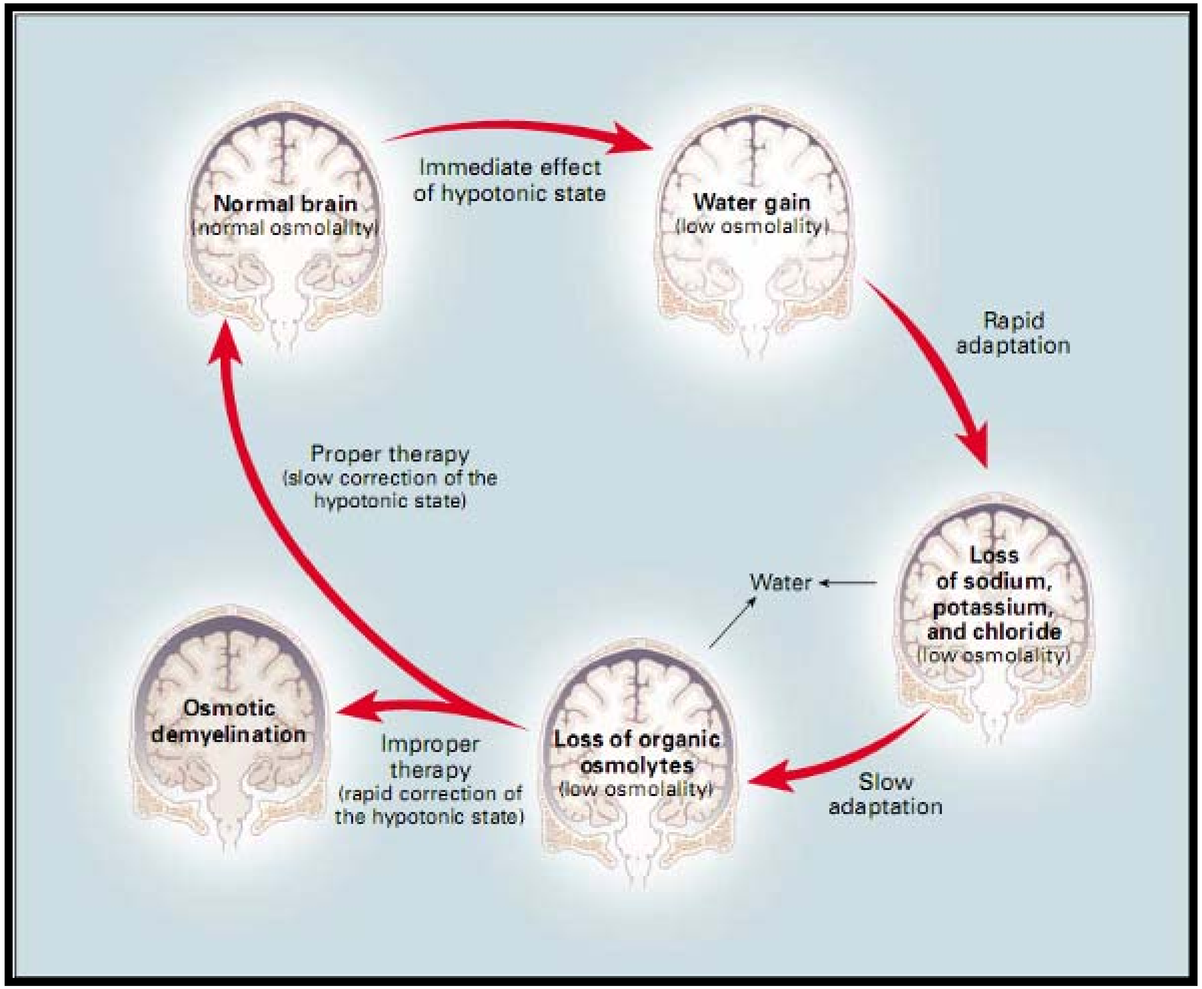
Effects of hyponatremia on the brain and adaptive responses



Androgue & Madias, N Engl J Med 2000;342:1581-89

Clinical features of hyponatremia

- Acute hyponatremia (<48 hr)
  - Seizures
  - Coma
  - Respiratory distress

- Severe cerebral edema
- Risk of death from untreated hyponatremia

- Chronic hyponatremia (>48 hr)
  - Frequently mild or no symptoms
  - Headache
  - Restlessness
  - Muscle cramps
  - Nausea and vomiting
  - Lethargy
  - Confusion and disorientation

- Adaptation minimizes brain swelling
- Risk of injury from overtreated hyponatremia

Clinical settings of acute hyponatremia

- Water intoxication due to compulsory excessive fluid intake
  - Patients with severe psychosis
  - Use of ecstasy (N-methyl-3,4-methylenedioxyamphetamine)
  - Marathon runners
- Postoperative iatrogenic hyponatremia

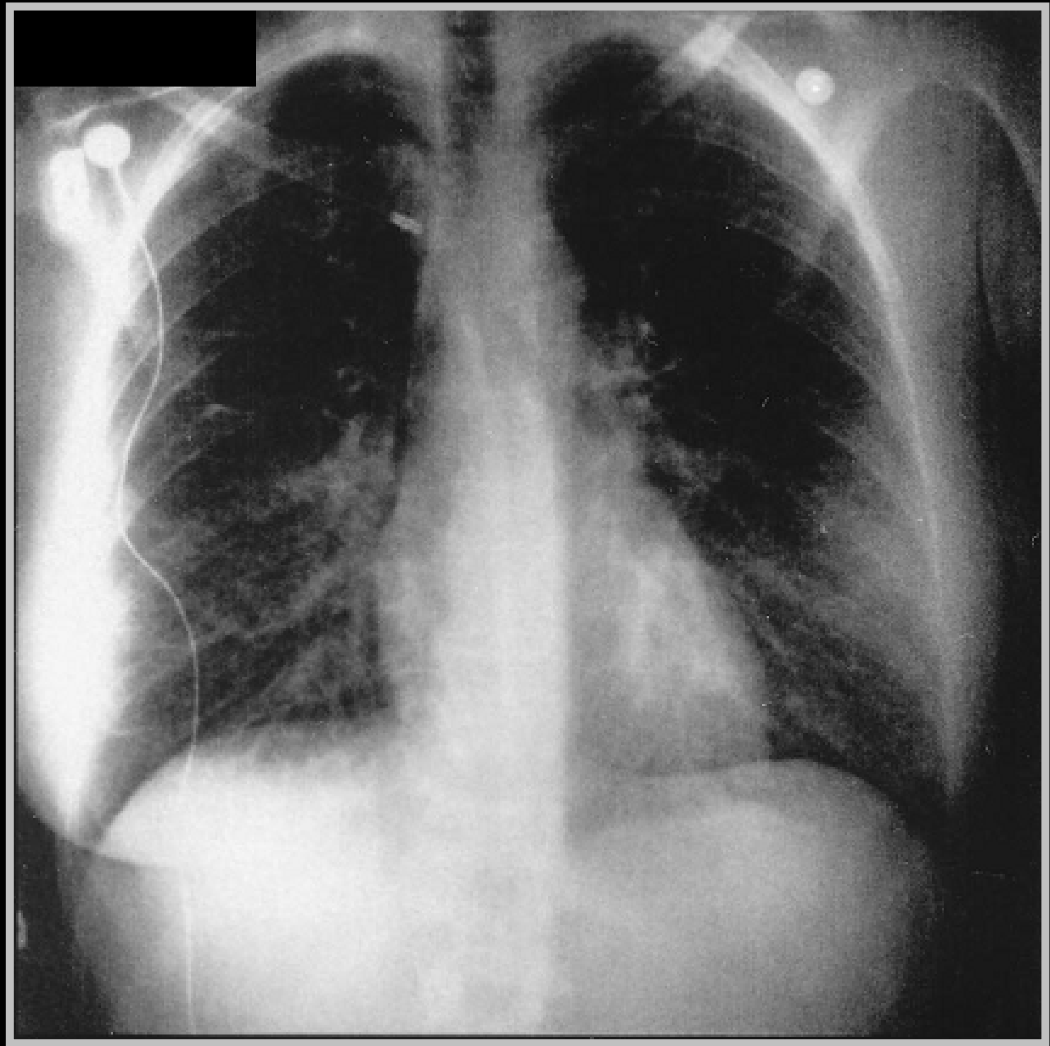
Acute hyponatremia and brain edema in a marathon runner

Hyponatremic brain edema

Normal brain

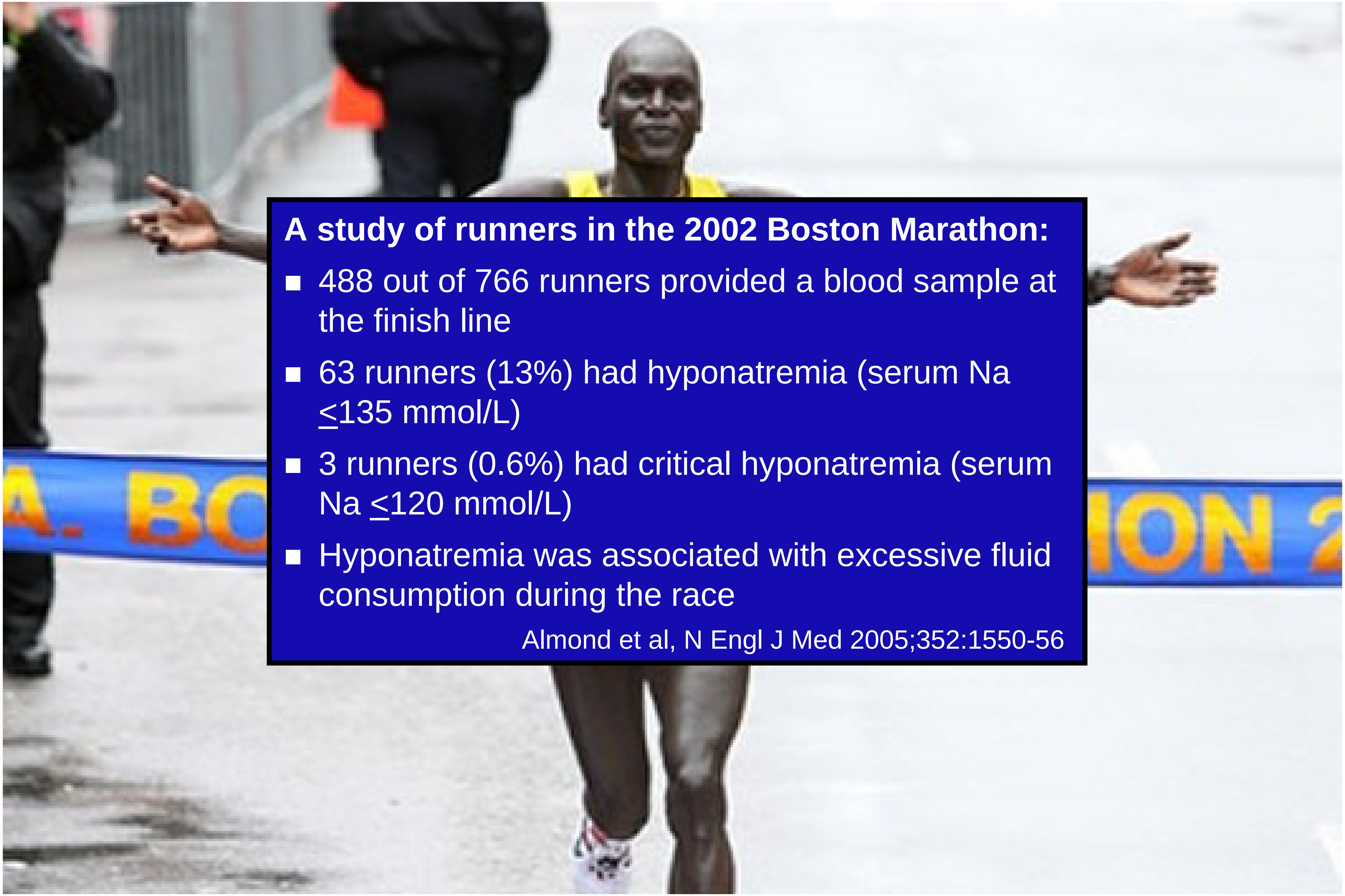
Ayus et al, Ann Int Med 2000;132:711-14

Noncardiogenic pulmonary edema



Ayus et al, Ann Int Med 2000;132:711-14

A. BOSTON MARATHON 2
1



A study of runners in the 2002 Boston Marathon:

- 488 out of 766 runners provided a blood sample at the finish line
- 63 runners (13%) had hyponatremia (serum Na $\leq$135 mmol/L)
- 3 runners (0.6%) had critical hyponatremia (serum Na $\leq$120 mmol/L)
- Hyponatremia was associated with excessive fluid consumption during the race

Almond et al, N Engl J Med 2005;352:1550-56

Chronic hyponatremia

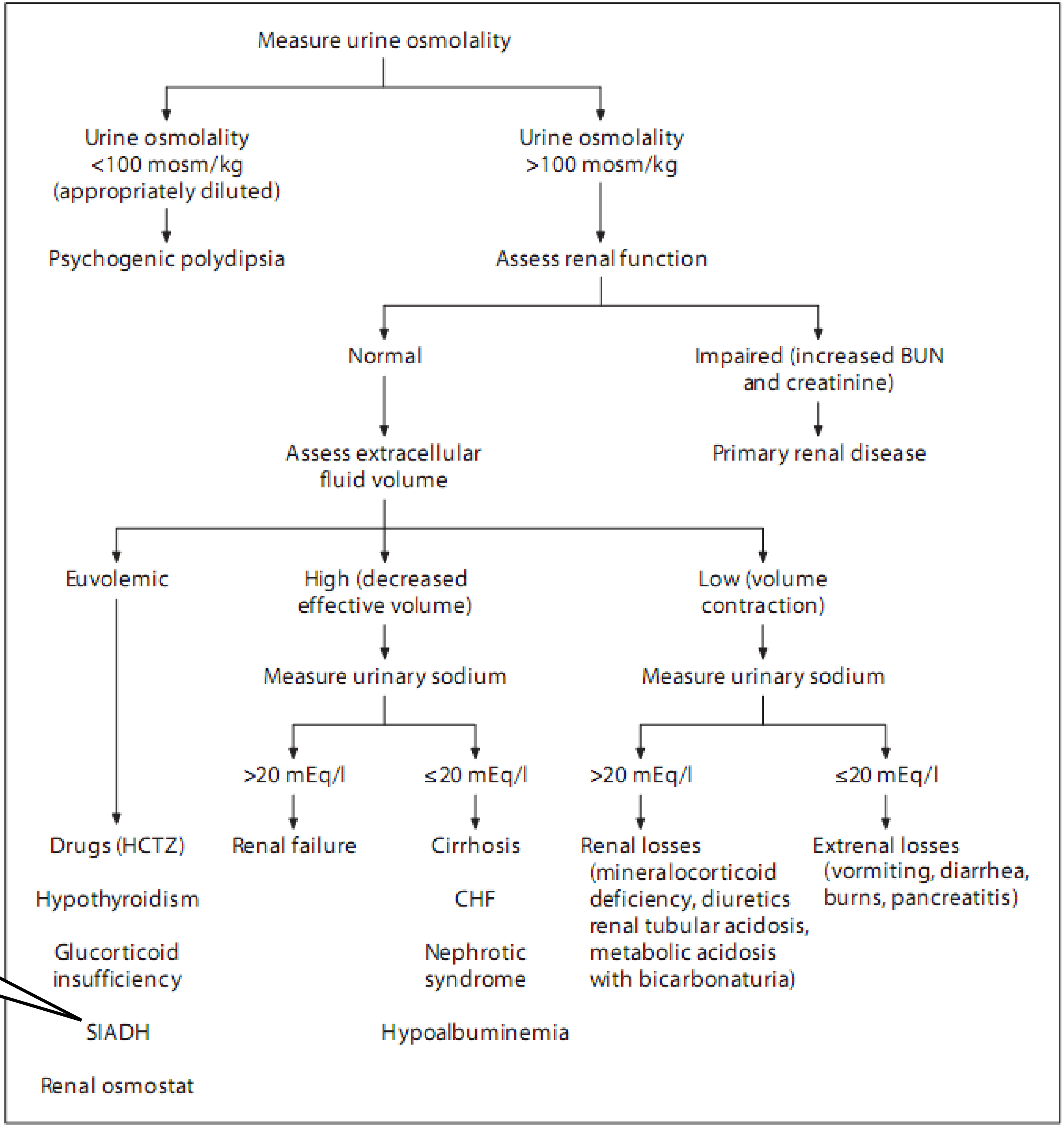
- Frequently “asymptomatic”
- Patients with “asymptomatic hyponatremia” have been found to have a number of problems:
  - Attention impairment
  - Gait instability
  - Falls
  - Increased risk of bone fractures

Algorithm for the diagnosis of hyponatremia

Rai et al, Am J Nephrol 2006;26:579-89

Diagnostic criteria for SIADH:

- Decreased serum osmolality (<275 mOsm/kg)
- Urine osmolality >100 mOsm/kg
- Clinical euvolemia
- Urine Na >40 mmol/L with normal dietary salt intake
- Normal thyroid and adrenal function
- No renal disease
- No recent use of diuretic agents

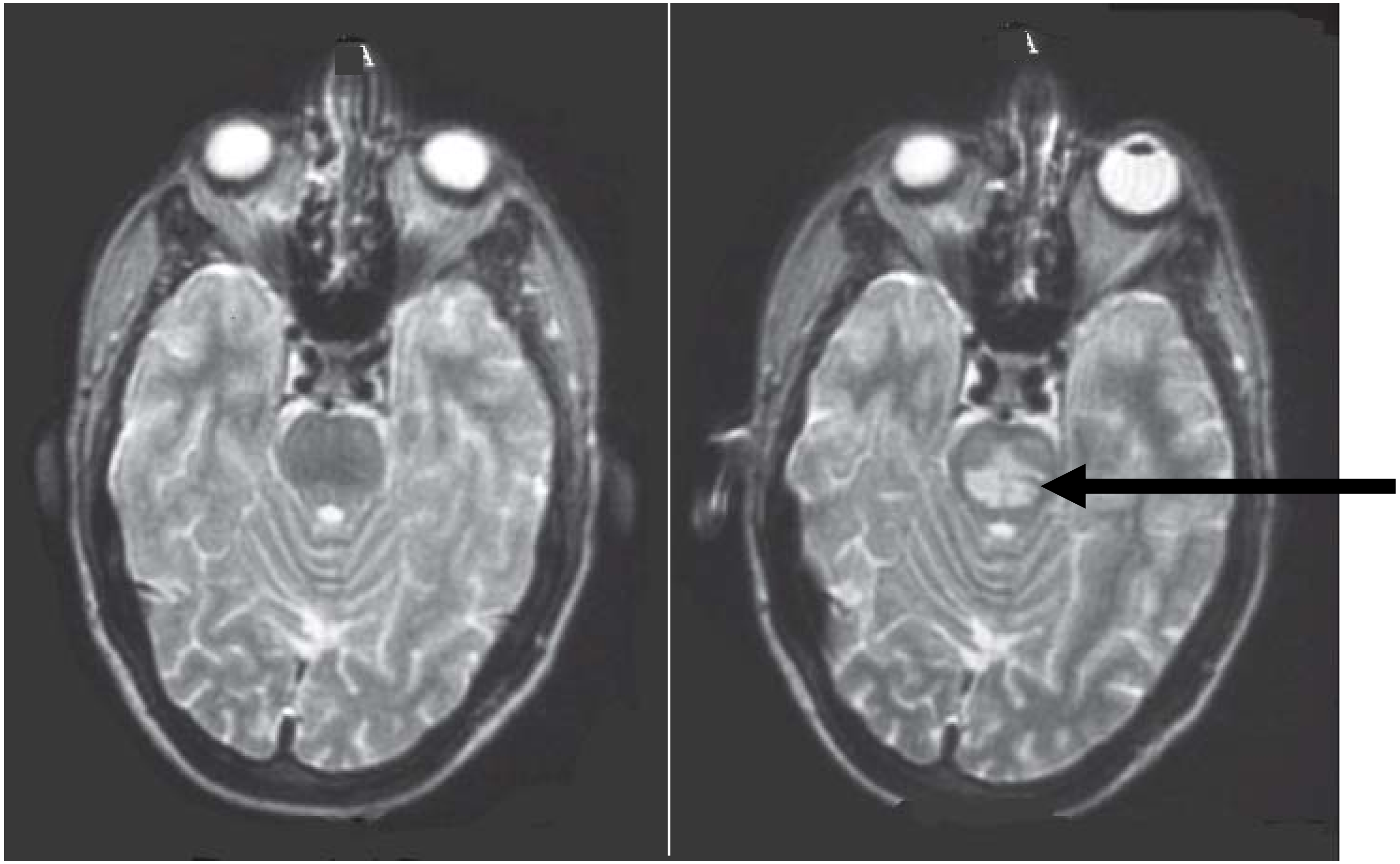


Treatment of hyponatremia can be a dilemma!

- The rate of correction of the serum Na is determined by whether hyponatremia is acute or chronic
- The definition of acute or chronic is largely based on the severity of the clinical features
- Life-threatening acute hyponatremia requires rapid correction of serum Na
- In contrast, the treatment of chronic hyponatremia should be cautious because too rapid correction of the serum Na can result in dangerous osmotic demyelination injury of the brainstem

Osmotic demyelination syndrome

Normal brain | Central pontine myelinolysis



Sveinsson et al, Icelandic Med J 2008;94:665-71

Treatment of acute hyponatremic encephalopathy

- Rapid elevation of the serum Na is necessary, particularly if the clinical manifestations are severe
- Raising the serum Na 4-6 mmol/L over 2-3 hours appears enough to prevent serious neurologic complications
- Administer 3% NaCl (513 mmol/L), 1-2 ml/kg IV per hour
- Should elevate the serum Na approximately 1-2 mmol/L per hour
- Subsequently, the rate of correction should be less than 10 mmol/L per 24 hours

How much hypertonic saline should be administered?

Androgue-Madias formula:

$$\text{Change in serum Na} = \frac{\text{infusate Na} - \text{serum Na}}{\text{total body water} + 1}$$

- Estimates the effect of 1 liter of any fluid infused on serum Na
- Assumes all of the infusate is retained; does not consider urine losses of electrolyte or water

Adrogué et al. N Engl J Med. 2000;342:1581-89

Chronic hyponatremia: rate of correction and outcome

- Clinical observations suggest that the risk of demyelination injury of the brain is increased if the rate of correction of the serum Na is faster than 12 mmol/L in the first 24 hours and 18 mmol/L in 48 hours
- This is particularly important in patients with extreme hyponatremia (serum Na <105 mmol/L)

Treatment of chronic hyponatremia: recommended rates of correction

- Goals:
  - 6-8 mmol/L in 24 hours
  - 12-14 mmol/L in 48 hours
  - 14-16 mmol/L in 72 hours
- Limits:
  - Less than 10 mmol/L in 24 hours
  - Less than 18 mmol/L in 48 hours
  - Less than 20 mmol/L in 72 hours

Sterns et al, Semin Nephrol 2009;29:282-99

Isotonic saline

- Effective in correcting hyponatremia caused by volume depletion
  - Eliminates volume stimulus for vasopressin secretion
  - Unpredictable onset of water diuresis
- In SIADH, isotonic saline is ineffective and may lower the serum sodium
- If the sodium contained in a liter of saline is excreted in less than a liter of urine; the net effect is free water retention
- Thus, we reserve isotonic saline for hyponatremic patients who require treatment for volume depletion

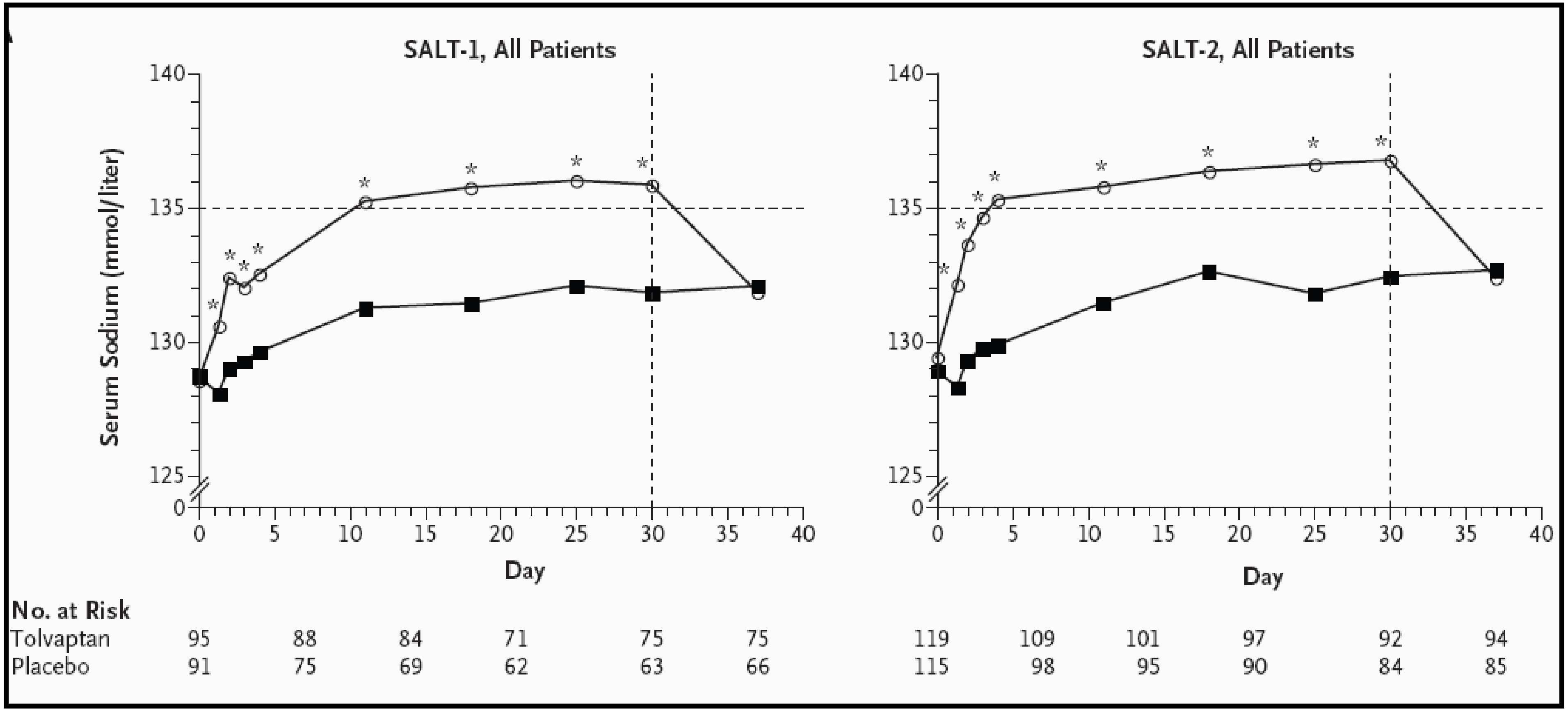
Treatment of sustained euvolemic and hypervolemic hyponatremia

- Conventional treatment options are suboptimal because of limited efficacy and poor safety and tolerability
- Identify and treat the underlying cause
- Fluid restriction 0.5-1.0 L/day is the mainstay but poorly tolerated long-term
- Drug therapies:
  - Loop diuretics plus increased salt intake
  - Demeclocycline 600-1200 mg/day
  - Lithium 600-900 mg/day
  - Urea 30 g/day
  - Vasopressor receptor antagonists

What level of fluid restriction should be recommended?

$\frac{UNa + UK}{SNa}$	**Fluid restriction**
>1	<500 ml per day
1	500-700 ml per day
<1	<1000 ml per day

Treatment hyponatremia with tolvaptan
Randomized controlled trial

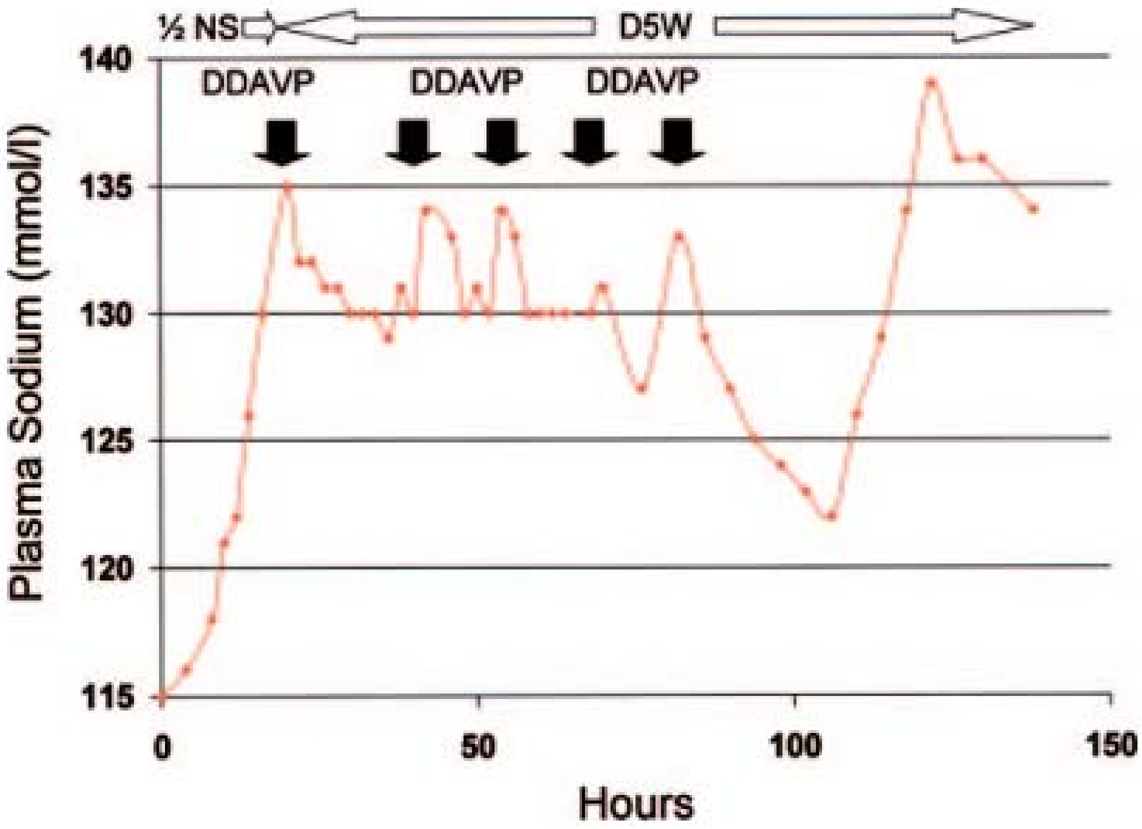


Schrier et al, N Engl J Med 2006;355:2099-122

Overcorrection of serum sodium

- When a reversible cause of water retention is corrected, vasopressin levels fall and the excretion of dilute urine causes serum Na to rise rapidly
- Maximally dilute urine increases the serum Na by >2 mmol/L/hr
- Can occur when excessive water drinking is discontinued or impaired renal water excretion is corrected
- Continued vigilance is essential:
  - Monitor urine output and measure serum Na frequently
- If urine output suddenly increases, then one should attempt to counteract the elevation of serum Na
  - Administer 5% dextrose IV
  - Administer desmopressín (DDAVP) parenterally

Reversal of inadvertent overcorrection of hyponatremia



Perianayagam et al, Clin J Am Soc Nephrol 2008;3:331-6

Case Presentation

- A 67 year old female was brought to the emergency department following a seizure that occurred in the setting of progressive weakness for several days
- There was a history of recently diagnosed small cell lung cancer
- On physical exam she was lethargic and confused; Wt 60 kg, BP 125/75 without orthostatic drop, P 90; lungs were clear and there was no edema
- Laboratory studies
  - Blood: Na 112 mmol/L, K 4.2 mmol/L, Cl 76 mmol/L, CO_2 26 mmol/L, creatinine 80 µmol/L (0.9 mg/dL), osmolality 234 mOsm/kg
  - Urine: Osmolality 660 mOsm/kg, Na 102 mmol/L, K 64 mmol/L
- CT scan of the brain showed evidence for mild cerebral edema but no other abnormalities

Diagnosis

- How do you judge the volume status of the patient?
  - Euvolemic
- What is a likely cause of the hyponatremia?
  - SIADH due to ectopic production of vasopressin by the lung cancer
- Is the hyponatremia acute or chronic?
  - Serious neurological signs and symptoms indicate acute hyponatremia with brain edema
  - Duration unknown, but probably a significant chronic component

Immediate management

- How should this patient be treated?
  - Hypertonic saline with close monitoring
  - The goal is to raise the serum Na by ~5-6 mmol/L over 2-3 hours
- How much hypertonic (3%) saline should be administered?
- Concurrent furosemide therapy may be required to increase free water clearance
- Closely monitor the patient’s clinical status, urine output and and measure serum Na every 1-2 hours

Immediate management

- How should this patient be treated?
  - Hypertonic saline with close monitoring

Androgue-Madias formula:
Change in serum Na = infusate Na – serum Na ÷ total body water + 1
Change in serum Na = 513 mmol – 112 mmol/L ÷ 30 L + 1 = 12.9 mmol/L
Thus, 1 L of 3% saline will increase the serum Na by 12.9 mmol/L
6 ÷ 12.9 = 0.465 L => 155 mL per hour will be needed

- Concurrent furosemide therapy may be required to increase free water clearance
- Closely monitor the patient’s clinical status, urine output and and measure serum Na every 1-2 hours

Long-term management

- Fluid restriction
- How much?
- To get any meaningful improvement in serum Na, would need to completely eliminate all p.o. or i.v. electrolyte-free H_2O
- Additional strategies:
  - Increase daily solute load (salt tablets, urea)
  - Furosemide
  - Tolvaptan
- The patient needs continued close monitoring

Long-term management

- Fluid restriction

Estimation of electrolyte-free water excretion:

Urine Na + K ÷ serum Na

166 ÷ 112 = 1.4

>1 indicates that no free-water excretion is occurring

- Additional strategies:
  - Increase daily solute load (salt tablets, urea)
  - Furosemide
  - Tolvaptan
- The patient needs continued close monitoring


Thank you for your attention!