Approach to Hyponatremia

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Objectives

- Understand the physiology associated with hyponatremia
- Describe symptoms associated with hyponatremia
- Identify how the diagnostic work up incorporates renal physiology.
- List the various causes of hyponatremia
- List the different treatment strategies that can be utilized to resolve hyponatremia.

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Sodium Disorders = Water Disorders

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Key Hormones Maintain Volume and Tonicity

- Kidneys are good at 2 things: Water and Sodium retention

- Na reabsorption → Angiotensin II (AT2) and aldosterone
- Water reabsorption → Anti-diuretic hormone (ADH)

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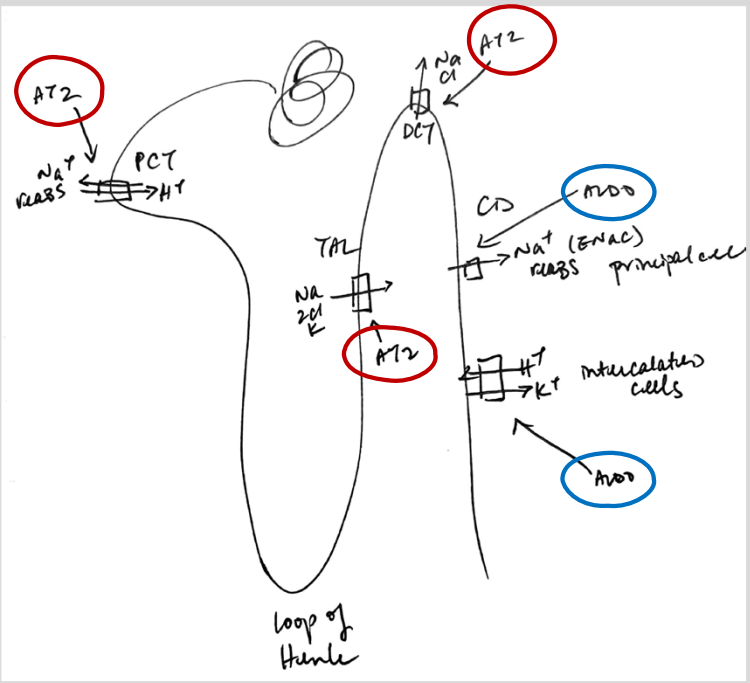
AT2 and Aldo → vasoconstriction and Na retention



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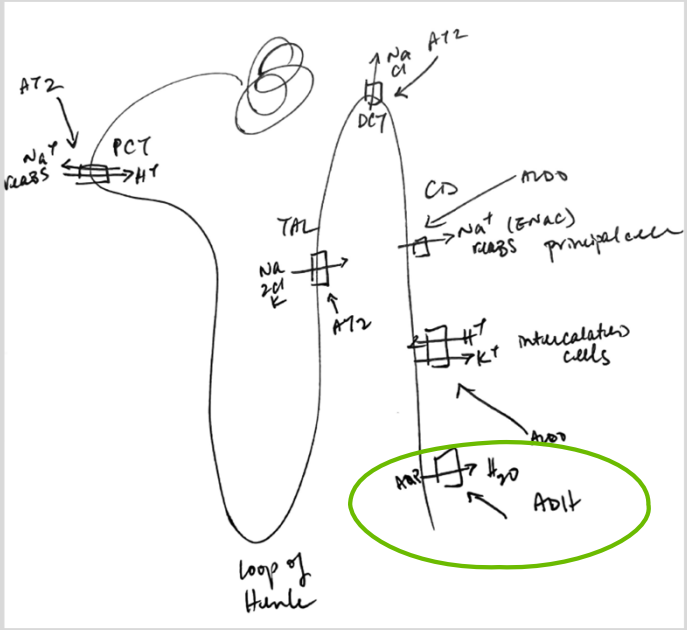
ADH → water retention and responds to tonicity and volume



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Of note, Age and Kidney Disease Impair Dilution and Concentration

- AKI/CKD
  - If advanced CKD → UOSm ranges from 200-300 mOsm/kg
  - Due to reduced GFR (impaired free water excretion), volume expansion, urea osmotic diuresis

- Older age
  - UOsm range 92 mOsm/kg → 400-700 mOsm/kg by 80s
  - Due to reduced GFR
  - Increased medullary blood flow

Kidneys by Muhammad Shabraiz from Noun Project (CC BY 3.0)
old person by ainul muttaqin from Noun Project (CC BY 3.0)

Karam and Tuazon, Clin Geriatr Med, 2013
Cowen et al, Endo Metab Clin North Am, 2013
Epstein, JASN, 1996
Lindeman et al, J Lab Clin Med, 1966
Rose and Post, Clinical Physiology of ABE Disorders, 5th edition

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Hyponatremia is common in hospitalized patients, the elderly, and patients with comorbidities

- 15 - 53% of hospitalized patients
- 7-11% in community dwelling individuals
- More common in elderly and if comorbidities
  - 6% in non-geriatric hospital wards v. 22% geriatric wards
  - Elderly pts with CAP, SAH, COPD, cancer → incidence 8%, 16%, 16%, 38%

Grattagliano et al, J Prim Health Care, 2018
Zhang and Li, Eur Ger Med, 2020
Brinkkoetter et al, Sci Rep, 2019

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Increase Mortality with Hyponatremia

	Mortality Rate (%)	Mortality Risk
Heart Failure	31	1.8
Cirrhosis	26-73	2.1
Myocardial Infarction	13.8-24.1	2.0
Pulmonary Embolism	16.6	1.53
Pneumonia	5.4	1.3
CKD	17.3-29.6	1.12-1.32
Cancer		4.28
Hospitalized Pts	3.4-5.9	1.37-1.55
ICU Pts	14.3	1.3
General Population	3.4-5.9	1.14-8.0

Hoorn and Zietse, AJKD 2013
Abu Zeinah et al, Eur J Cancer Care, 2015

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Symptoms of Hyponatremia

- Altered mental status, seizure, confusion
- Fall prevalence 27.9% (OR 3.02)
  - Every 5 mmol/L drop in [Na]s → risk of falling increased 32%
  - 128.73 millisecond slower reaction time if hyponatremic
  - Resolution of hyponatremia →
    - Timed UP and Go test improved by 2.5 seconds
    - Nerve conduction velocity increased 14.3%
- Fractures in 4% of hyponatremia patients

Gunathilake et al, J Am Geriatr Soc 2013
Nigro et al, J Am Geriatr Soc 2015
Barsony et al, J of Biological Chemistry 2011
Barsony et al, Molecular and Cellular Endocrinology 2022
Ayus et al, NDT 2012
Filmyer et al, Schizophrenia Research 2019
Vandergheynst et al, Eur J Clin Invest 2016

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Main Mechanisms of Hyponatremia

Impaired dilution of urine

- "appropriate" high ADH (hypovolemia or low EABV)
- "inappropriate" high ADH in response to other stimuli (pain, nausea, meds, hypocortisolism, etc)
- Diuretics (nonosmotic)
- Kidney disease

Low volume of electrolyte free urine

- Low solute, low protein intake
- Oliguria

Drinking Water by Smashing Stocks from Noun Project (CC BY 3.0)
urine by Llisole from Noun Project (CC BY 3.0)

Yau and Buchkremer, AKDH 2024

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Approach to Diagnosis

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Step 1: Confirm "True/Hypotonic" Hyponatremia

Serum osmolality

Low (< 280 mosm/kg)
Hypotonic Hyponatremia

Normal (280-295 mOsm/kg)
Isotonic Hyponatremia
- Elevated serum proteins
- Hyperlipidemia

High (>295 mosm/kg)
Hypertonic Hyponatremia
- Hyperglycemia
- Mannitol, sorbitol, glycerol, etc
- Iodinated contrast

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Traditional Schema

Low (< 280 mosm/kg)
Hypotonic Hyponatremia

Check Volume Status

Hypovolemia (30%)

UrNa < 10 mEq/L (extrarenal salt loss)
- Dehydration
- Diarrhea
- vomitting

UrNa > 30 Eq/L (renal salt loss)
- Diuretic use (8%)
- ACE inhibitors
- Nephropathies
- Mineralocorticoid deficiency

Euvolemia
- SIADH (35%)
- Postoperative
- Psychogenic polydipsia (5%)
- Low solute, beer potomania
- Primary adrenal (glucocorticoid) deficiency
- Diuretics, ACE inhibitors
- Hypothyroidism

Hypervolemia (20%)
- CHF
- Liver Disease
- Advanced CKD
- Nephrotic Syndrome (rare)

Grattagliano et al, J Prim Health Care, 2018

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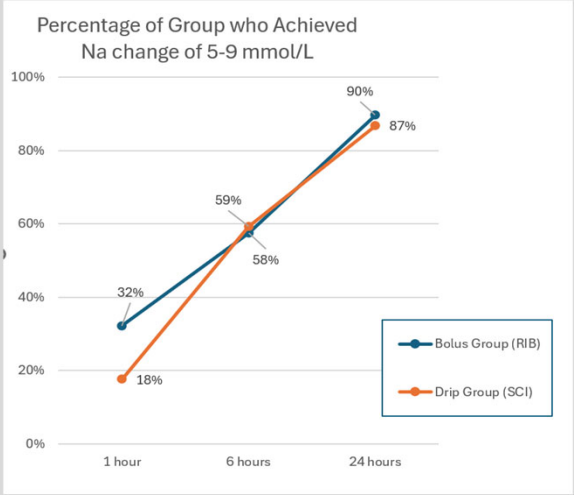
New Schema

Hypotonic Hyponatremia Confirmed

Acute or severe symptoms?

Yes
Consider
hypertonic saline

Bolus is better than drip



Baek et al, JAMA Internal Med 2021, PMID 33104189

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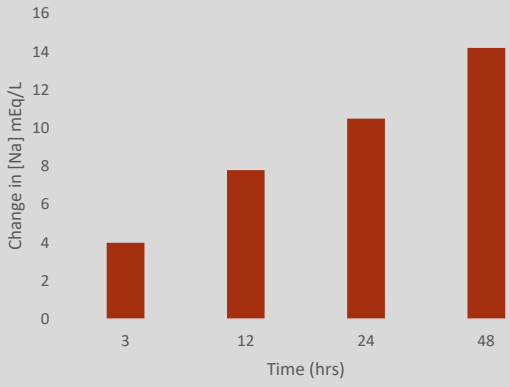
Na change of 4-6 mEq/L improves severe symptoms

- Worthley and Thomas (n=5)
  - Mean Na 105 mmol/L
  - Given HTS, 30 min later mean Na 112 mmol/L
- Sarnaik et al (n=60, 69 episodes)
  - After HTS, mean Na change 3 mmol/L within 4 hours
- Ayus et al (n=64, 71 episodes)
  - Mean Na 117 mmol/L
  - After HTS, mean Na change 4 mmol/L within 3 hours
  - Majority had symptom improvement



Sarnaik et al, Critical Care Med 1991, PMID 2055051
Worthley and Thomas, British Med J 1986, PMID 3080118
Ayus et al, AJKD 2015, PMID 25465163

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New Schema

Hypotonic Hyponatremia Confirmed

Acute or severe symptoms?

Yes
Consider hypertonic saline

No
Check urine osmolality

Assess ADH response

ADH is off

<100 mOsm/L
- Primary polydipsia
- Low solute, beer potomania

> 100 mOsm/kg

ADH is on

Question is, is it **appropriate** or **inappropriate** based on UrNa

US Hyponatremia Recommendations, Verbalis et al, Am J Med, 2013
EU Hyponatremia CPG, Spasovski et al, NDT, 2014

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New Schema

Hypotonic Hyponatremia Confirmed

Acute or severe symptoms?

Yes
Consider hypertonic saline

No
Check urine osmolality

<100 mOsm/L
- Primary polydipsia
- Low solute, beer potomania

> 100 mOsm/kg
Check urine sodium

Assess RAAS response

UrNa <10 mmol/L

RAAS is on
(High ADH appropriate)

UrNa > 30 mmol/L

US Hyponatremia Recommendations, Verbalis et al, Am J Med, 2013
EU Hyponatremia CPG, Spasovski et al, NDT, 2014

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New Schema

Hypotonic Hyponatremia Confirmed

Acute or severe symptoms?

Yes Consider hypertonic saline

No Check urine osmolality

<100 mOsm/L
- Primary polydipsia
- Low solute, beer potomania

> 100 mOsm/kg
Check urine sodium

UrNa <10 mmol/L
Then assess volume
- Hypovolemia
- Capillary Leak, cytokine release
- Low EABV state (CHF, cirrhosis)
- Remote diuretic use

UrNa > 30 mmol/L

RAAS is off (or on diuretic/CKD)
(High ADH is inappropriately elevated)

US Hyponatremia Recommendations, Verbalis et al, Am J Med, 2013
EU Hyponatremia CPG, Spasovski et al, NDT, 2014

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New Schema

Hypotonic Hyponatremia Confirmed

Acute or severe symptoms?

Yes Consider hypertonic saline

No Check urine osmolality

<100 mOsm/L
- Primary polydipsia
- Low solute, beer potomania

> 100 mOsm/kg
Check urine sodium

UrNa <10 mmol/L
Then assess volume
- Hypovolemia
- Capillary Leak, cytokine release
- Malignant ascites
- Low EABV state (CHF, cirrhosis)
- Remove diuretic

UrNa > 30 mmol/L
Rule out diuretic use or kidney disease?

Then assess volume
- Vomiting
- Renal/cerebral salt wasting
- Primary/secondary adrenal insufficiency
- Severe hypothyroidism (TSH usually > 50)
- SIADH

US Hyponatremia Recommendations, Verbalis et al, Am J Med, 2013
EU Hyponatremia CPG, Spasovski et al, NDT, 2014

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SIADH is Diagnosis of Exclusion

Box 4. Common Causes of SIADH

CNS disease: Brain abscess, encephalitis, head trauma, intracranial hemorrhage, meningitis, tumor

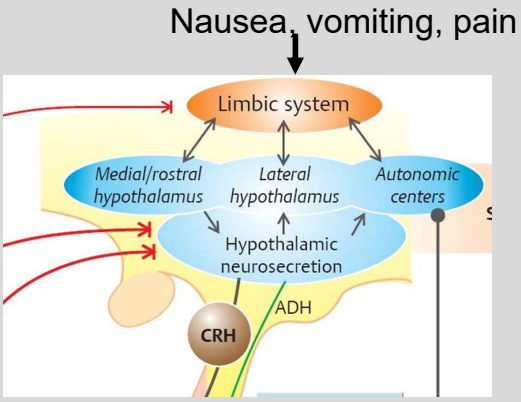
Drugs: Amiodarone, carbamazepine, oxcarbazepine, 3,4-methylenedioxy-methamphetamine (MDMA, "Ecstasy"), nicotine, phenothiazines, opioids, selective serotonin re-uptake inhibitors, tricyclic antidepressants, cyclophosphamide, chlorpropamide, vincristine

Malignancy: Most commonly small cell carcinoma of the lung followed by head and neck cancer and non–small cell lung cancer

Pulmonary disease: Acute respiratory failure, COPD, pneumonia, tuberculosis

Other: HIV infection, idiopathic, postoperative state, reset osmostat

Genetic – X linked recessive GOF T2AVP receptor (OMIM 300539)



Winn Seay et al, AJKD Core Curriculum 2019

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Often Adrenal and Thyroid Function not checked in Euvolemic Hyponatremia

	Barnes et al	Katoch et al	Tzoulis et al	Greenberg et al	Cuesta et al	Diker-Cohen et al
Number of pts	110 SIADH	100 with AMS, hypoNa	139 hypoNa	1524 SIADH	573 SIADH	564 euv hypoNa
TFTs (%)	50.9	100	61.1	64	91	69
Adrenal Function Test (%)	91.1	100	31.7	33	84	29
% of pts dx with hypothyroid/AI	3.6/3.6	8/2	0/0.7	NR	0/3.8	1/1

Prevalence of thyroid disorder/AI in hyponatremia ~3%

Prevalence of hyponatremia in patients with hypopituitarism was 9.6%

In 80.7%, hyponatremia was key to diagnosis

Diker-Cohen et al, Int and Emer Med J, 2018
Miljic et al, Endocrine, 2017

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Approach to Management

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When correcting sodium, determine

1. Na goal (rate of change)

- Is my patient at risk of ODS?

2. Management Strategy

- What is the cause?
- How can I help with renal free water excretion (or reduce intake)?
- Is my patient at risk of over-correcting my goal rate? (or under-correcting?)

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Risk factors of ODS and over-correction seem to overlap

Risk of ODS

- Hypokalemia
- Alcoholism
- Malnutrition
- Advanced liver disease
- Na ≤ 105 mmol/L

Risk of Overcorrection

- Hypokalemia < 3.5 mEq/L
- Weight < 60 kg
- Low solute, EtOH abuse, primary polydipsia
- Hypovolemia

ODS risk is "unlikely"

- acute water intoxication
- Na ≥ 120 mmol/L unless other risk factors

Verbalis et al, Am J Medicine 2013, PMID 24074529
Pelouto et al, Eur J Endocrinology 2023, PMID 36881992

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If you over-correct beyond your Na goal, consider re-lowering based on ODS Risk

- **Low to moderate risk of ODS**
  - Goal sodium change 4-8 mEq/L in first 24 hours
  - Consider re-lowering if changes more than 10-12 mmol/L*
- **High risk of ODS**
  - Goal sodium change of 4-6 mEq/L in first 24 hours
  - Consider re-lowering if changes more than 8 mmol/L

Verbalis et al, Am J Medicine 2013, PMID 24074529
Brain Damage by Muhammad Owais from Noun Project (CC BY 3.0)

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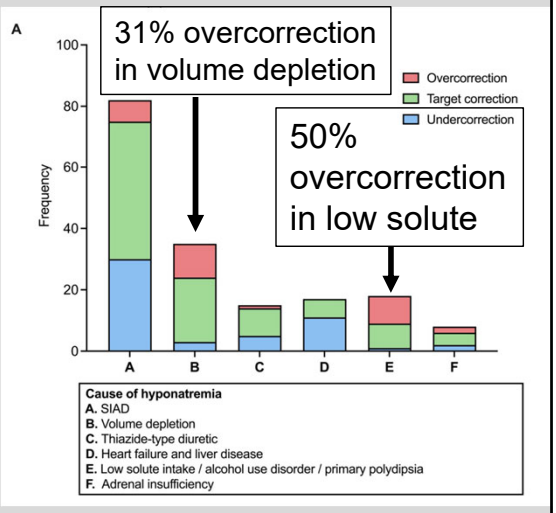
Who is at risk of over-correcting?

N=180, mean Na 120 mmol/L

32% over-corrected

	Odds ratio (95% CI)	
	Univariable	Multivariable
Body weight (per kg)	0.95 (0.92–0.98)	0.96 (0.92–0.99)
Baseline plasma sodium (mmol/L)	0.88 (0.82–0.95)	0.86 (0.79–0.94)
Volume depletion	2.71 (1.16–6.33)	3.07 (1.06–8.83)
Hypokalemia[a]	3.70 (1.53–8.92)	4.40 (1.45–13.35)
Number of boluses	0.45 (0.23–0.89)	0.34 (0.13–0.88)

[a]Plasma potassium < 3.5 mmol/L.



Pelouto et al, Eur J Endocrinology 2023, PMID 36881992

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Main Therapies of Hyponatremia

Limit fluid intake

Impaired dilution of urine

- Normalize volume/EABV
- Suppress ADH (stop triggering meds, pain, nausea, cortisol), Tolvaptan, loop diuretic
- Stop offending diuretics
- Treat kidney disease/Dialysis

Low volume of electrolyte free urine

- Increase solute (urea, protein, Na, K) intake, SGLT2i
- Treat kidney disease/Dialysis, loop diuretic

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urine by Llisole from Noun Project (CC BY 3.0)

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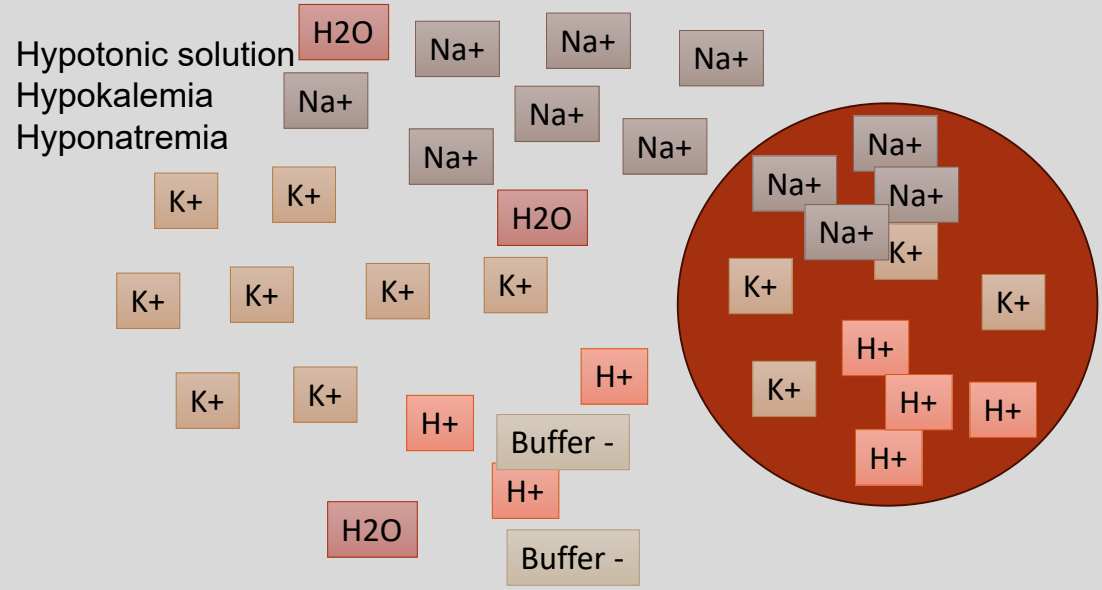
Correction of KCl in Hyponatremia

Hypotonic solution
Hypokalemia
Hyponatremia



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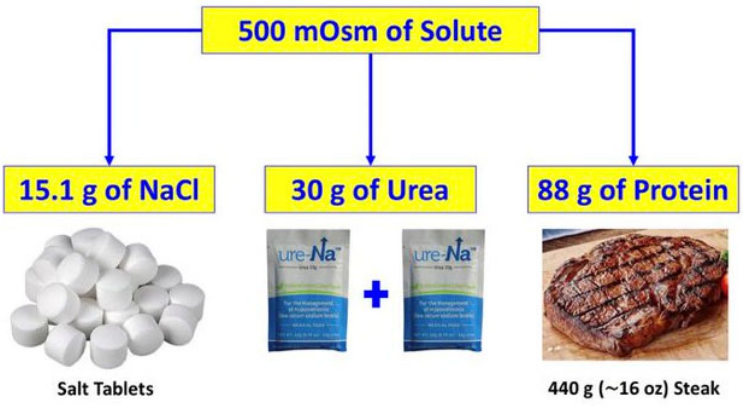
Inducing Solute Diuresis



1g salt tablets = 34 mOsm

90 g protein by protein powder

SGLT2 inhibitors

Compared to placebo, increased Na by ~ 3 mEq/L

Courtesy of Helbert Rondon, MD @NephroMD
Monnerat et al, Eur J Endocrinol 2023
Refardt et al, JASN 2019

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Urea is considered a medical food (not drug)

ure-Na™

UreaAide

1 tablet = 1.875 g

Need 8 tablets for 15 g (1 powder packet)

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For SIADH specifically, how effective are therapies?

Treatment	Patients (n)	Rate of Na change (mEq/L/d)	Overly Rapid correction in 24/48h (%)	Change in [Na] >= 5 mEq/L (%)	[Na] > 130 mEq/L (%)	[Na] > 135 mEq/L (%)
No treatment	138	1.5	0.7%	**39%**	**43%**	19%
Stop offending Rx/insult	30	2.0	10%	**47%**	**57%**	27%
Fluid Restriction (FR)	748	2.0	2.6%	44%	29%	10%
FR + NS	263	1.5	2.5%	42%	25%	8%
FR + Salt tabs	151	1.0	3.0%	**46%**	**37%**	11%
Isotonic Saline	437	2.0	2.1%	36%	20%	4%
Hypertonic Saline	86	4.0	16.9%	60%	26%	13%
Tolvaptan	225	4.0	12.1%	**78%**	**74%**	40%

Verbalis et al, Am J Med 2016

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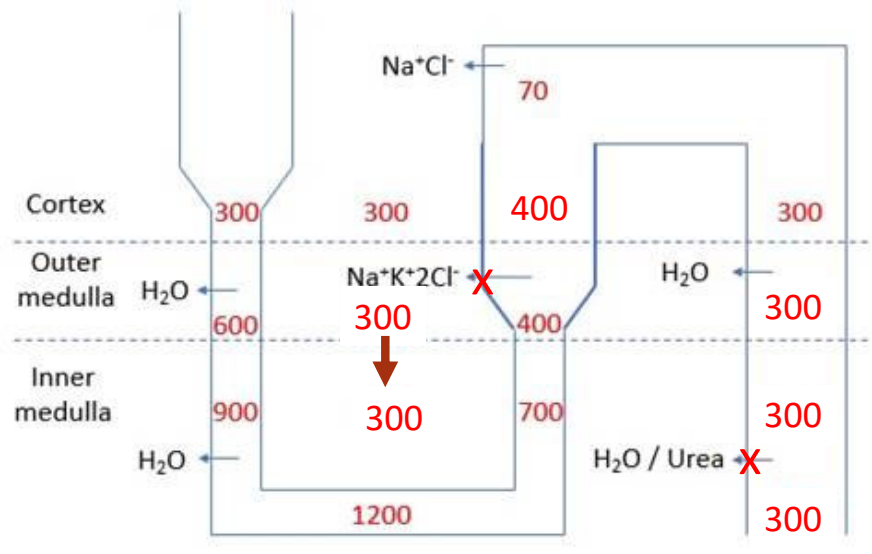
Increase free water excretion with loop diuretic



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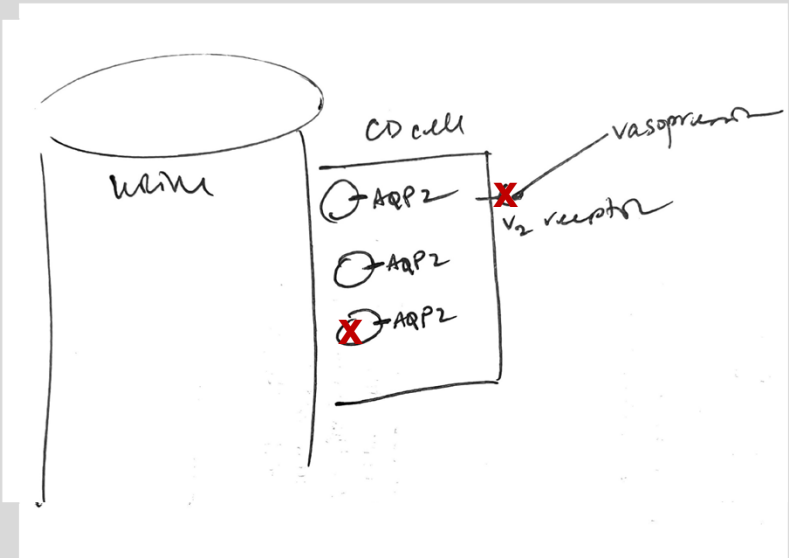
Vaptans target the MOA of SIADH



Long term use: Monitor LFTs

In ADPCKD (starting dose 60 mg daily), increased incidence of LFT evaluation more than 3x upper limit of normal

Dose for SIAD or hypervolemic hyponatremia (CHF/cirrhosis) is 15-60 mg daily

Schrier et al, NEJM 2006
Rondon-Berrios and Berl, Best Practice & Res Clin Endocrin & Metab 2016

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Summary: My Approach to Hyponatremia

- Sodium disorders are water disorders
- Symptoms of hyponatremia and hyponatremic encephalopathy may be nonspecific
- Use a systematic approach to diagnosis of hyponatremia
- Management relies on 3 parameters
  - Determine risk of ODS and risk of over-correction
  - Identify underlying cause, then develop management plan based on cause/mechanism

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