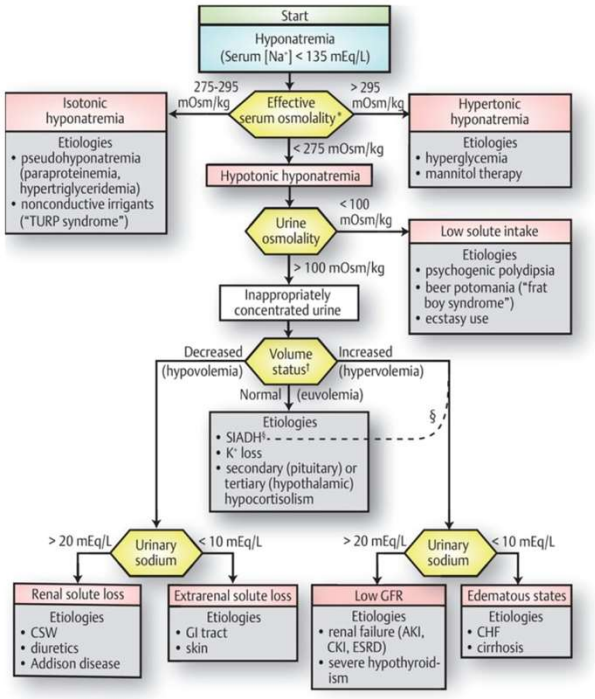
Hyponatremia: The Big Picture

PennState

1

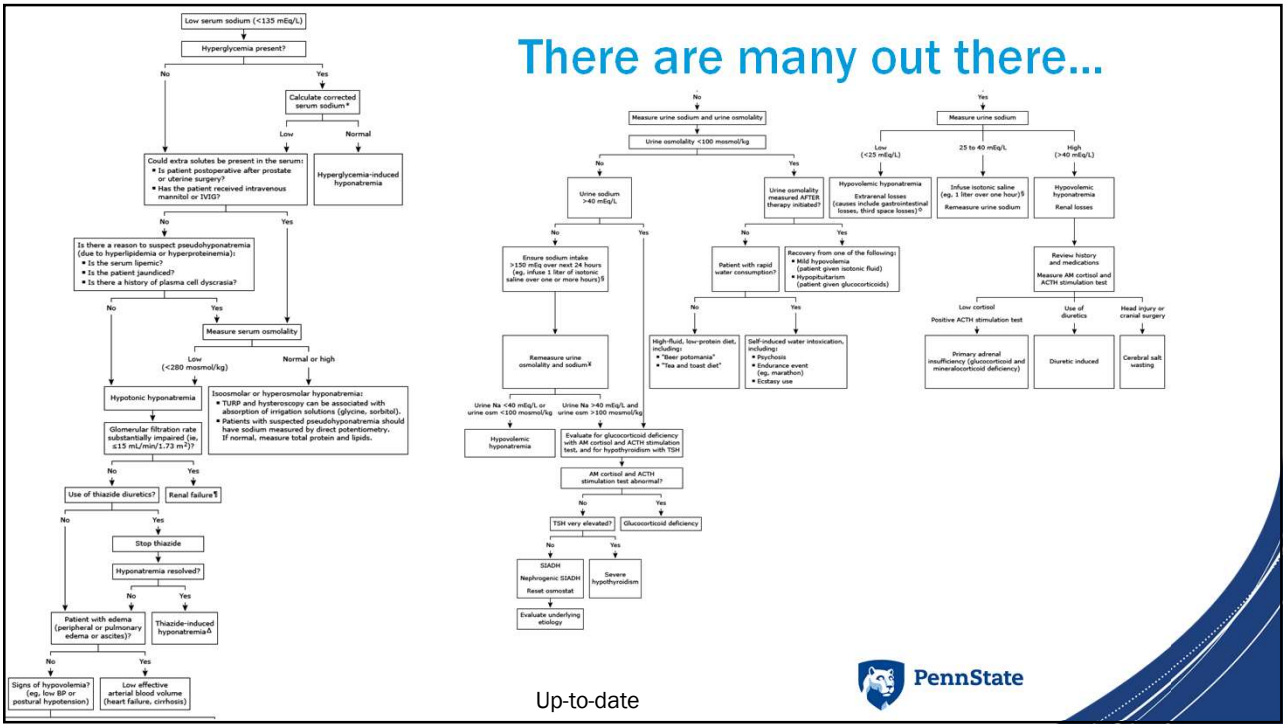
The clinical algorithm



Greenberg

2

There are many out there...



Up-to-date

PennState

3

Let's walk through an NCCU example case

- 58 yr old man comes in with diffuse SAH
- Na starts to downtrend on daily BMP
  - 141, 137, 132…
  - What could be going on?

PennState

4

Sx to look out for:

- mild ([Na] < 130 mEq/L) or gradual hyponatremia: anorexia, headache, difficulty concentrating, irritability, dysgeusia, and muscle weakness.
- severe (< 125 mEq/L) or a rapid drop (> 0.5 mEq/hr:) neuromuscular excitability, cerebral edema, muscle twitching and cramps, nausea/vomiting, confusion, seizures, respiratory arrest and possibly permanent neurologic injury, coma or death.

PennState

5

Chronicity

< 48 hours is considered acute

>48 hours duration or of unknown duration is chronic

➢hyponatremia that occurs outside the hospital is usually chronic and asymptomatic except in marathoners and MDMA ("ecstasy") drug users

PennState

6

Any names or ages used on the upcoming slides are fictitious and not referring to an actual patient.

Our own NCCU guidelines

CSW vs. DI vs. SIADH:

	Cerebral Salt Wasting (CSW):	Diabetes Insipidus (DI):	Syndrome of inappropriate antidiuretic hormone secretion (SIADH):
Urine Output	Increased	Increased	Decreased
Urine Osmo	High	Low	High
Urine Na	High	Low	High
Serum Osmo	Low	High	Low
Serum Na	Low	High	Low
Volume Status	Hypovolemic	Normal to Hypovolemic	Hypervolemic
Plasma ADH Levels	Normal	Low	High
Treatments	Give volume Replace Na (HTS, salt tabs) Fludrocortisone	Drink to thirst, Central DI treat w/ DDAVP Consider 0.45% NS	Fluid restriction Replace Na Conivaptan

7

CNS Etiologies of SIADH

CNS disorders

1. infection:
   a. encephalitis
   b. meningitis: especially in peds
   c. TB meningitis
   d. AIDS
   e. brain abscess
2. head trauma: 4.6% prevalence
3. increased ICP: hydrocephalus, SDH…
4. SAH
5. brain tumors
6. cavernous sinus thrombosis
7. ★ post craniotomy, especially following surgery for pituitary tumors, craniopharyngiomas, hypothalamic tumors
8. MS
9. Guillain-Barré
10. Shy-Drager
11. delirium tremens (DTs)

PennState

8

CNS Etiologies of CSW

Any intracranial disease that results in renal salt loss, producing hyponatremia and a decrease in extracellular fluid volume

>thought to be secondary to natriuretic factor or direct neurological manifestations

>also many camps that believe this to be an extension of SIADH despite the clinical algorithms we use to differentiate between them

Table 5.5 Comparison of CSW and SIADH[13]

Parameter	CSW	SIADH
★ Plasma volume	↓ (< 35 ml/kg)	↑ or WNL
★ Salt balance	negative	variable
Signs & symptoms of dehydration	present	absent
Weight	↓	↑ or no Δ
PCWP	↓ (< 8 mm Hg)	↑ or WNL
CVP	↓ (< 6 mm Hg)	↑ or WNL
Orthostatic hypotension	+	±
Hematocrit	↑	↓ or no Δ
Serum osmolality	↑ or WNL[a]	↓
Ratio of serum [BUN]:[creatinine]	↑	WNL
Serum [protein]	↑	WNL
Urinary [Na^+]	↑↑	↑
Serum [K^+]	↑ or no Δ	↓ or no Δ
Serum [uric acid]	WNL	↓

PennState

9

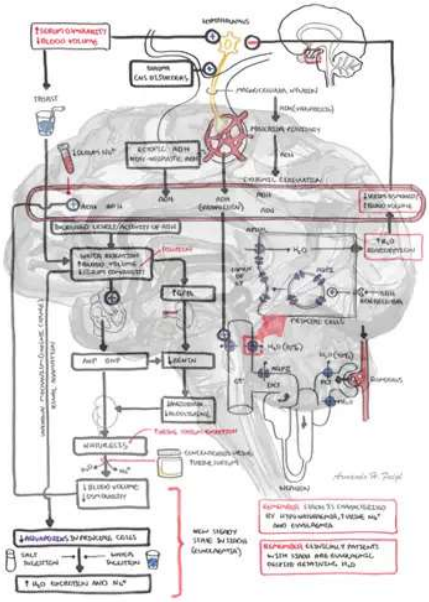
The simplified diagnostic W/U for Low Na

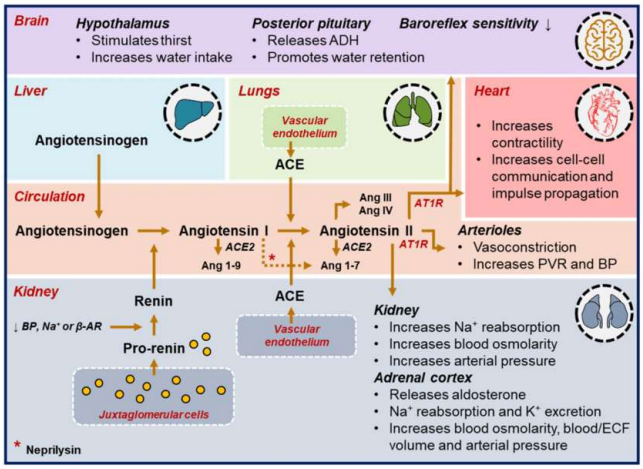
Serum osmolality → Urine osmolality → Volume status → Urine Na

PennState

10

But the system is dynamic, not steady-state

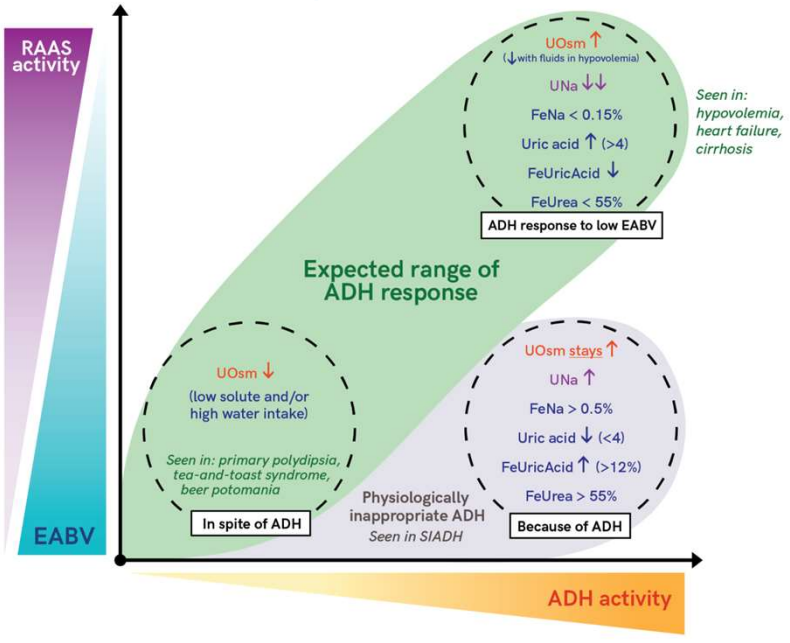




PennState

11

Let's reframe the W/U in terms of RAAS & ADH



12

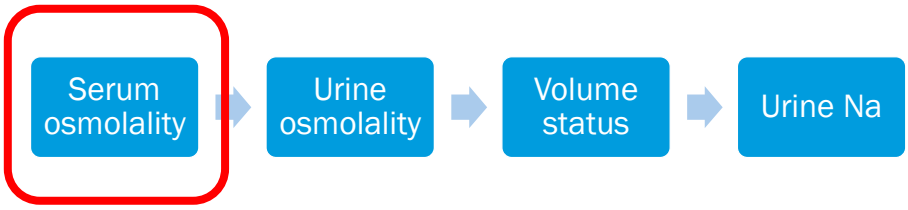
Let's go back to our case

- We know his sodium is low, and we are worried about CSW or SIADH
- What do we want to measure next? (for any hyponatremia pt)

PennState

13

First: Is it "true" hyponatremia?



PennState

14

Any names or ages used on the upcoming slides are fictitious and not referring to an actual patient.

True hyponatremia==low serum osmolality (<280)

This makes sense when we look at the equation for serum osmolality:

SOsm= 2 [Na+] + [Glu]/18 + [BUN]/2.8

BUT: if not low osms→could be hyponatremia w/ other osmoles at play

-hyperglycemia, high BUN
-ETOH, toxic alcohol, iodinated contrast

Note: Serum osmolality should not be measured serially unless you think there has been a major change in the system

PennState

15

Side note: what the heck is pseudohyponatremia?

Water content of plasma is 93% and solute content is 7%

When sodium level is measured, the serum sample is diluted and then corrected by that factor of 0.93.

If the solute content is much higher (high triglycerides or protein levels), then that correction factor is off and the measured sodium is not correct, so you can get ”low” sodium and normal or elevated osms.

Fun fact of the day: in the 50s serum sodium was measured by a process known as flame emission spectrophotometry (FES), in which a diluted sample of serum was sprayed across a flame.

PennState

16

Our patient has a low serum osm of 274 (<280)

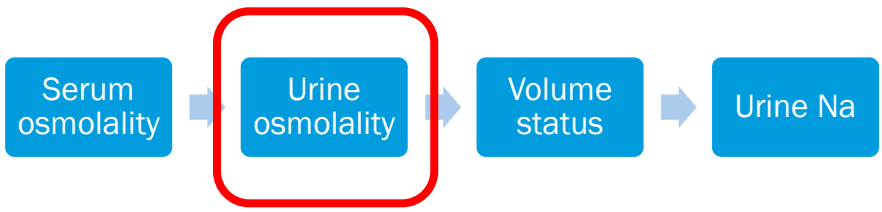
So now we know that there is a true hypo-osmolar hyponatremia

What's next?

PennState

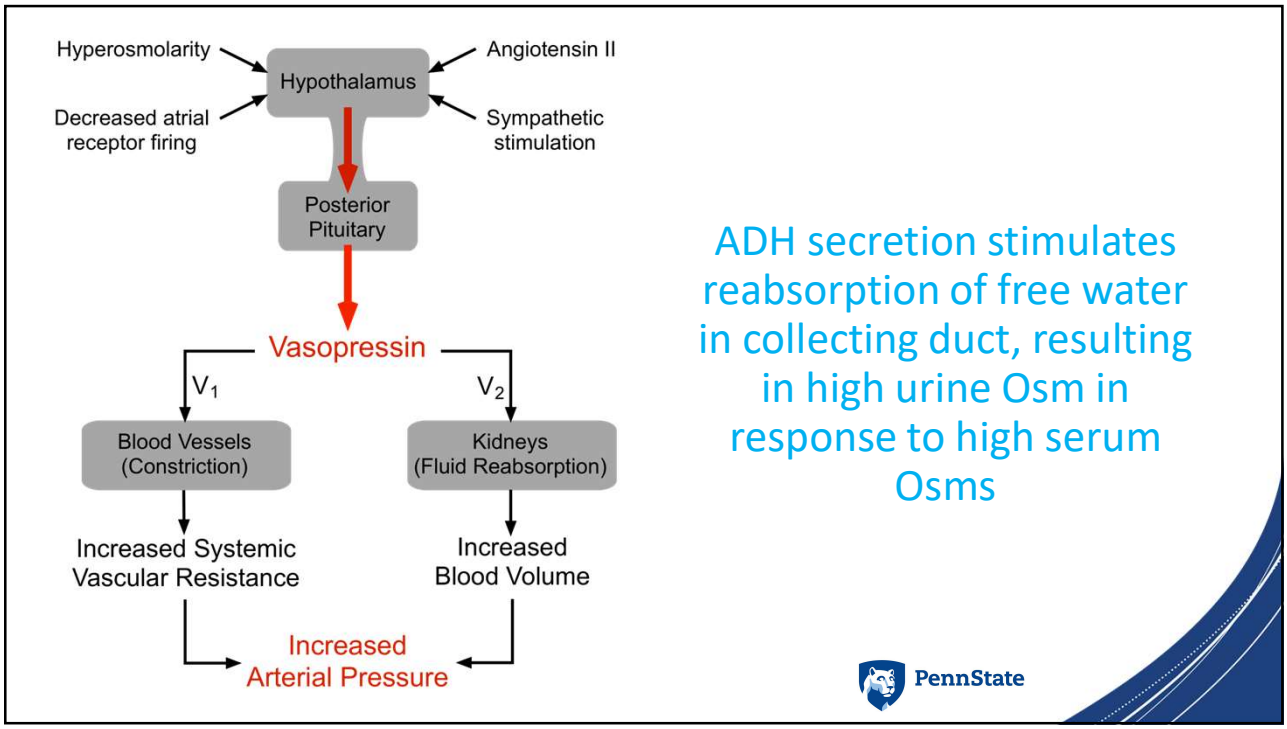
17

What is the ADH Activity



PennState

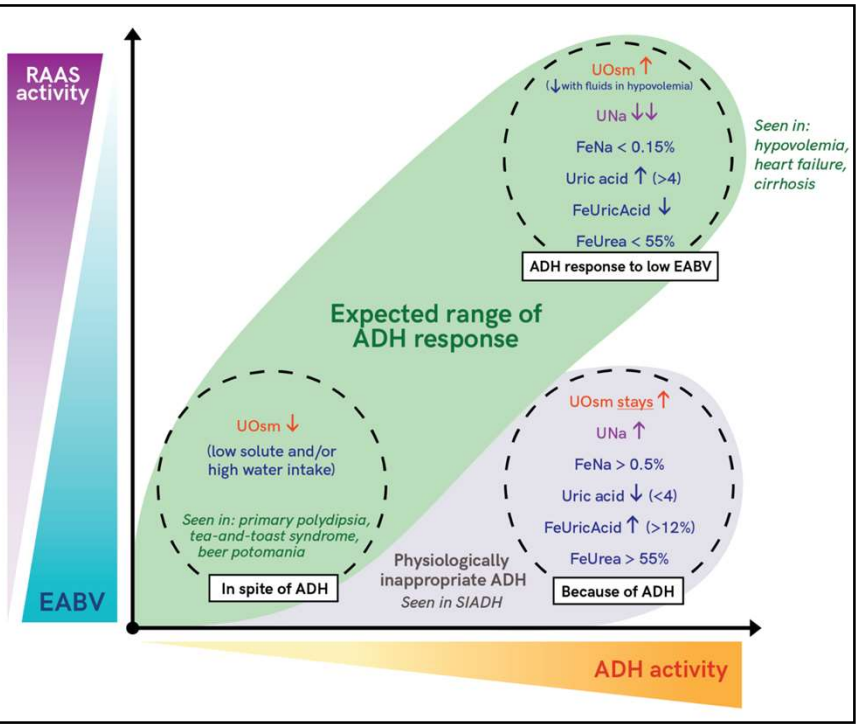
18



19

Our patient's urine osmolality was 292 (high, >100)

What do we check next?



20

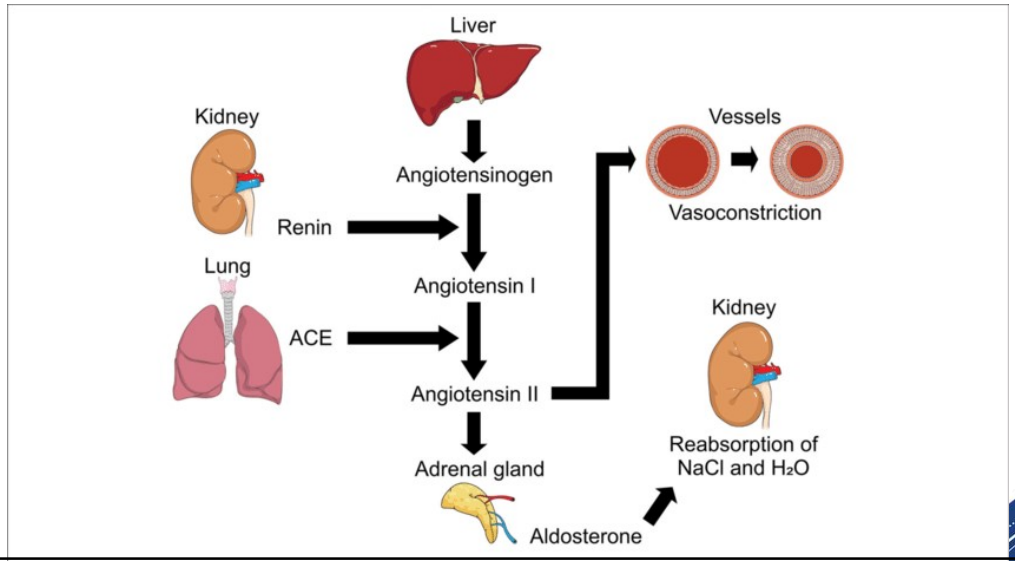
What is the RAAS Activity

Serum osmolality → Urine osmolality → Volume status → Urine Na

PennState

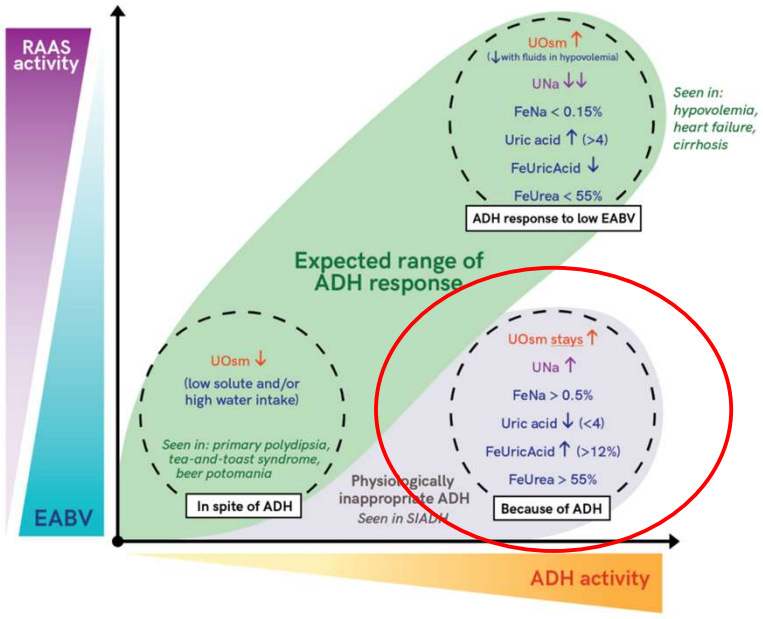
21

RAAS pathway activated by decreased renal perfusion & decreased serum sodium



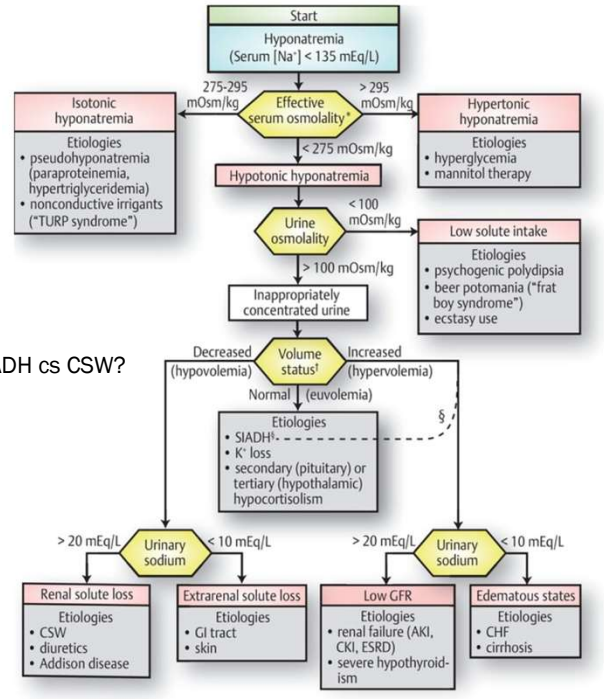
22

Our patient's urine sodium was 44



23

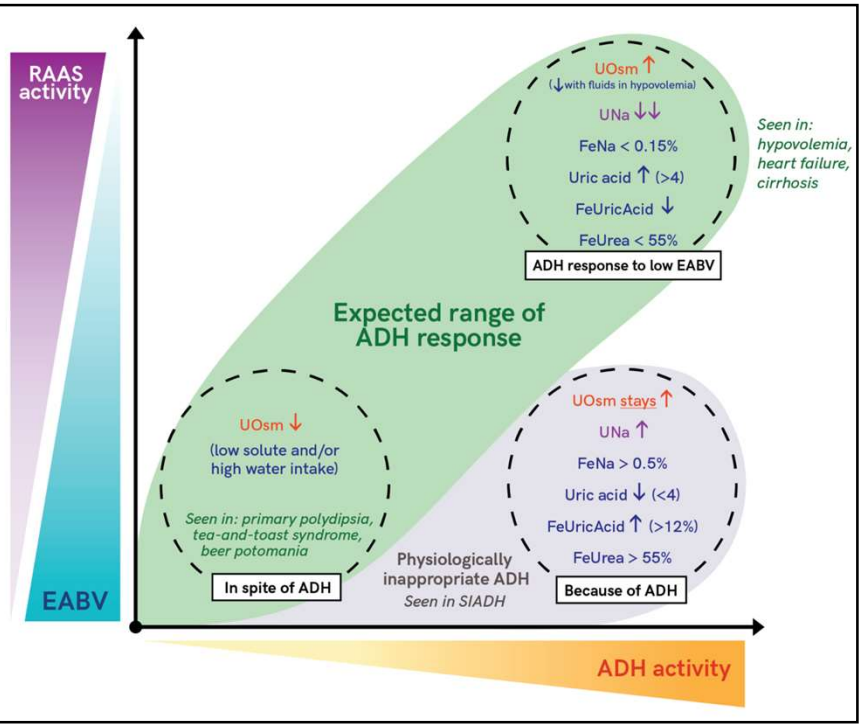
Where in the clinical algorithm could we have gotten tripped up?



SIADH cs CSW?

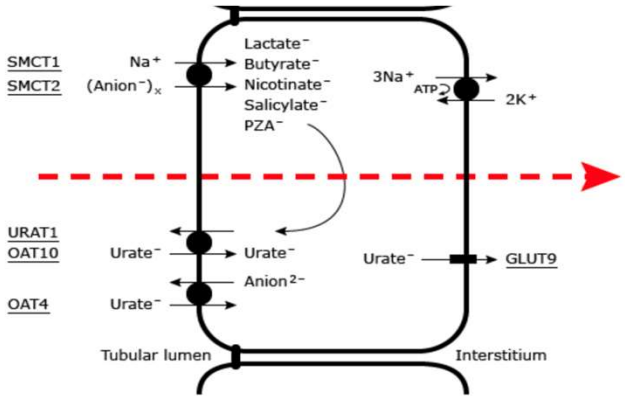
24

Uric Acid = 2.9
FeUricAcid = 7.69
FeNA=0.6



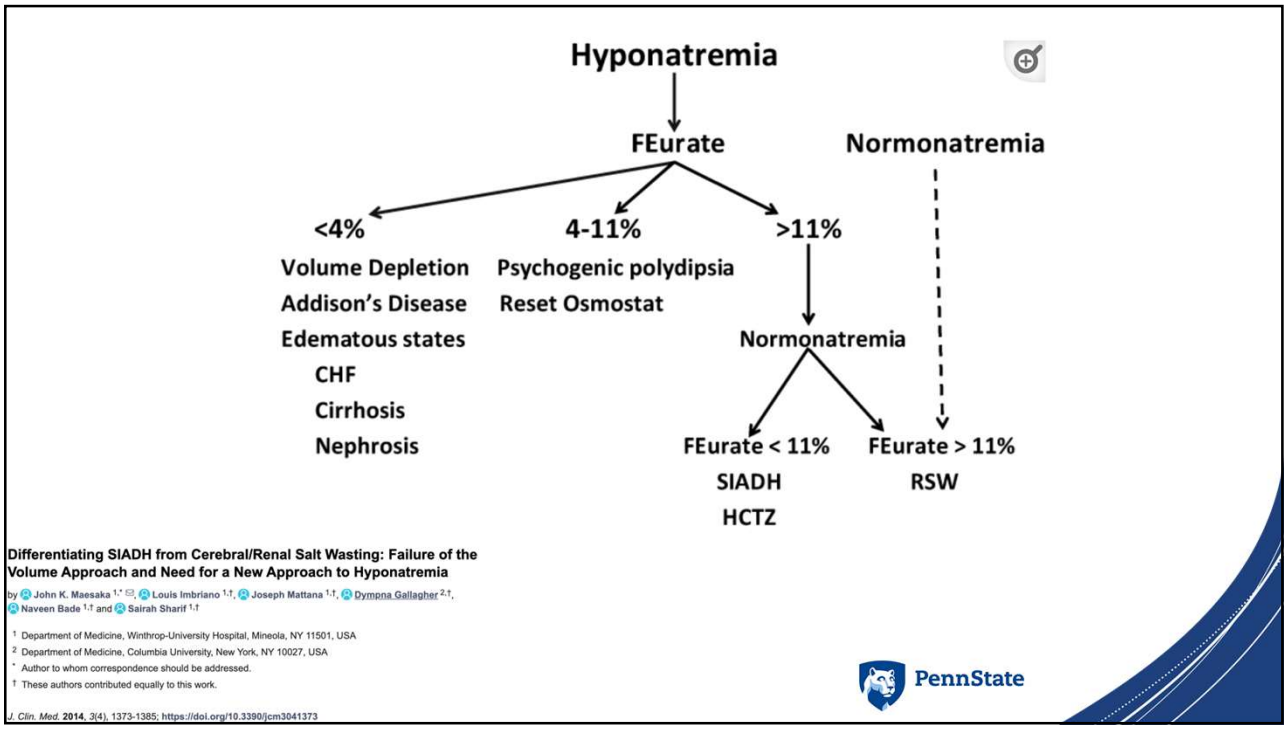
25

Hold up: If CSW has low volume then shouldn't uric acid be high in CSW???

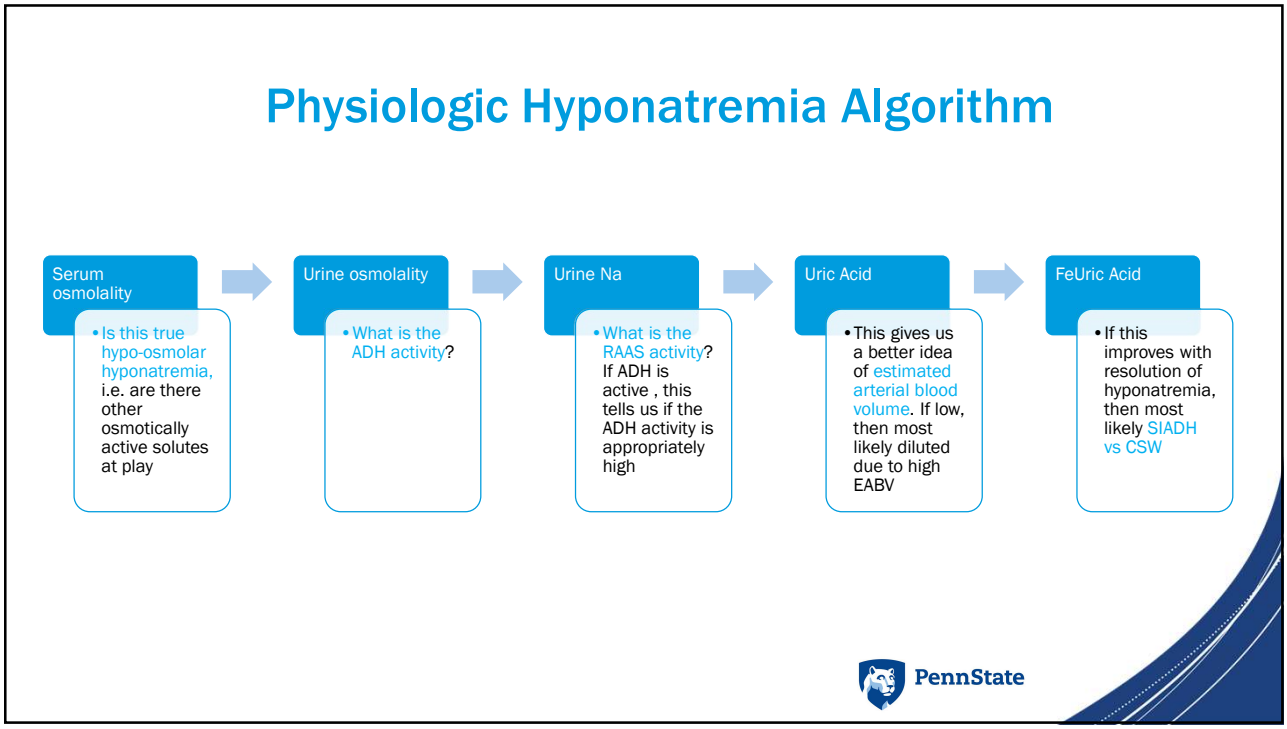


Sodium-dependent anion transport by SMCT1 and SMCT2 increases intracellular concentrations of monovalent anions that exchange with luminal urate (URAT1/OAT10). OAT4 appears to exchange urate with divalent anions. GLUT9 is the exit pathway for urate at the basolateral membrane.

26



27



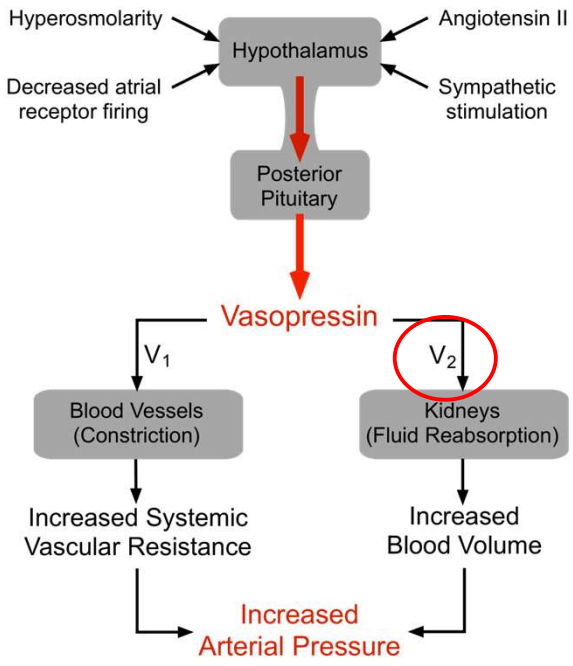
28

Pivoting

- How can we treat hyponatremia in SIADH other than with fluid restriction, 3%, 23.4%, mannitol, et

PennState

29



ADH secretion stimulates reabsorption of free water in collecting duct, resulting in high urine Osm in response to high serum Osms

PennState

30

The role of tolvaptan

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Tolvaptan, a Selective Oral Vasopressin V_2-Receptor Antagonist, for Hyponatremia

Robert W. Schrier, M.D., Peter Gross, M.D., Mihai Gheorghiade, M.D., Tomas Berl, M.D., Joseph G. Verbalis, M.D., Frank S. Czerwiec, M.D., Ph.D., and Cesare Orlandi, M.D., for the SALT Investigators*

PennState

31

Dual benefit in treating hyponatremia & addressing brain edema?

Research report

Tolvaptan attenuated brain edema in experimental intracerebral hemorrhage

Qiang Tan[a], Yuhan Li[b], Peiwen Guo[a], Jiru Zhou[a], Zhouyang Jiang[a], Xin Liu[a], Zhi Chen[a], Hua Feng[a,*]

[a] Department of Neurosurgery, Southwest Hospital, Third Military Medical University, Army Medical University, Chongqing 400038, China
[b] State Key Laboratory Of Silkworm Genome Biology, Southwest University, No. 2 Rd Tiansheng, Beibei District of Chongqing, 400715, China

PennState

32

Any names or ages used on the upcoming slides are fictitious and not referring to an actual patient.

Back to the basic tx paradigm

CSW vs. DI vs. SIADH:

	Cerebral Salt Wasting (CSW):	Diabetes Insipidus (DI):	Syndrome of inappropriate antidiuretic hormone secretion (SIADH):
Urine Output	Increased	Increased	Decreased
Urine Osmo	High	Low	High
Urine Na	High	Low	High
Serum Osmo	Low	High	Low
Serum Na	Low	High	Low
Volume Status	Hypovolemic	Normal to Hypovolemic	Hypervolemic
Plasma ADH Levels	Normal	Low	High
Treatments	Give volume Replace Na (HTS, salt tabs) Fludrocortisone	Drink to thirst, Central DI treat w/ DDAVP Consider 0.45% NS	Fluid restriction Replace Na Conivaptan

33

This is all good and nice, but…

- Most of our SAIDH pts in the ICU have SAH and we need to maintain at least euvolemia to decrease the risk of vasospasm
- So at the end of the day discerning SIADH from CSW tends to be more academic and doesn't really help guide tx all that much in many of our pts

PennState

34

Pro-tip for tx mild SIADH

- **Predictors if fluid restriction will work**: generally if patient is excreting free water
  - Urine-to-plasma electrolyte ratio:
    - **(Urine Sodium + Urine Potassium)/Serum Sodium**
      - if <1 (actively excreting free water), will likely respond to fluid restriction
      - if >1 (retaining free water), will likely NOT respond to fluid restriction alone
  - Urine osmolality
    - if UOsm <500 (rule of thumb), the patient will likely respond
    - if UOsm >500 (rule of thumb), the patient will likely NOT respond to fluid restriction alone
- **Salt tabs**:
  - Doses commonly prescribed are often not high enough, and if we increase dosing, can often lead to medical side effects (e.g. HTN)
  - Makes patients thirsty and they will just drink more water
  - Retrospective cohort study shows modest (5.2 mEq/L) improvement in serum sodium in euvolemic hyponatremia after 48 hr tx

PennState

35

Discussion & Questions

UNa reveals RAAS activity. UOsm reveals ADH activity.
ADH secretion is appropriate only when RAAS is active.

36