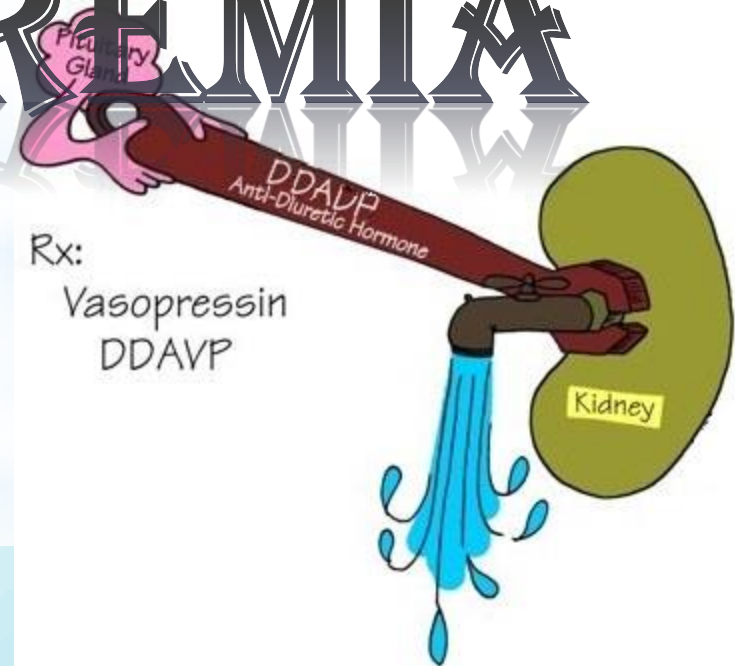


INDICATION OF DDAVP IN HYPONATREMIA




**TORONTO GENERAL
HOSPITAL**

17th International Congress of Nephrology, Dialysis, and Transplantation

Tabriz, Iran 19-22 November 2019



International Society of Nephrology



Iranian Society of Nephrology

* HypoNatremia

- * GIM/Nephrology Epitome
- * Most Clinician/ Nephrologists find it challenging
- * Rapid Tonicity correction of chronic & profound hyponatremia
 - * May result in Osmotic Demyelination
 - * Cause permanent brain damage

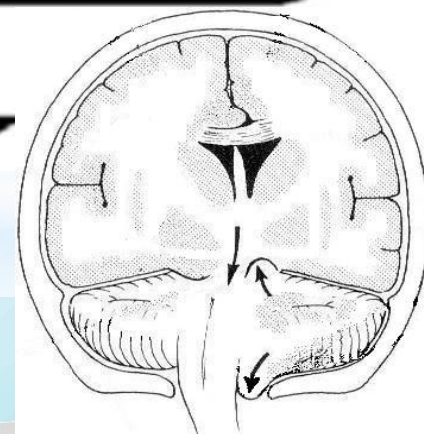
DDxVP



**Rapid Correction
H₂O diuresis**

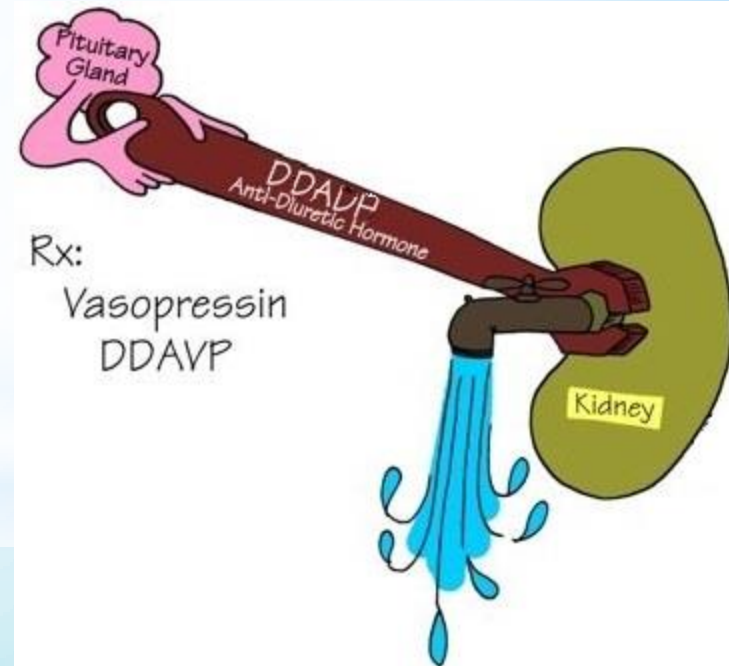
**OSMOTIC DEMYELINATION SYNDROME
BRAIN CELL SWELLING & HERNIATION**

Worsening HypoNa →



- * **High-risk groups for CPM**
- * **Chronic alcoholism, malnutrition, Hypokalemia, liver disease,**
- * **Burn, dialysis patients**
- * **HIV-AIDS, diuretic overuse, eating disorders (anorexia or bulimia)**
- * **Rapid hyperNa post HypoNa brain surgery causing DI**

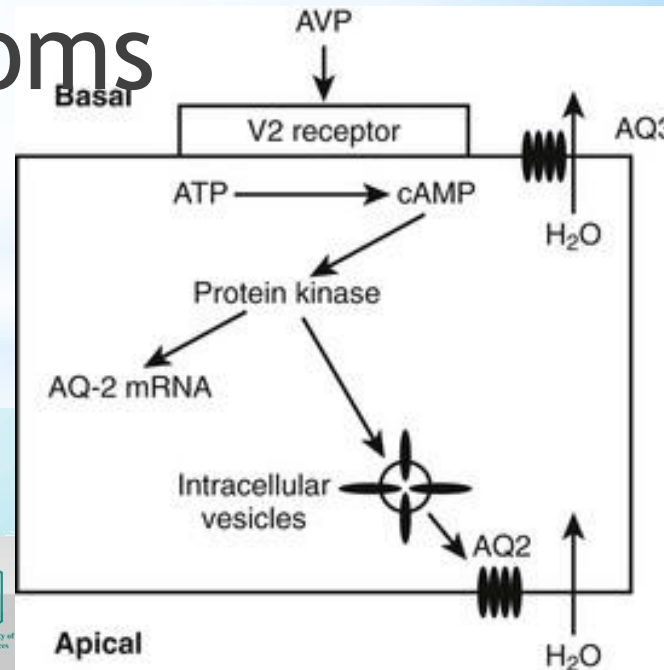
- * **DDAVP (Desmopressin)**
- * **(1-deamino-8-D-arginine vasopressin), a synthetic vasopressin receptor agonist**
- * **Prevent aquaresis**
- * **→ ↓the rate of PNa correction**



*DDAVP:

Response to DDAVP could be different depend on V2 receptor density & sensitivity

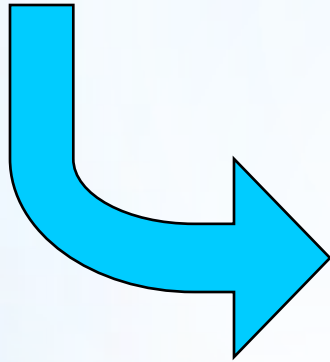
DDAVP can lead to worsening hypona with neurological symptoms



*No Significant H₂O Diuresis

Input
Na+K

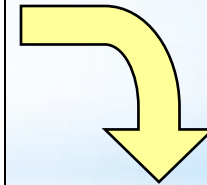
H₂O



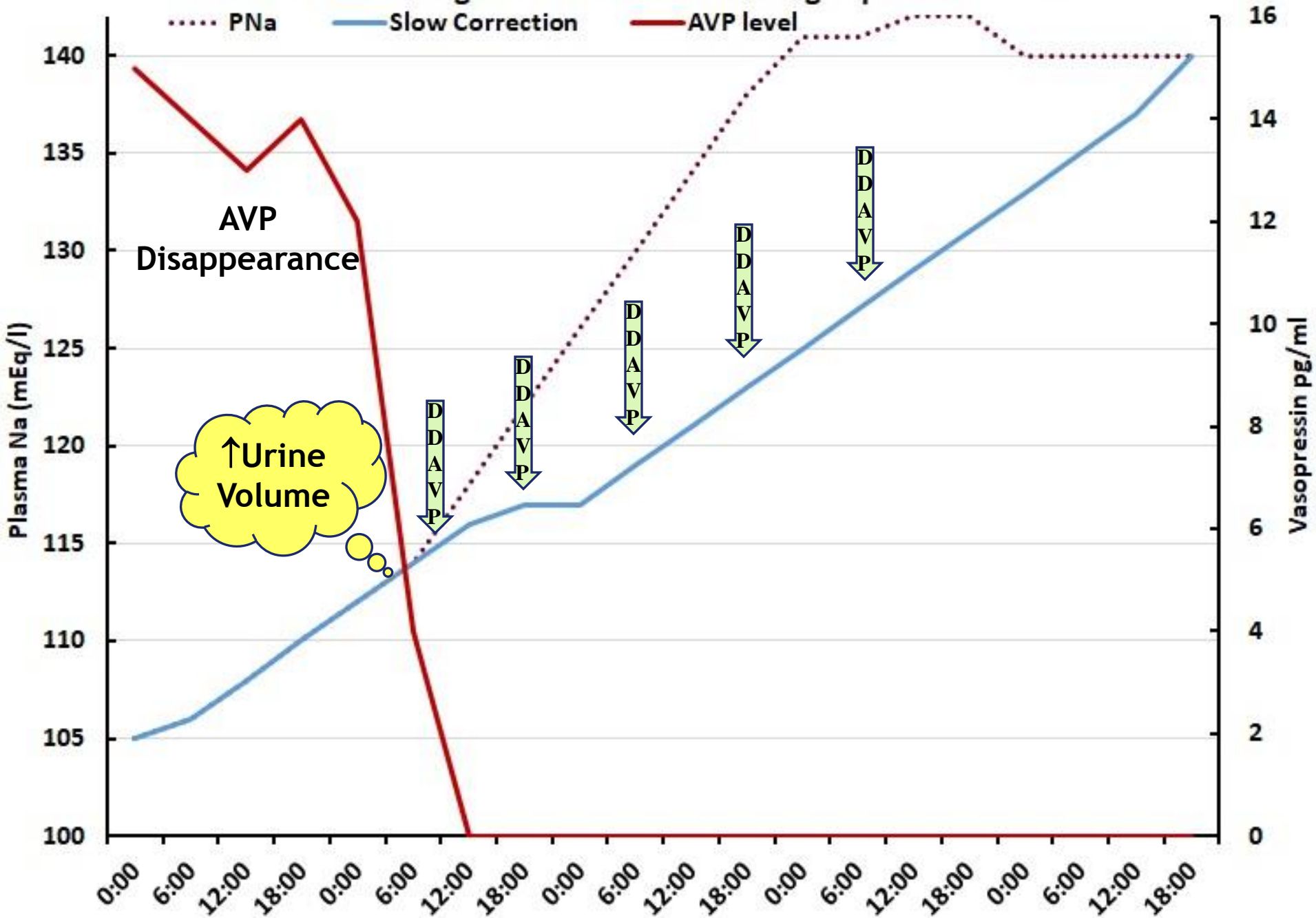
[Na⁺] = $\frac{\text{Na}^+}{\text{H}_2\text{O}}$

DDAVP
Output

Na+K
H₂O

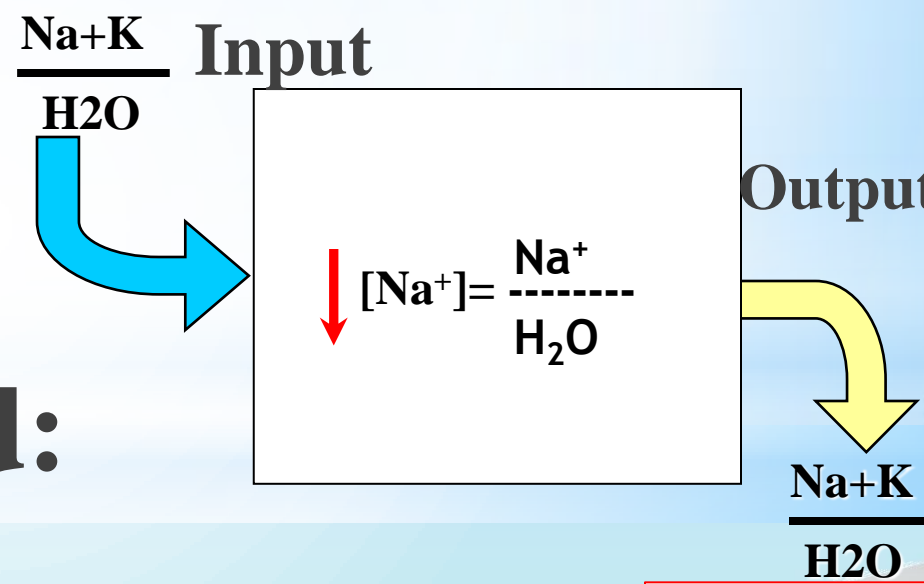


Schematic diagram of DDAVP Preventing Rapid Correction



*DDAVP; CURRENT STRATEGIES:

- * Not Considered?
- * Wait & React: 6-12h,
- * To Rapid Correction:
- * Proactive:
- * Rescue:
- * Re-lowering Na
- * Physiology Based:
- * Balance



Urine Osm
UNa
UK
UVolume:UCr

*Case 1

* 61 ♀, Alcoholic, ↓LOC \hat{c} BP=96/64

* Admitted to ICU,

* Serum Na 108, K 2.2

* Correction rate calculated using a complicated formula?!

* 8-12 mmol/day ?????!

* Case 1: 2nd day

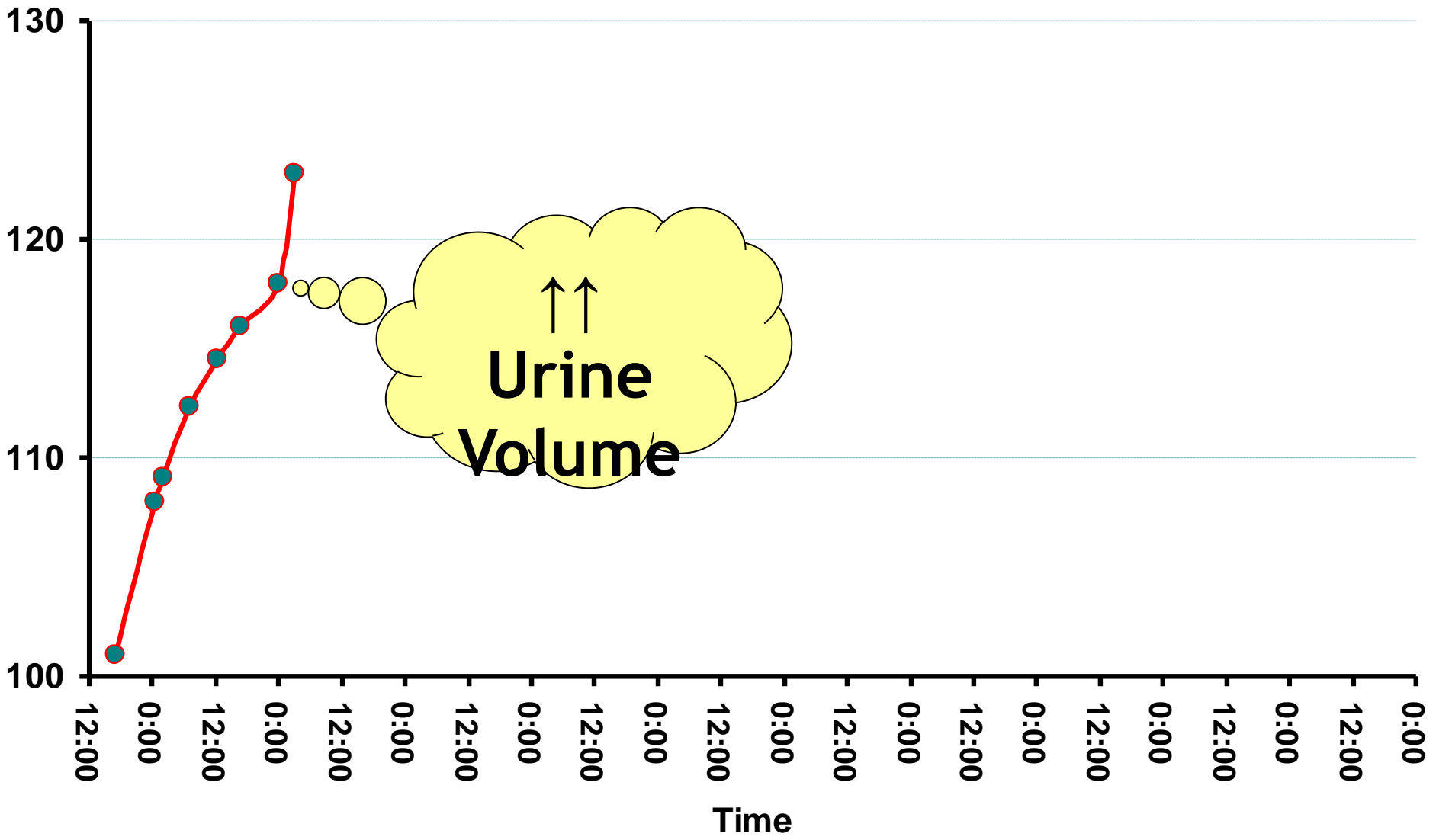
* LOC improved

* Obeying few commands

* No focal neurological deficit

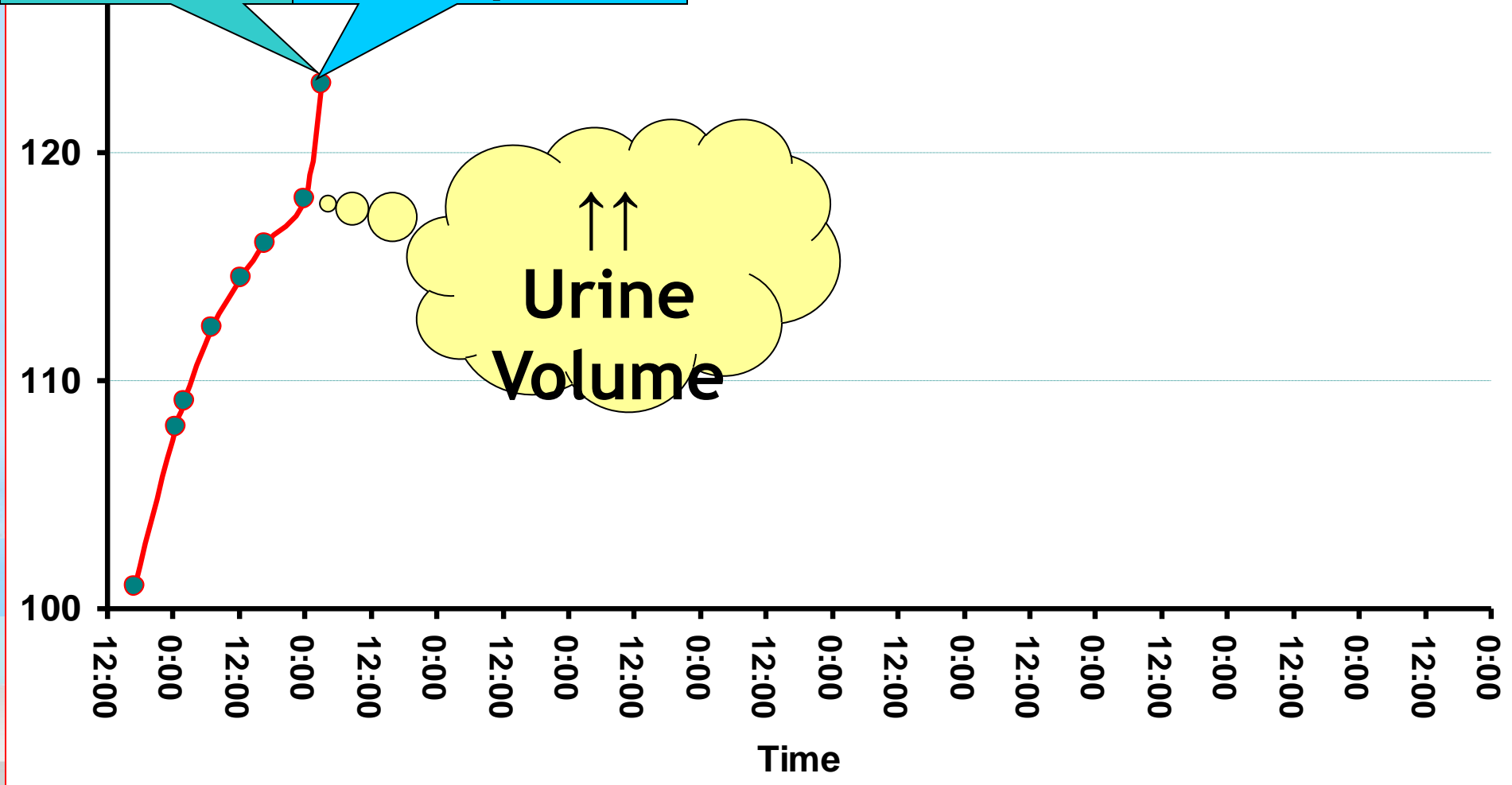
* Significant ↑Urine output

* [Na⁺] Trend



* [Na⁺] Trend

DDAVP **Match Urine output**



* Hospital course

- * D2 afternoon, developed dysarthria, dysphonia, ↓ O2 desat → Intubated
- * Working Dx: Aspiration?
- * Day 3rd, Quadriplegic, Brisk reflexes, bilateral Babinski sign
- * ↑ T2-weighted signal in; **Basis pontis, Hippocampi, Caudate, Bilateral lateral geniculate, & basal ganglia**

1.5T MR02TWIN

Ex: 6686

Ax T2 FLAIR

Se: 4/9

Im: 10/26

Ax: 123.6 (COI)

256 x 192

R_s

ET: 0

TR: 9002.0

TE: 146.2

HEAD

5.0thk/1.0sp

Lin

W:297 L:148

A_s

SWCHSC SB

PATIENT1708

1943 Jun 08 F ID1708

Acc: ACC1708

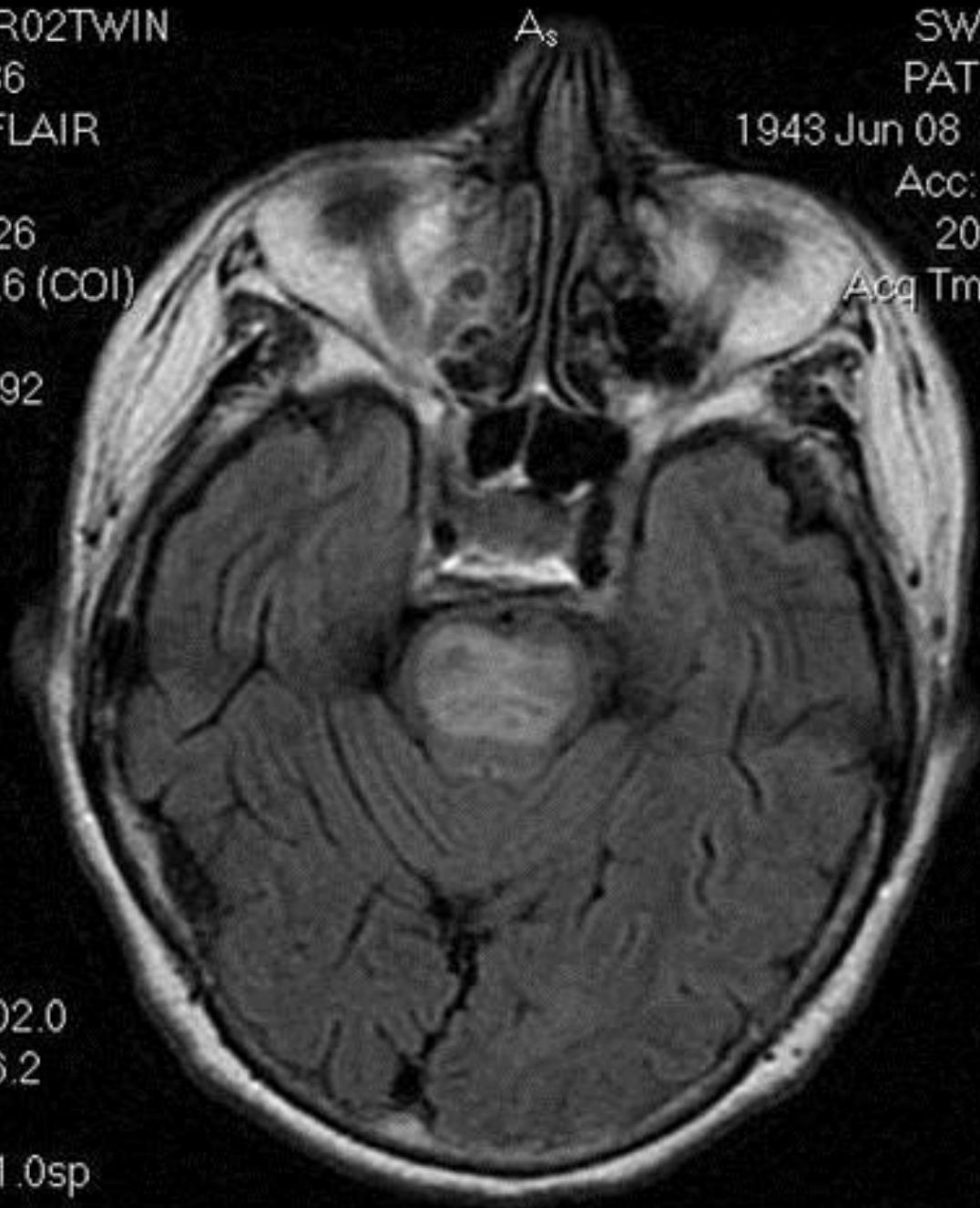
2004 Mar 26

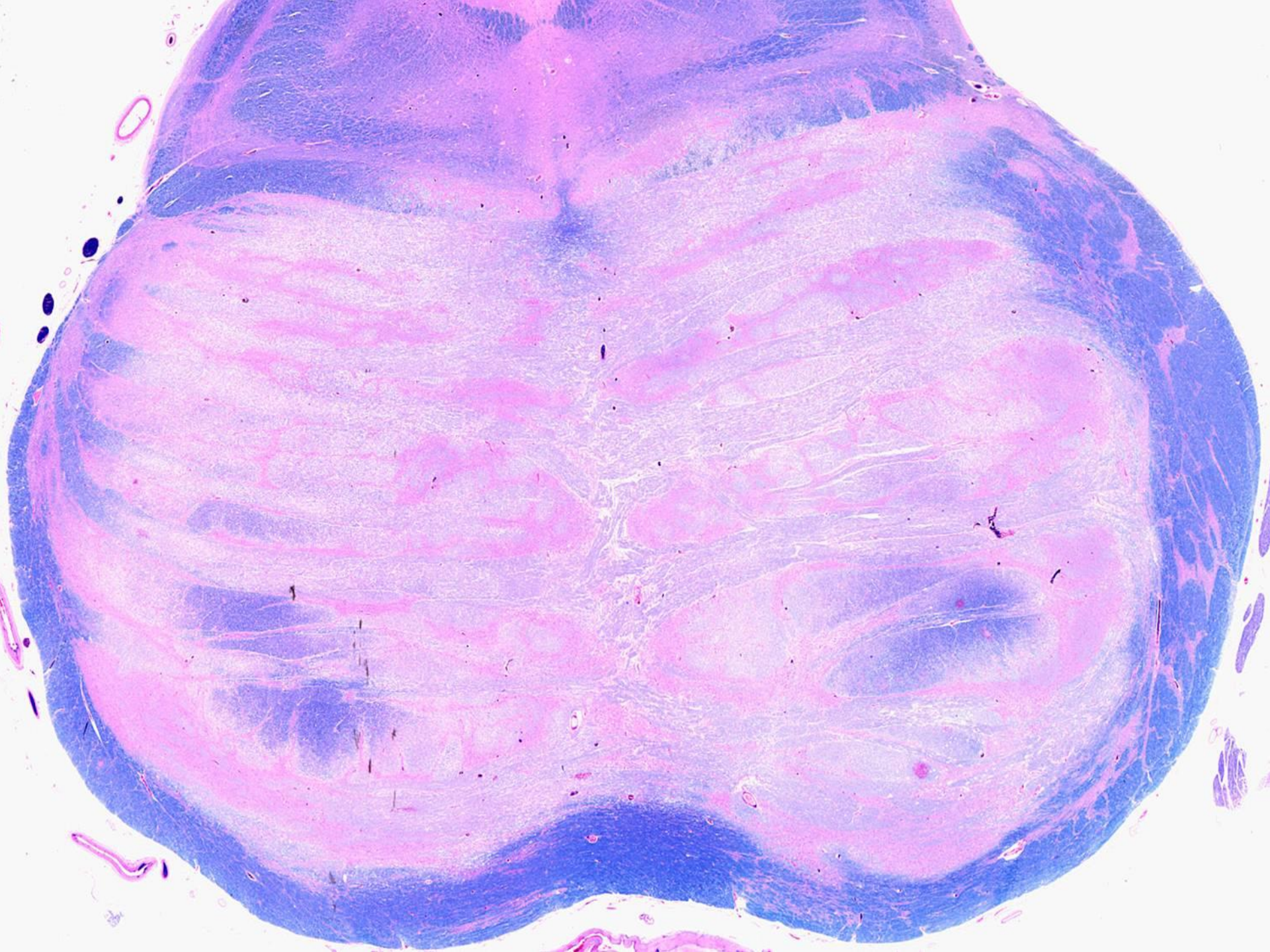
Acq Tm: 18:43:15

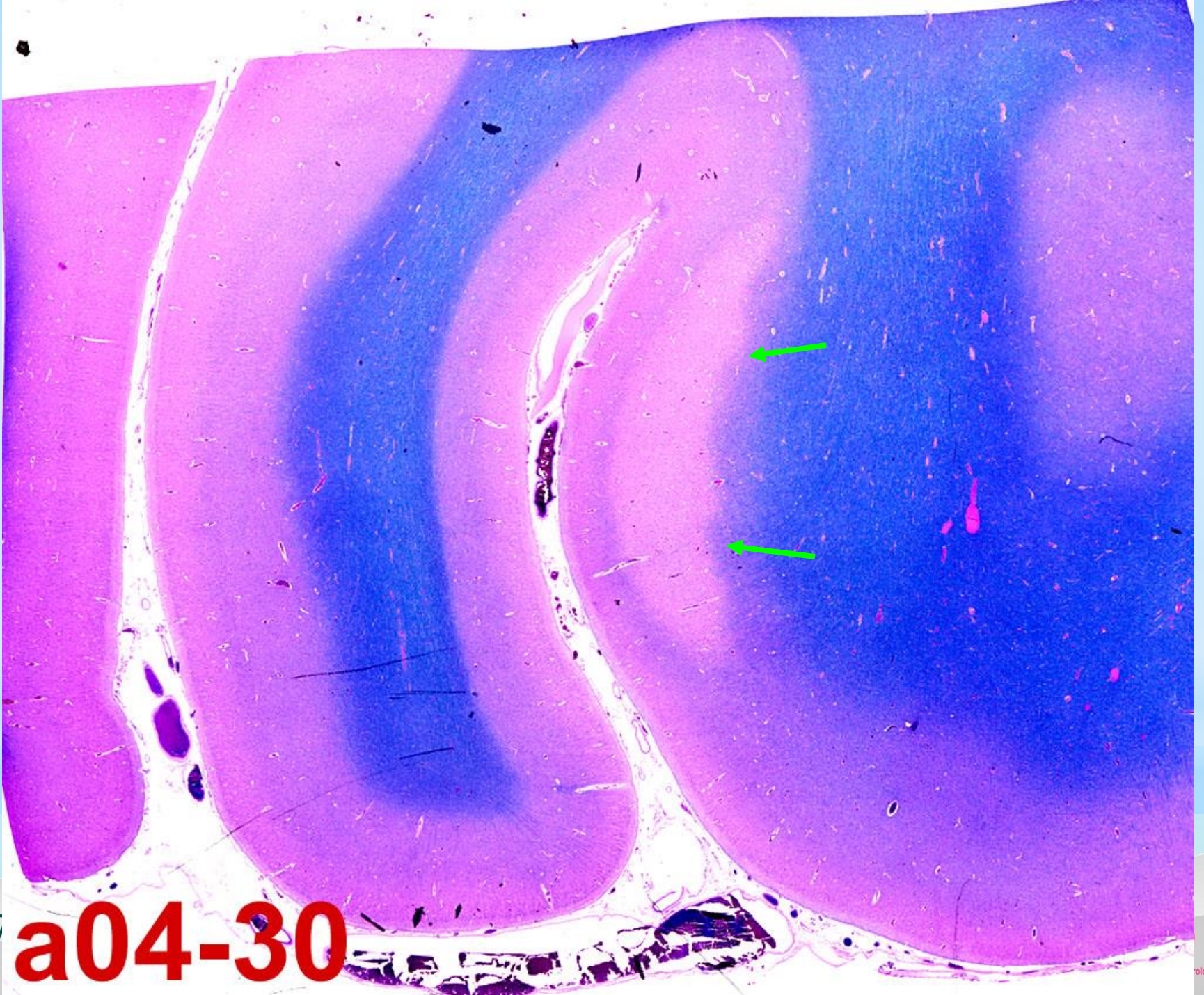
L_i

P_i

DFOV: 22.0 x 22.0cm



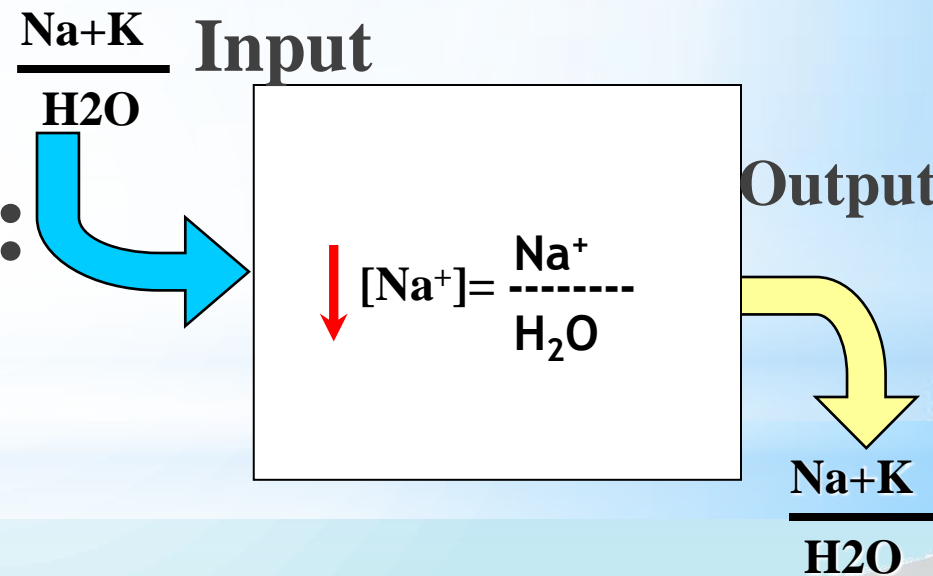




17 **a04-30**

*WHAT IS YOUR STRATEGY:

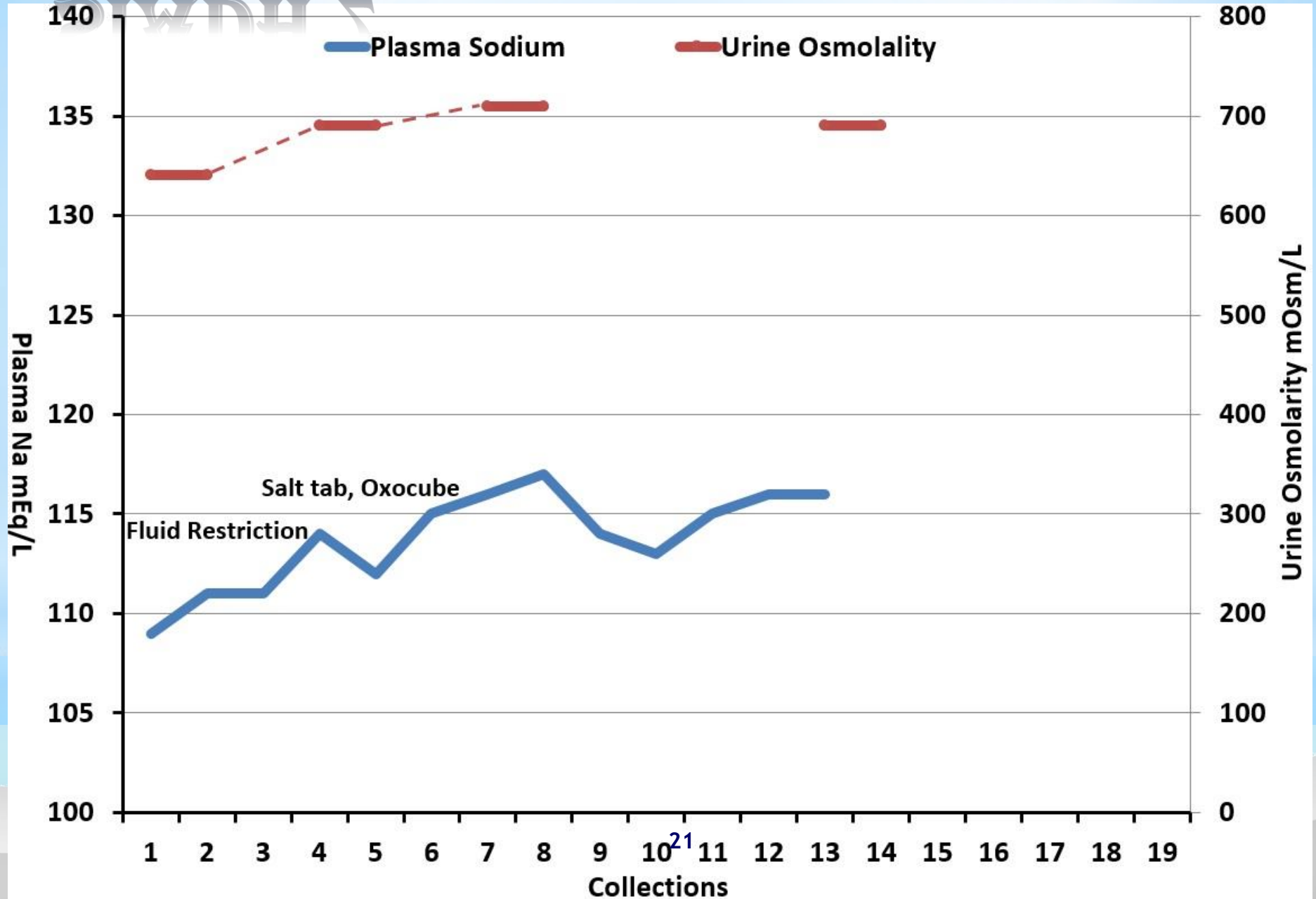
1. Don't Give:
2. Wait & React:
3. Proactive
4. Rescue
5. Physiology Based:
Consider Balance
& Individualize:



* Case 2

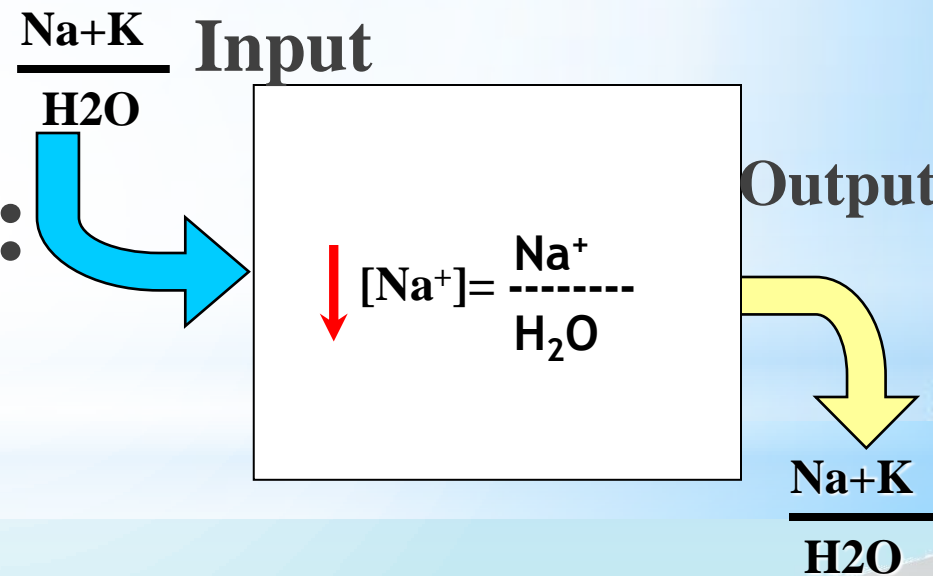
- * 46M pilot, healthy with dizziness, found to have Na 109
- * No other sign or symptom, Unremarkable Physical Exam
- * CXR reported normal but in review a 1 cm nodule Rt. mid lung zone
- * CT chest found 1.5 cm nodule on RML of lung
- * Biopsy showed Carcinoid tumor
- * Patient was labeled as **SLADH** and started on

* SIADH 2



*WHAT IS YOUR STRATEGY:

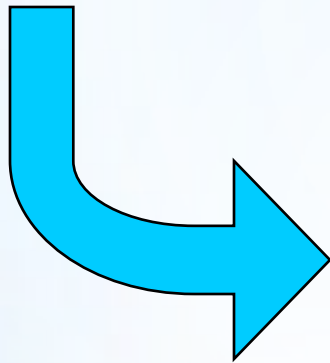
1. Don't Give:
2. Wait & React:
3. Proactive
4. Rescue
5. Physiology Based:
Consider Balance
& Individualize:



* Halperin Tonicity Balance

Input

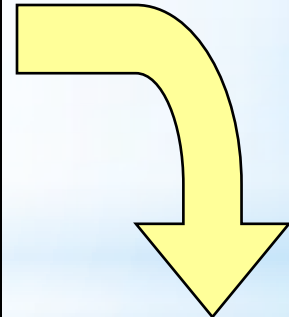
$\frac{\text{Na}+\text{K}}{\text{H}_2\text{O}}$



$$[\text{Na}^+] = \frac{\text{Na}^+}{\text{H}_2\text{O}}$$

Output

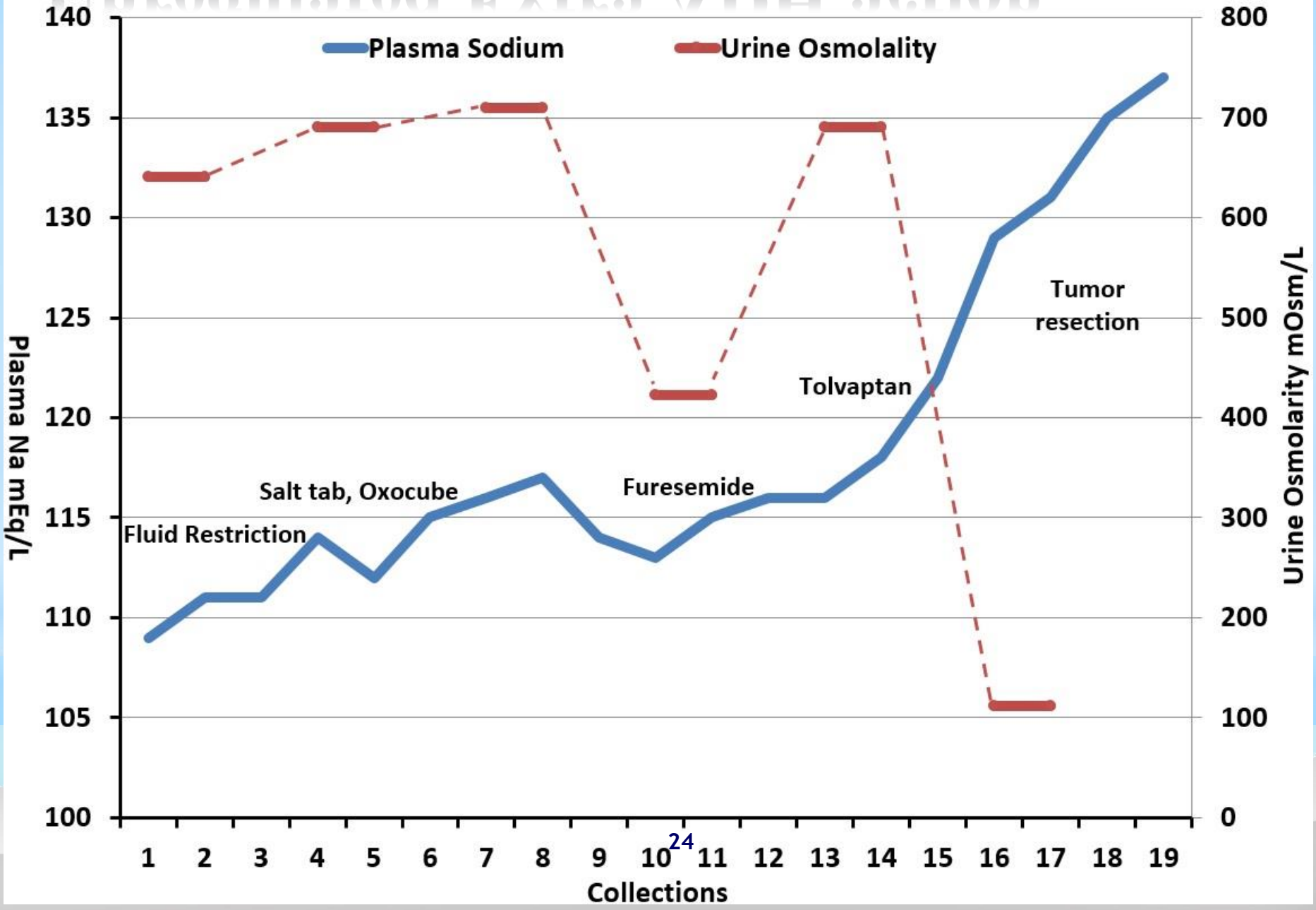
$\frac{\text{Na}+\text{K}}{\text{H}_2\text{O}}$



Always $\uparrow\uparrow$ Urine Osm
 $\uparrow\uparrow\uparrow$ ADH



Unregulated Extra ADH action



* Unregulated Extra / Ectopic ADH Secretion / ADH-like Action

- * Significant Hyponatremia with high urine osmolality
- * No significant response to fluid restriction, limited response to salt tab, Oxo cube, urea powder/tab
- * No obvious Osmotic or non osmotic physiologic stimulus for ADH
- * Ectopic ADH or unregulated ADH like substance (Oxytocin, Neuropeptide Y, Peptide YY, ?ANP,...) Secretion
- * ADH measurement not usually helpful, ↑Urinary Aquaporin-2 (AQP2)
- * Worsening of hyponatremia with IV NS or other isotonic solution
- * Good response to Vaptan, ?tumor resection or ?Chemotherapy → ↓Urine Osm & ↓Urine AQP2

Brenner and Rector's The Kidney, 10th Edition

Schrier's Diseases of the Kidney , 9th Edition

Harrison's Principles of Internal Medicine, 19th Edition

17th

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*Case 3.

- *77F Metastatic Ovarian cancer failed chemo admitted with weakness and found to have Na 120, P Osm 253
- *With low PO intake, but tries to drink adequate amount of fluids as instructed
- *On Exam Normotensive & clinically euvolumic!?
- *Her Cr is 66umol/L, K 3.5, BS 5.1
- *Urine Osm 202, UNa 30, UK is 33

*WHAT IS YOUR STRATEGY:

- 1. Don't Give:**
 - 2. Wait & React:**
 - 3. Proactive**
 - 4. Rescue**
 - 5. Physiology Based:**
- Consider Balance
& Individualize:**

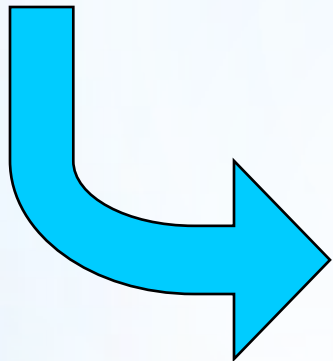
* Halperin Tonicity Balance

Input

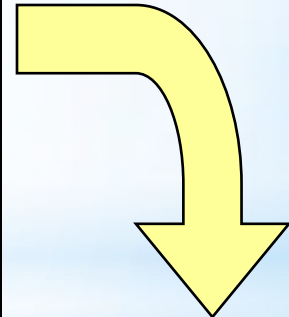
Output

Na+K

H₂O



$$[\text{Na}^+] = \frac{\text{Na}^+}{\text{H}_2\text{O}}$$

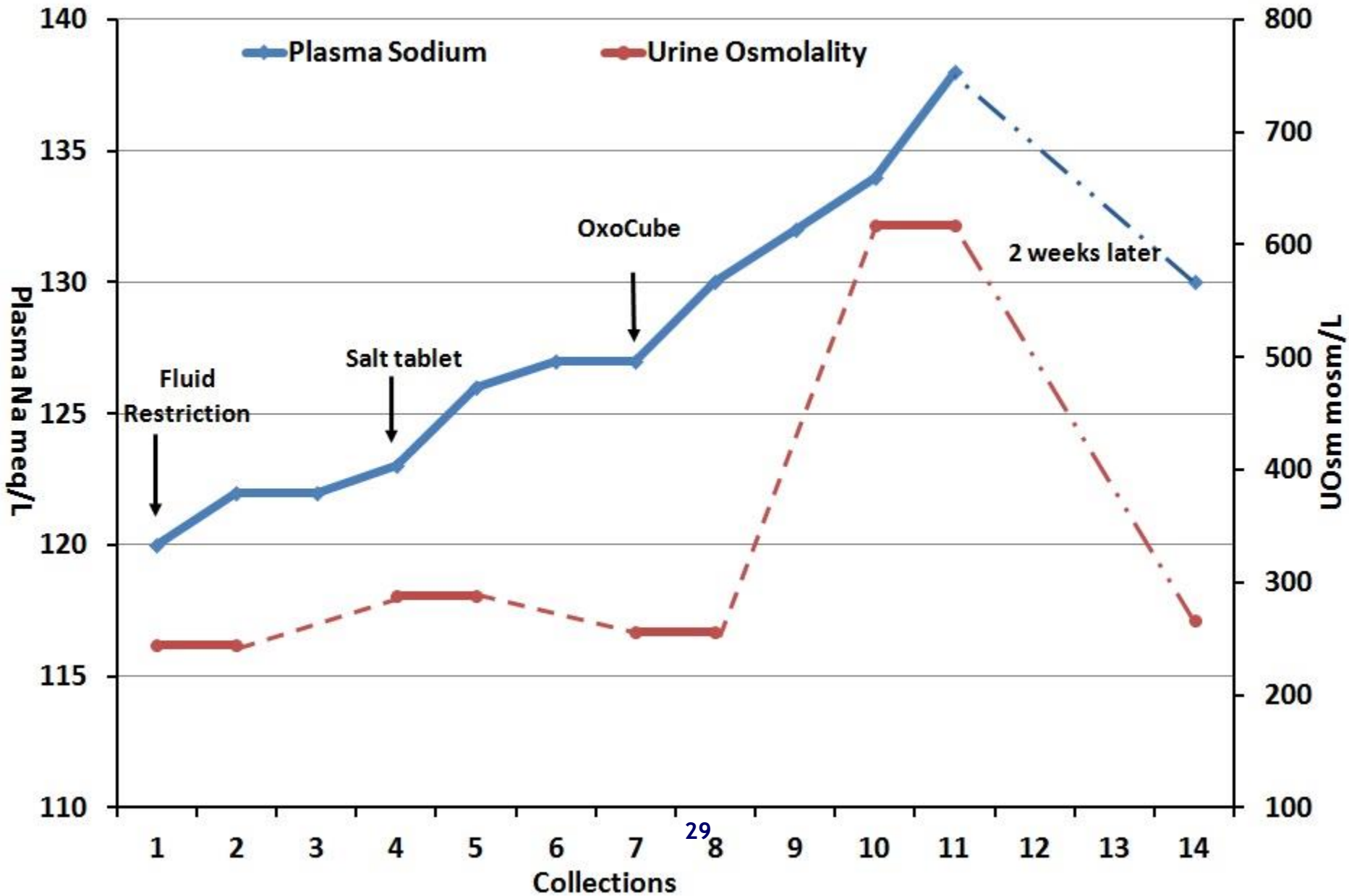


Na+K

H₂O

Urine Osm 204
 UNa 30 mmol/L
 U K 33 mmol/L
 U Volume 1.2 L

* Low Osmole Intake



* Low Osmole intake

- * Decrease PO intake of main excretory osmoles including Electrolytes & Protein metabolites (Urea)
 - Intake of $(\text{CH}_2\text{O})_n$ or $(\text{CH}_2)_n$ with free H_2O intake
 - Elderly with decrease PO intake but free H_2O intake
 - Loss of appetite resulting from cancer or chemo
 - Mucositis, pharyngitis, caused by tumor, chemo/radiation
- * Common instructions: Drink large amount of H_2O to stay healthy, flush your kidney
- * → Low Osm excretion rate
- * Decrease Distal delivery → ↑ Basal Permeability
- * Low Urine osmolality ($\text{UOsm} < \text{POsm}$ or slightly $> \text{POsm}$), Very low Urine AQP-2
- * Low electrolytes, ($\downarrow \text{Na}$, $\downarrow \text{Cl}$, $\downarrow \text{Urea}$) excretion rate
- * Excellent response to IV NS, Salt tablet, urea tab, urea crystal, Oxo-cube
- * ↑ Osm Intake → hyponatremia corrects → ↑ Urine osmole excretion rate

Brenner and Rector's The Kidney, 10th Edition

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17th

International Congress of Nephrology, Dialysis, and Transplantation

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Turkey, 14-18 November 2016



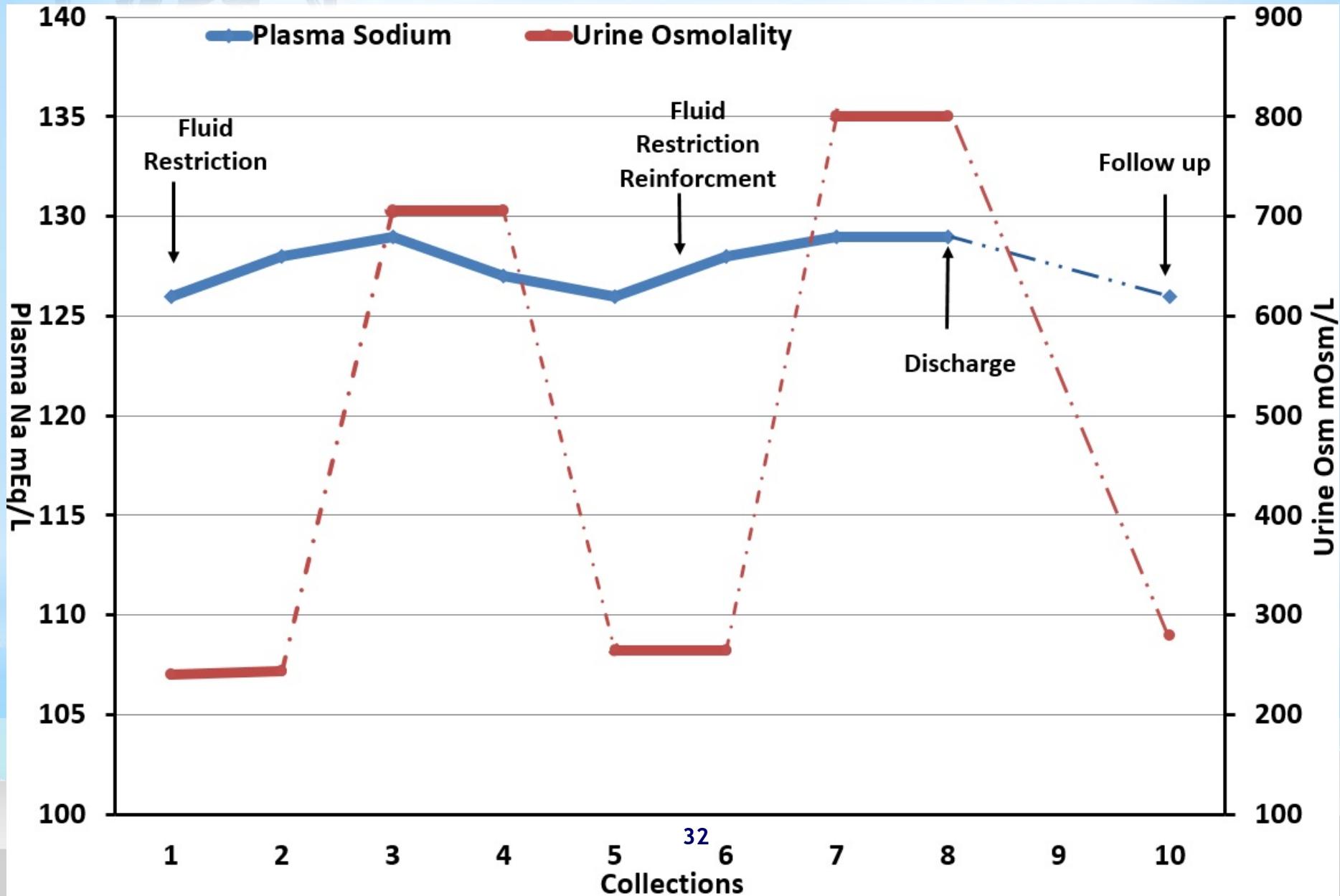
International Society of Nephrology

Iranian Society of Nephrology

* Case 4.

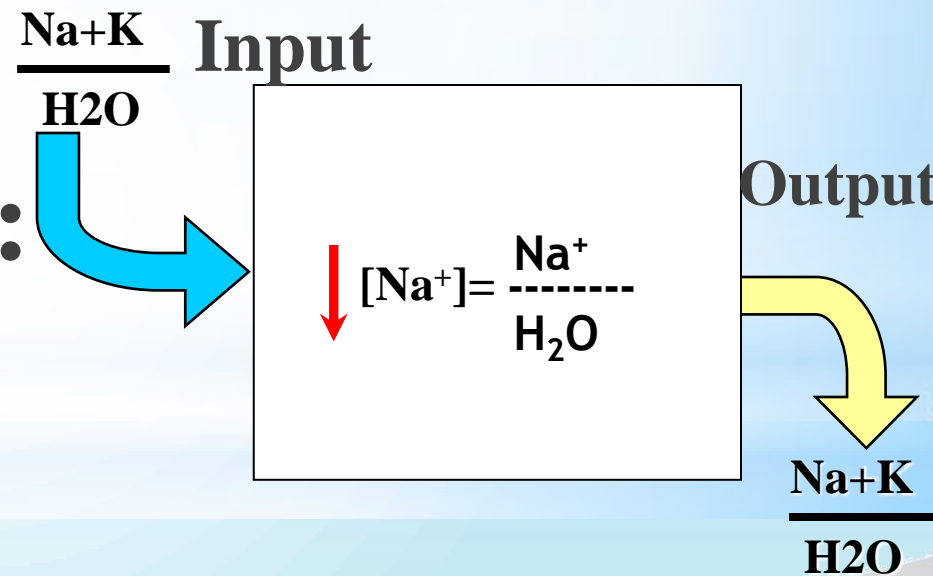
- * 55M Presented with blast crisis found hyponatremic with PNa of 126
- * He was claimed clinically Euvolumic!?
- * His sodium was hovering around a baseline of 125-130, Sodium not corrected, asymptomatic
- * His Na remained low for several months response to fluid restriction, salt/Urea tab

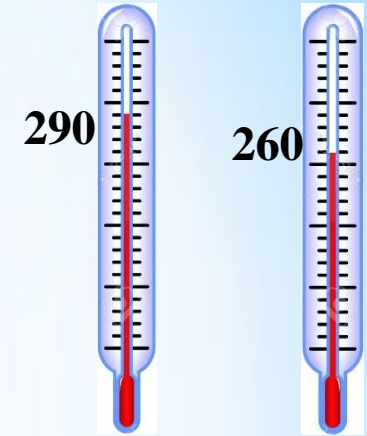
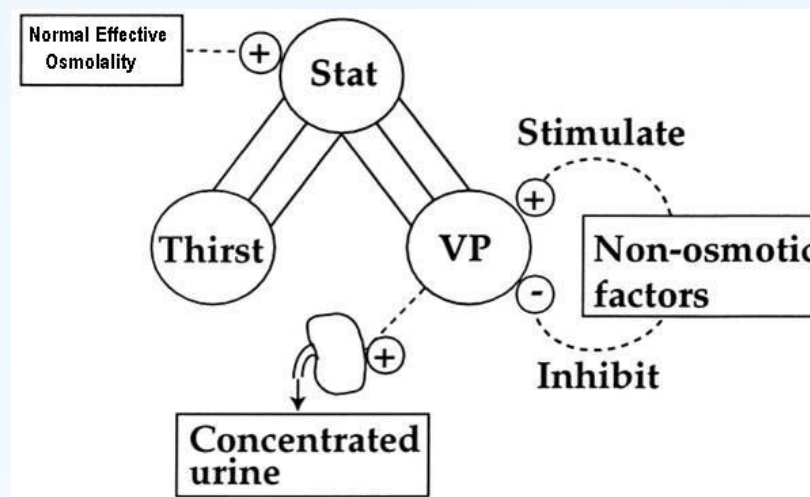
* CASE 4



*WHAT IS YOUR STRATEGY:

1. Don't Give:
2. Wait & React:
3. Proactive
4. Rescue
5. Physiology Based:
Consider Balance
& Individualize:

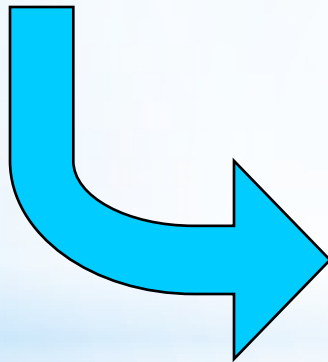




Input

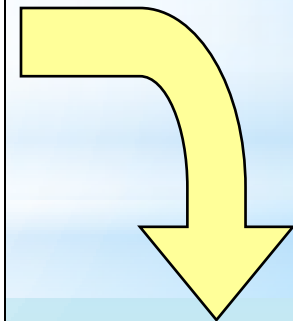
Na+K

H2O



$$[Na^+] = \frac{Na^+}{H_2O}$$

Output



Na+K

Urine Osm varies & changes to maintain PNa at lower level

* Reset Osmostat Criteria

- * Persistent mild Hyponatremia; ADH secretion threshold is reset downward to a lower effective osmolarity (subnormal threshold for ADH secretion)
- * But Renal concentrating and diluting capacities are appropriately normal
- * Euvolemic, Diagnosis of exclusion with Normal fractional urate excretion
- * Water challenge result in a dilute urine and a water deprivation or salt/urea tab result in a concentrated urine
- * Occurs up to ~36% of patients labeled as SIADH
- * Tx including Fluid restriction, salt, urea, & oxocube tablets does not successfully raise the PNa
- * Reset osmostat classically occurs in neurologic conditions such as epilepsy and paraplegia, pregnancy, malignancy, Lewy body dementia & malnutrition
- * Healthy individuals with a chronic mild hyponatremia (125-130 mEq/L)
- * 1951 grenade explosion may have caused the osmostat to reset!
- * Other acute conditions like severe pulmonary, neurologic, or malignant processes
- * Therapeutic efforts to raise [Na] not very effective & appear to be unnecessary

Schrier's Diseases of the Kidney , 9th Edition

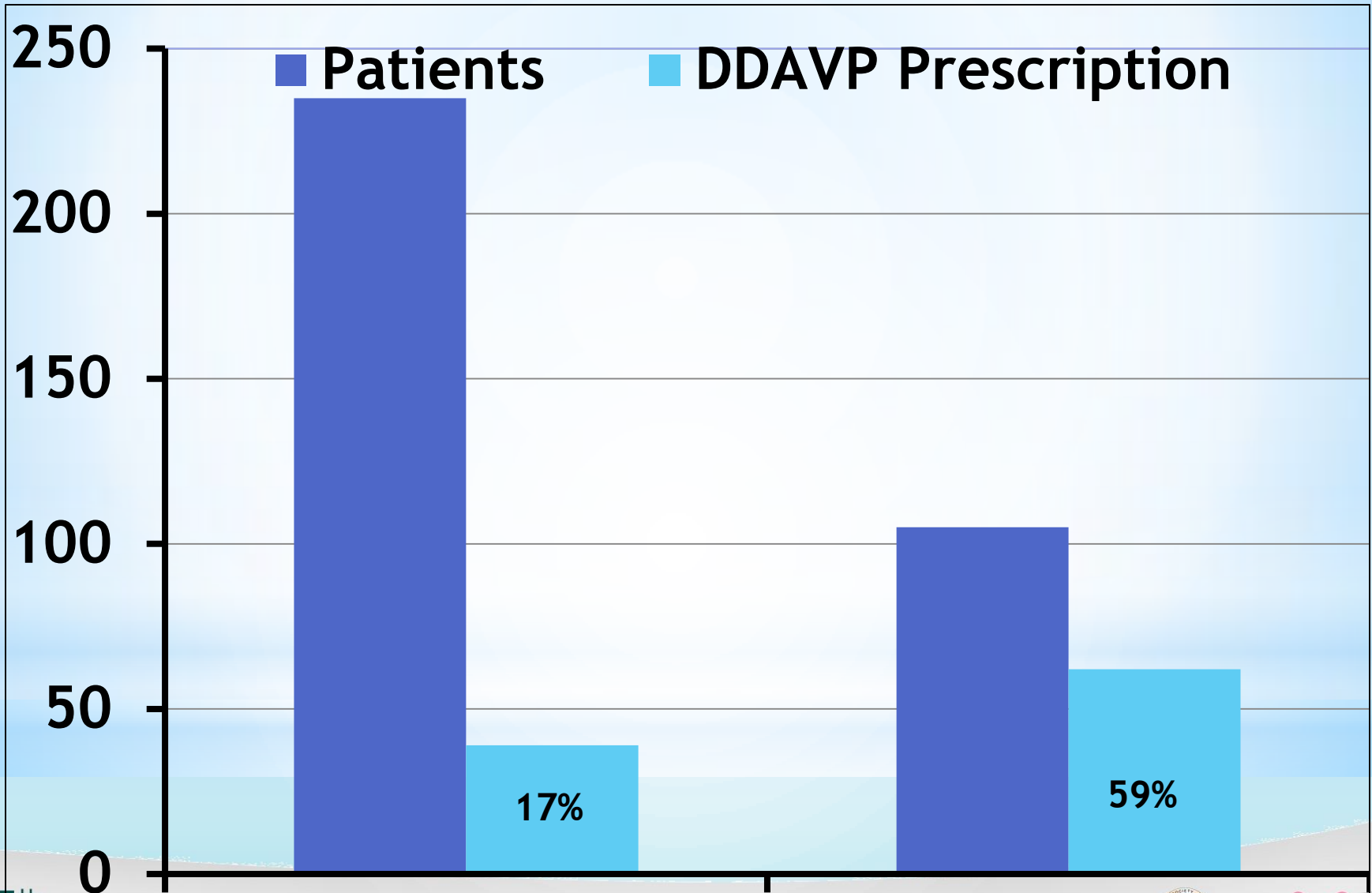
Brenner and Rector's The Kidney, 10th Edition

Normal fractional urate excretion identifies hyponatremic patients with reset osmostat. [J Nephrol.](#) 2012 Sep-Oct;25(5):833-8. [Imbriano LJ](#), [Ilamathi E](#), [Ali NM](#), [Miyawaki N](#), [Maesaka JK](#)

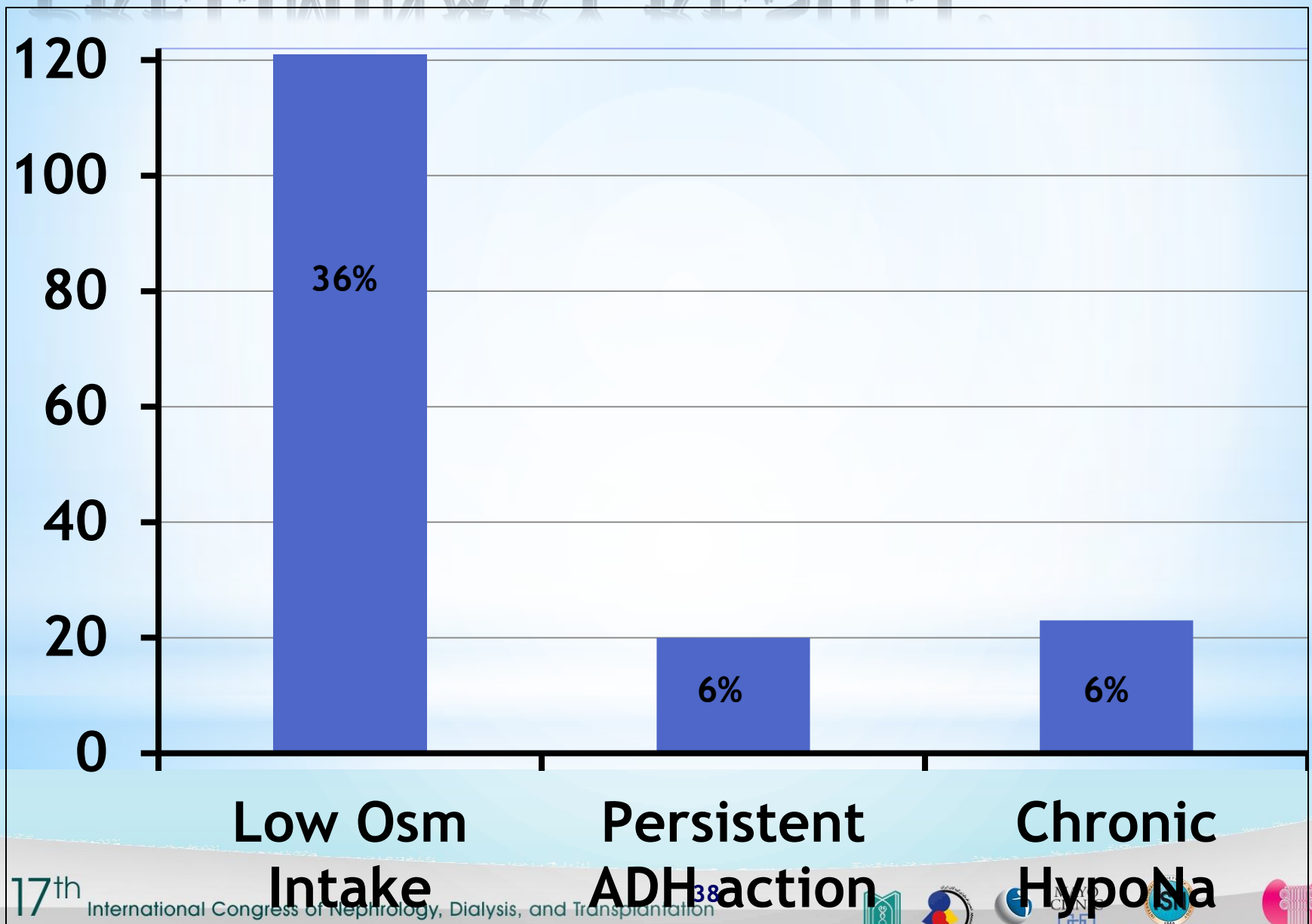
*UHN STUDY:

Retrospective study, electronic charts of 340 patients with moderate to severe hyponatremia were reviewed. PNa at presentation, UOsm, the correction rate, Nephrology consult (if requested), DDAVP prescription, justification of its usage and its influence on the length of hospital stay were examined

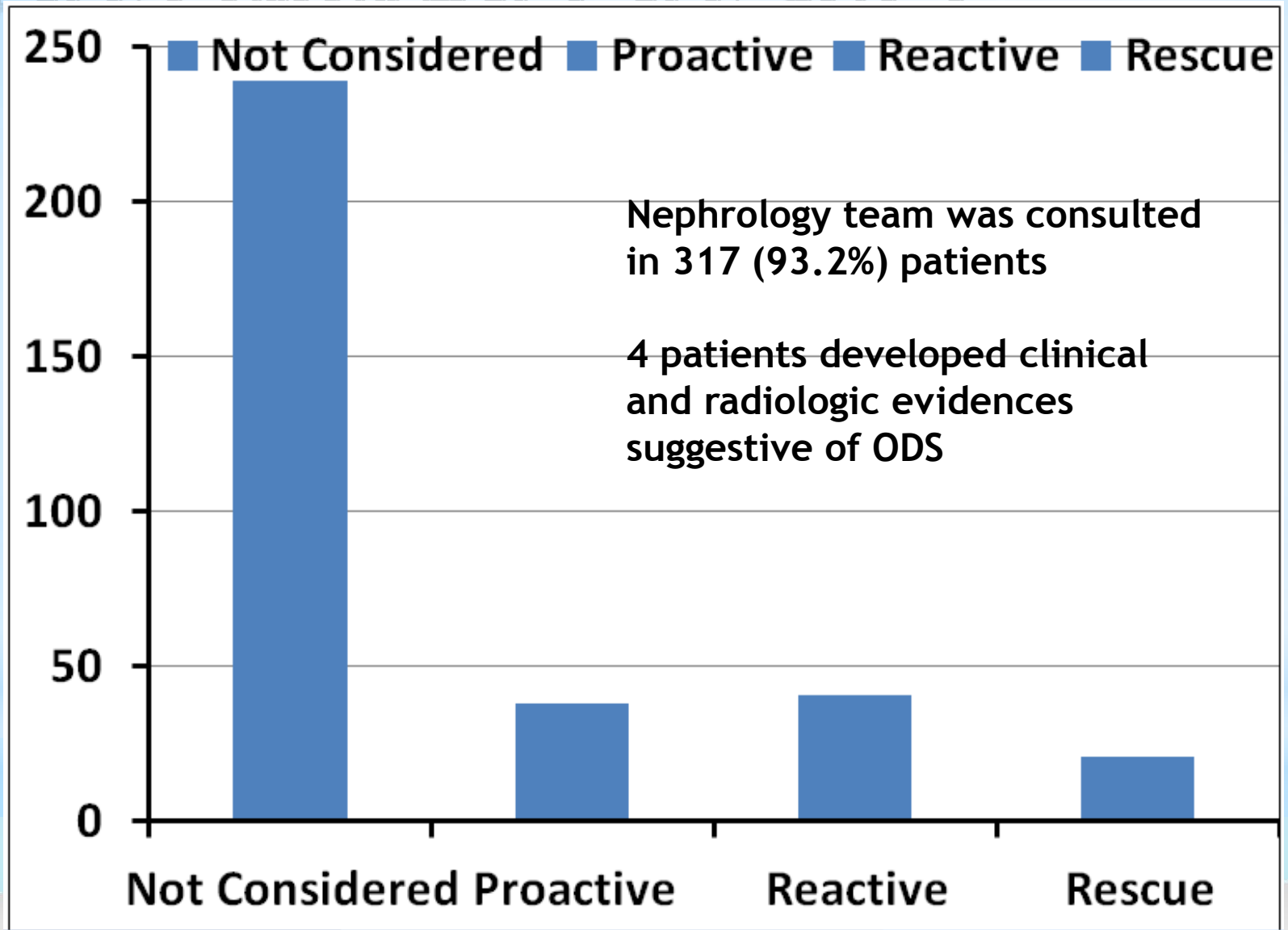
* PRELIMINARY RESULT:



*PRELIMINARY RESULT:



*PRELIMINARY RESULT:



* INDICATION OF DDAVP:

- * Very Severe Hyponatremia <115 , specially <106
- * Moderate Hyponatremia <125 in high risk group
- * Low ECF Hyponatremia
- * Vanishing Non-Osmotic Stimulus in the Tx course
- * Low Osmotic Intake; if Osmotic Input could cause rapid correction

- * **DDAVP; NOT INDICATED:**
- * **Acute HypoNa**
- * **Ectopic ADH HypoNatremia**
- * **Persistent Non-Osmotic stimulus for ADH secretion (CHF, Cirrhosis,... chronic)**
- * **Low Osmotic Intake; if Osmotic Input < Output**
- * **Reset Osmostat**

*SUMMARY:

- * To prevent Rapid correction of hyponatremia by kidney due to turning off ADH secretion
- * Significant Hyponatremia (Severe or moderate)
- * $UOsm > Posm \rightarrow$ ADH action
- * Not in Ectopic ADH secretion
- * ADH secretion due to Non-Osmotic stimuli or Low ECF volume
- * Not really indicated in someone with reset osmostat or with longstanding chronic hyponatremia difficult to suppress ADH
- * If concern about rapid correction watch for large urine

17th International Congress of Nephrology, Dr. H. S. Ghadimi, Tabriz, Iran 19-22 November 2019
output $>120/h$ and frequent $[Na]$



* **SUMMARY:**

* In severe hyponatremia with evidences of ADH action: **Proactive DDAVP** prescription: indicated

* In moderate hyponatremia, close monitoring of PNa correction rate/Urine Volume and “**Reactive method of DDAVP**” prescription is more appropriate

* Inappropriate DDAVP prescription could result in **↑length of hospital stay.**