



52 yo woman with
hyponatremia

Sharon H. Chou, MD

Endorama

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[History of Present Illness]

- 52 yo black women with PMHx sig. for primary sclerosing cholangitis and ulcerative colitis who was admitted from Liver Clinic with hyponatremia (Na 125).

History of Present Illness

- Two months ago, she was hospitalized for pneumonia.
 - May have been told her sodium was slightly low then.
- Since then, reports worsening fatigue, memory issues.
- 1.5 months ago, she was started on sertraline 100 mg BID for anxiety.
- Drinks 2L of water per day.
- Diet includes bacon, Chinese food, chicken noodle soup.

[Past Medical History]

■ Past Medical History

- Primary sclerosing cholangitis, dx in 2005
- Quiescent ulcerative colitis
- Anxiety/Depression
- Vitamin A deficiency

■ Medications:

- Sertraline 100 mg BID
- Alprazolam 0.5 mg QHS
- Ursodiol 500 mg TID
- Mesalamine 800 mg QID
- Tramadol 50-100 mg q6 hrs prn
- Vitamin A 8,000 daily

[Social History]

■ Family History:

- Mother: stroke in her 70s
- Father: DM2, CHF diagnosed in his 70s
- Brother: MI at 41 yo
- Brother: CHF diagnosed at 45 yo
- Sister: “liver problem”

■ Social History:

- Logistic analyst for Caterpillar
- Has 2 children
- No history of tobacco use
- Occasional alcohol use

[ROS]

- Constitutional: **Weight loss of 20 lbs over past 5 months due to little appetite.** No fevers, chills.
- Eyes: No blurry vision.
- ENT: **Mild thirst.**
- Respiratory: No shortness of breath, cough.
- Cardiovascular: No chest pain, **+ palpitations.**
- Gastrointestinal: No nausea, vomiting. **Occ. abdominal pain.** No diarrhea.
- Genitourinary: No dysuria. **Normal urinary frequency.**
- Musculoskeletal: No myalgias.
- Skin: **Pruritis.**
- Neurological: No headache. **+ peripheral neuropathy.**
- Psychiatric/Behavioral: **Anxiety.**

Physical Exam

- BP 126/86 | Pulse 100 | Temp 36.3 °C (97.3 °F) | Resp 18 | Ht 160 cm (5' 2.99") | Wt 60.147 kg (132 lb 9.6 oz) | BMI 23.50 kg/m² | SpO₂ 100%
- Constitutional: Patient appears well-developed, well-nourished, in no acute distress.
- Eyes: Conjunctivae are not injected. **Sclerae icteric**. Pupils are equal, round, and reactive to light. Extraocular movements are intact.
- ENT: **Mucous membranes moist**.
- Neck: Supple. No thyromegaly or nodules palpated.
- Cardiovascular: Regular rhythm, tachycardic. No murmurs appreciated. Intact distal pulses.
- Respiratory/Chest: Normal respiratory effort. No wheezes or crackles.
- Gastrointestinal/Abdomen: Normoactive bowel sounds. Soft. **Mild tenderness in RUQ. Liver edge palpable ~2cm beyond rib cage**. Nondistended.
- Musculoskeletal/extremities: **No peripheral edema**.
- Neurological: Alert and oriented to person, place, and date. Normal deep tendon reflexes. No asterixis.
- Skin: Skin is warm and dry. No acanthosis nigrans noted.
- Psychiatric: Normal mood and affect.

[Labs]

125 88 13 } 98
2.9 22 0.7 }
Ca 9.7

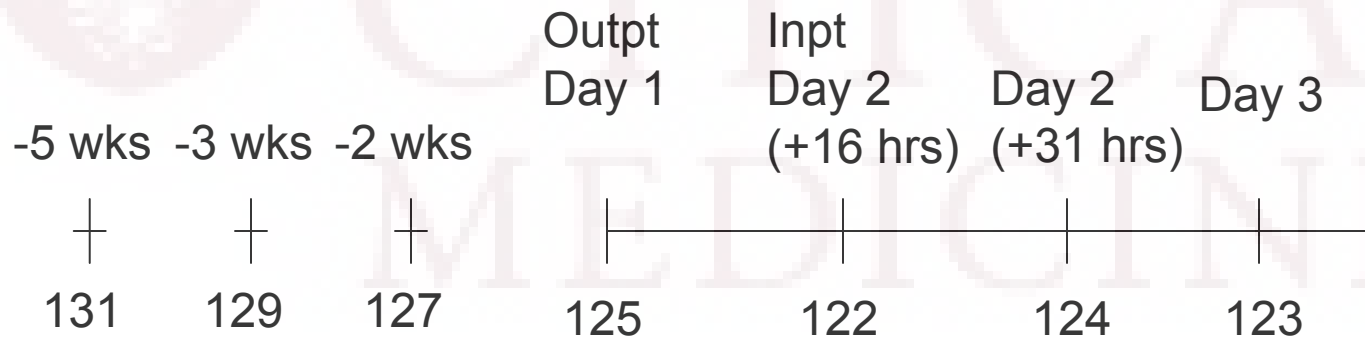
~~9.6 9.5 321
27.8~~

- Total protein 6.9, albumin 3.1, total bilirubin 10.5, alk phos 1027, AST 93, ALT 40
- PT 12.7, INR 1.0
- Hep B core ab, Hep B surface Ab and Ag, Hep A AB, RPR nonreactive

[Hospital Course]

Hospitalist Admission Note:

HypoNa: Likely hypovol hypoNa. Pt notes poor PO w/ loss of appetite and weight loss. Will check urine lytes, osmolality and rule out hypothyroidism and adrenal insuff but most likely simply hypovol hypoNa. Started IVF. Follow.



TSH 1.84
Random Cortisol
11.9, 15.3
Cort stim:
14.5→27.3→29.4

NS at 100 cc/hr

1L fluid restriction

[Hyponatremia work-up]

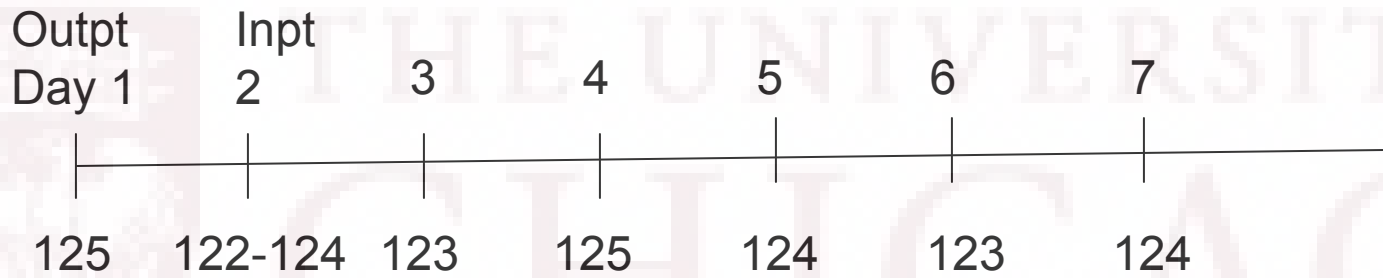
- Serum Na 125
- Plasma osm 286
- Urine Osm 530
- Urine Na 114
- Urine Cr 56
- FeNa 1.1%

Initial Assessment & Plan

52 yo woman with PMHx sig. for PSC and UC complicated by recurrent cholangitis who was admitted from liver clinic with hyponatremia and liver transplant work-up.

- Hyponatremia: Not acutely symptomatic though some of the fatigue and memory problems are probably related. Has adequate salt in her diet and drinks a reasonable amount water. Appears euvolemic on exam. Urine osm is inappropriately concentrated at 530. Urine Na of 114 does not suggest dehydration; not on diuretics. Her labs are consistent with SIADH but denies any nausea, pulmonary problems, CNS problems. Recently started on Zoloft. TSH nl. Random cortisol likely adequate.
 - Agree with 1L fluid restriction.
 - Would recommend gradual withdrawal of Zoloft.
- Hypokalemia: This may be from high salt diet (bacon, Chinese food). Her blood pressure is normal, suggesting against hyperaldosteronism.
 - Please check urinary potassium.

[Hospital Course cont.]



NS at 100 cc/hr

NaCl 1 gram BID

1L fluid restriction
Wean off sertraline

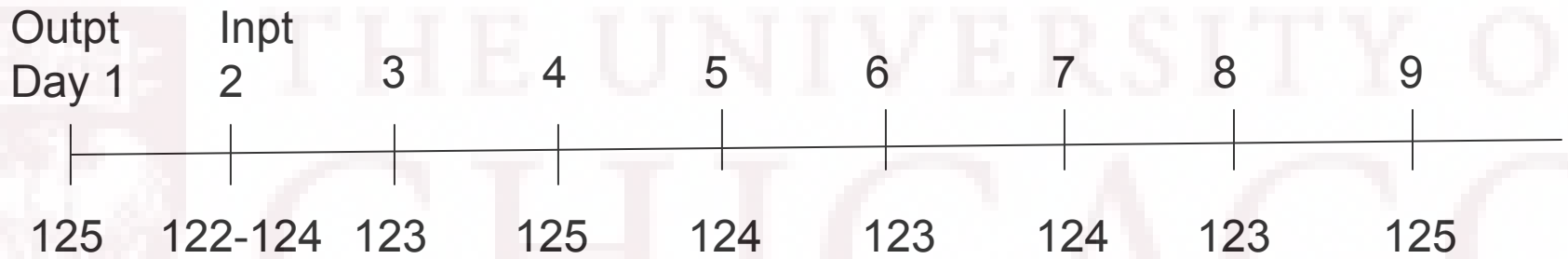
Serum osm 286
Urine osm 530
Urine Na 114
Urine Cr 56

Serum osm 288
Urine osm 790
Urine Na 118
Urine Cr 105

[Hospital Course cont.]

- SPEP normal
- UPEP
- Total cholesterol 1484
- HDL 31
- LDL (unable to calculate)
 - 1257
- Triglycerides 538

[Hospital Course cont.]



NS at 100 cc/hr

139!!! 136!!!

1L fluid restriction
Wean off sertraline

NaCl 1 gram BID

[Hospital Course cont.]

■ Hypokalemia

- K 2.9, up to 3.6 (with supplementation)
- Urine K 54
- Trans-tubular K gradient 6
- K 3.0 (3.6)

■ Hypercalcemia

- Ca 10.4, up to 11.1
- Phos 2.7-3.5
- PTH 27 (Ca 11.2)
- 25OH vit D 21 (2 months prior), 6 during the hospitalization
- Normal ionized Ca

[Hospital Course cont.]

- Started on pravastatin 40 mg daily, cholestyramine 4 grams BID.
- Follow up in Endocrine Clinic.

Clinical Questions

- Given modern instruments, how does hyperlipidemia still affect electrolyte assays?
- What is going on with her cholesterol?
- How do we treat her?



Pseudohyponatremia

XIN YI, PHD

CHEMISTRY FELLOW



Pseudohyponatremia

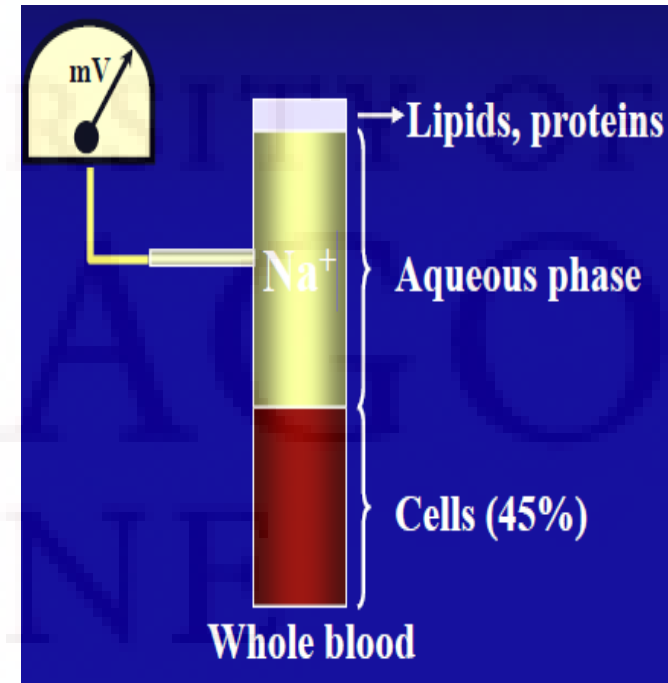
- Refers to the falsely low sodium concentrations measured in plasma when significant hyperproteinemia, hyperlipidemia or hypercholesterolemia is present.
- The measured sodium concentration does not reflect the true sodium concentration in the specimen. – *Analytical error*
- Distinct from the physiological dilutional hyponatremia that can be caused by an osmotic shift of water from cells to the bloodstream. -- it does not reflect a deficiency in total body sodium stores, but the blood sodium is, in fact, low. *The measurement is correct*

What caused falsely low result?

- There are 2 methods for measuring electrolytes in blood sample.
- Ion-selective electrode (ISE).

Instrument	Method
High-throughput analyzer	Indirect ISE (<i>dilution step</i>)
Whole blood analyzer	Direct ISE

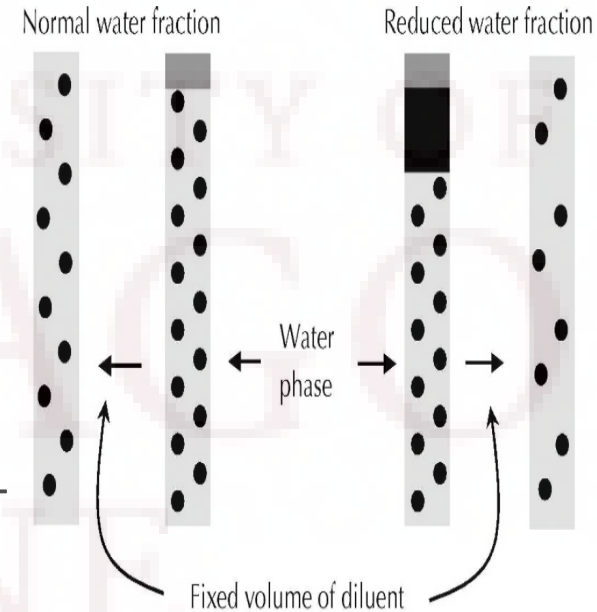
- ***Dilution step*** causes falsely decreased Na if high lipids or protein present.
- Sodium change most noticeable since it's the solute with the highest concentration in blood with a narrow reference range, but other analytes (K, Cl, etc) can be affected as well.



How the Dilution Step Introduces Error

Sodium is only in the water phase of plasma

- 1 gram Na within a 1L specimen
 - Specimen = 0.8 L of H₂O and 0.2 L lipid
 - $[Na] = 1 \text{ g}/0.8 \text{ L} = 1.25 \text{ g/L}$
- Now with dilution step:
 - Dilute 100x with water (1 L specimen + 99 L water)
 - So total volume = 100 L, total water volume = 99.8 L
 - So, $[Na] = 1 \text{ gram} / 99.8 \text{ L} = 0.01002 \text{ g/L}$
 - **Correcting for dilution: multiply x 100 → 1 g/L**
- Dilution factor is not 100 for the water!
- $99.8 \text{ L} / 0.8 \text{ L} = 124.75$



High Cholesterol as a cause of Pseudohyponatremia

We mostly expect high TGs as a cause of pseudohyponatremia

- But cholesterol...?
- Cholesterol does not cause visible turbidity in plasma compared with hypertriglyceridemia.



High cholesterol is a *known but uncommon* cause of pseudohyponatremia

- Seen in the context of obstructive jaundice, where the cases described in the literature have all involved **lipoprotein X**.

Approaches we will take

We are trying to set up a standardized approach to the processing of samples suspicious of pseudohyponatremia.

Measure **Lipemic index (for all samples), cholesterol, triglycerides if available.**

Any one of these three is High → Switch to direct ISE method to measure electrolytes.

[Looking back...a clue]

- Plasma osm **286** (normal: 289-309)
 - Hypotonic hyponatremia: true excess of free water relative to Na
 - Hypertonic hyponatremia: excess of another effective osmole (glucose) that draws water intravascularly
 - Isotonic hyponatremia: suggests presence of excessive lipids or proteins
- Calculated plasma osm = $2\text{Na} + \text{BUN}/2.8 + \text{glu}/18 = \mathbf{260}$
- The **measured** osmolality should not exceed the **predicted** by more than 10 mOsm/kg.
 - Presence of osmolar gap suggests something else is in the blood.

Patient's lipoprotein metabolism profile

Test	Result	Flag	Unit	RefValue
Cholesterol, Total	2301	h	mg/dL	
Triglycerides	447	h	mg/dL	
HDL Cholesterol	<3	l	mg/dL	
LDL Cholesterol	2053	h	mg/dL	

10/02/2007:
 TC 280
 TG 79
 HDH-C 78
 LDL-C 186

LpX was detected in this sample and is included as a major portion of LDL cholesterol.

Apolipoprotein B	236	h	mg/dL	48 - 124
LDL Triglycerides	308	h	mg/dL	<=50
VLDL cholesterol	247	h	mg/dL	<30
VLDL triglycerides	138	h	mg/dL	<120
Lp(a) Cholesterol	<3		mg/dL	<3

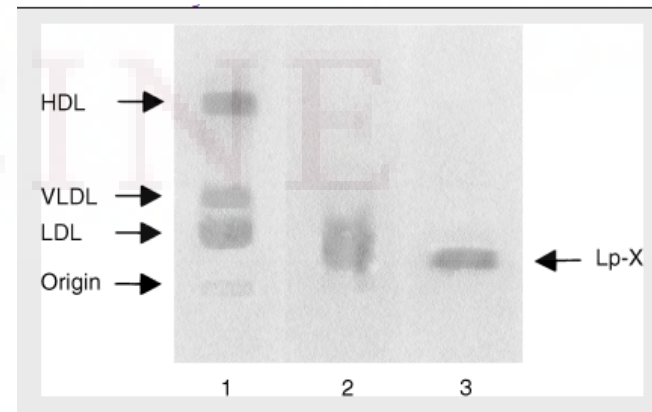
LpX

Present

Undetectable

What is Lipoprotein X?

- Mostly phospholipids and free (unesterified) cholesterol
- Albumin is the main protein
 - ApoA1, apoC
- Diagnosed by electrophoresis



[Lipoprotein X: causes]

- Cholestasis
 - Bile lipoprotein accumulates and refluxes into the plasma pool → binds albumin to form LpX
- Lecithin cholesterol acyl transferase (LCAT) deficiency
 - Unable to esterify free cholesterol in HDL → excess free cholesterol and phospholipids binds with apoA (not albumin).
 - HDL cannot mature and is rapidly cleared.
- IV infusion of Intralipid emulsion
 - Increased unesterified cholesterol, phospholipid, and LDL

Lipoprotein X: complications

- Hypercholesterolemia
 - No ApoB (LDL receptor)
 - Mostly taken up by nonparenchymal liver cells—no feedback control on hepatic cholesterol biosynthesis
 - 5x increased activity of HMG-CoA reductase in the liver and decreased uptake of chylomicron remnants by hepatocytes
 - ?LpX leaching cholesterol from hepatocytes
- Tendon xanthomata
- Hyperviscosity syndrome
- May not be atherogenic and may decrease atherosclerosis.
 - Not taken up by macrophages
 - Inhibits oxidization of LDL products.

Walli et al. [J Clin Invest.](#) 1984 Sep;74(3):867-79.

Chang et al. [J Lipid Res.](#) 2004 Nov;45(11):2116-22.

[Lipoprotein X: treatment]

- Statin therapy
 - Mostly excreted in bile, concern for toxicity; can also induce acute cholestatic hepatitis
 - Simvastatin, pravastatin reduce cholestasis, total bile acid levels among pts with primary biliary cirrhosis.
- Ursodeoxycholic acid
 - Reduces intestinal cholesterol absorption and bile acid reabsorption
- Bile acid sequestrants

Back to the Patient

	Adm	+4 wks	+5 wks	+12 wks
Total chol	1484	1961	1365	1443
HDL	31	32	37	26
LDL			1257	1359
Trig	538	406	355	288
ApoB (60-117)			246	266
Alk phos	1155	1198	1096	984
Total bili	10.3	8.2	7.4	6.0
Rx	Pravastatin 40 mg daily			Rosuvastatin 20 mg daily
	Cholestyramine 4 grams BID and ursodiol 500 mg TID			

Back to the patient: advanced treatment options

- Apheresis

- Consider in hyperviscosity syndrome, primary elevation of atherogenic lipoproteins (LDL)
- Invasive, transient effects

What is her risk of hyperviscosity syndrome?

- Viscosity (1.4-1.8): 2.2
- One case report of hyperviscosity syndrome in setting of PBC and lipoprotein X: serum viscosity of 2.9.
 - 1 week of blurred vision and paresthesia
 - Enlarging painful palmar xanthomas
 - Total cholesterol 2065, HDL 31, trig 455
 - Resolved with plasma exchange BUT recurred after 4 months.
 - Rosenson et al. [Gastroenterology](#). 1990 May;98(5 Pt 1):1351-7.

- What is her CAD risk?

- Coronary CT angiogram: no significant coronary artery stenoses

Back to the patient: advanced treatment options

■ ?Recombinant LCAT

- *Ex vivo* in LCAT deficient pt plasma:
 - ↓30% in unesterified cholesterol levels
 - ↑210% in cholesterol esters
 - ↑89% in HDL
 - Simonelli et al. **Biologicals**. 2013 Nov;41(6):446-9.
- Severe LCAT deficiency can occur in pts with advanced primary biliary cirrhosis and lipoprotein X.
 - Jahn et al. [Gastroenterology](#). 1985 Dec;89(6):1266-78.

LCAT pending...

Back to the patient:
advanced treatment options

■ **Transplant**

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[Take Home Points]

- When there is no treatment response, re-evaluate your diagnosis.
- Really check the plasma osm during the work up of hyponatremia.
- In patients with cholestasis and hyponatremia, consider pseudohyponatremia due to presence of lipoprotein X.
- It helps to know someone in the lab.

Pseudohyponatremia: the electrolyte exclusion effect

- Originally described in 1950s when electrolytes were measured by flame photometry.
 - Diluted serum sample
- Direct potentiometry was developed in the 1980s.
 - Undiluted sample
- More than 2/3 of labs in US use indirect ion potentiometry.
 - Diluted sample and then correct assuming plasma is 93% water.