Brigham and Women's Hospital
Founding Member, Mass General Brigham

A Challenging Case of Polyuria

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- Jefferson Medical College/Thomas Jefferson University
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- General Nephrology Fellowship @ Hospital of the University of Pennsylvania
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DISCLOSURES

Scientific advisory board for Calliditas Therapeutics

OBJECTIVES

- Develop a framework for approaching the evaluation of a patient with polyuria
- Identify potential causes and complications of polyuria

CASE

47M with metastatic de novo prostate cancer (mets to liver/lungs) admitted to MGH

- Rapid progression with development of malignant sacral mass with nerve root compression

- On degarelix (GnRH antagonist) and docetaxel (MT inhibitor)

- Awaiting liver biopsy to assess for small cell transformation

History

- Initially admitted with septic shock and peritonitis

- Underwent emergent ex-lap, found to have perforated sigmoid colon for which he underwent sigmoidectomy and end colostomy (1.5L stool output per day thereafter)

- Admitted to SICU
- Transiently on vasopressors (vaso 0.04 monotherapy)
- LR/NS boluses given for fluid resuscitation while NPO
- Subsequently found to have MSSA/PsA bacteremia + intra-abd cultures grew *Candida glabrata*
- Stabilized off pressors and transferred to the floor

History

- Subsequently developed acute onset **polyuria**
- **Daily UOP of 4-6L** for 8 days
- Concomitant **hypokalemia** despite consistent IV/PO repletion
- No LUTS, dysuria, urgency, frequency
- Felt significant thirst after days of being NPO with NGT in place

History

- Patient was uncharacteristically **agitated/angry and frustrated** with care, often limiting history

- No endorsed sx aside from polyuria and pain in his back/at the surgical site

- No ostomy issues; stable output

Past Medical History

PMH: HLD, HTN

PSH: Transperineal prostate biopsy, vasectomy, rhinoplasty, wisdom tooth extraction

SH: No tobacco, rare alcohol, occasional marijuana for nausea

FH: No history of kidney disease

Allergies: Chlorhexidine, shellfish

Home medications: APAP, amlodipine, melatonin, simethicone, tamsulosin 0.8mg daily

Inpatient medications: acetaminophen, cefazolin, LMWH ppx, fentanyl patch, omeprazole, pip-tazo, standing Kcl 40meq TID, phos-nak 1 packet QID

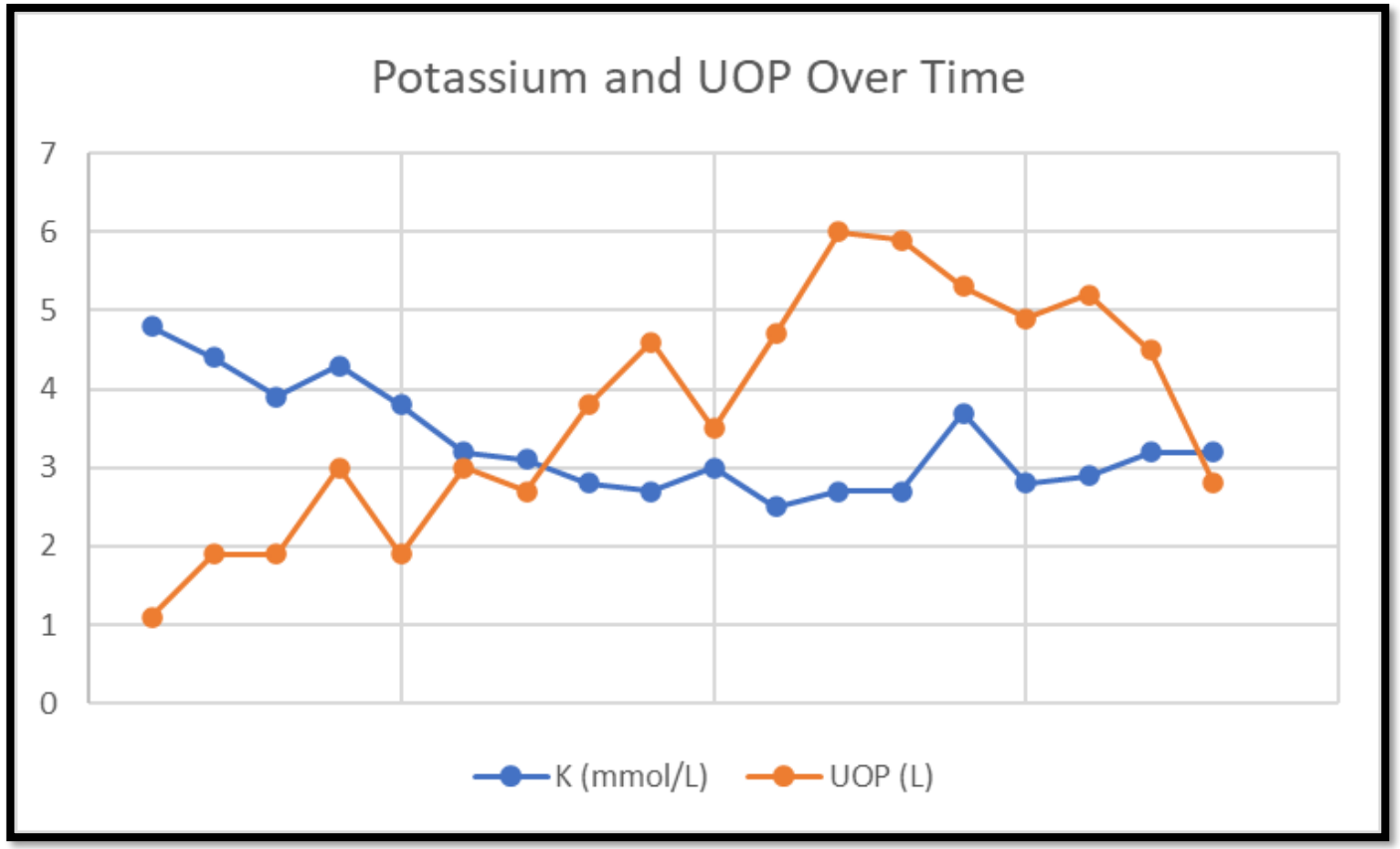
Physical Exam

VS T 36.8| HR 86 | **BP 154/90**| RR 18 | SpO2 98% on RA | 86.9kg
General – NAD
HEENT – MMM, sclera anicteric
Pulmonary – comfortable on RA, CTAB
Cardiac – tachycardic, no m/r/g;
Abdomen – soft, non-distended; non-tender
Skin – no rashes or erythema visible
Extremity WWP, no edema
Neuro: alert and oriented to person, place, time, and situation
Psych: Patient with intermittent acute bursts of agitation and irritation

Laboratory values

- UOsm on day prior to consult: 281
- UOsm day of consult: 294
- UNa 57, UK 57
- UA 1+ blood, no protein
- Cr 0.3-0.4 at the time of consult (after initial AKI, peak 1.15 on day of presentation)
- On presentation: Na 134, K 4.8, Cl 98, HCO3 24, BUN 39, Cr 1.15, Pi 5.1, Mg 2.2, Ca 9.9, Albumin 2.5
- On consultation: Na 141, K 2.7, Cl 100, HCO3 30, BUN 8, Cr 0.36, Glu 145, Ca 7.0, Albumin 2.5, Pi 1.5

Potassium trend



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Case Summary

48M with metastatic prostate cancer with mets to liver/lungs admitted to the hospital with disease progression now with acute onset polyuria and associated severe hypokalemia.

Daily UOP (by Foley) confirmed to be 4-6L

Labs notable for low potassium despite IV/PO repletion

Questions

- What would be the potential causes of the patient's polyuria?
- What additional tests would you send to evaluate causes of acute onset polyuria?
- Why is he persistently hypokalemic?

Question for the audience

What is the next best step in evaluation of his polyuria?

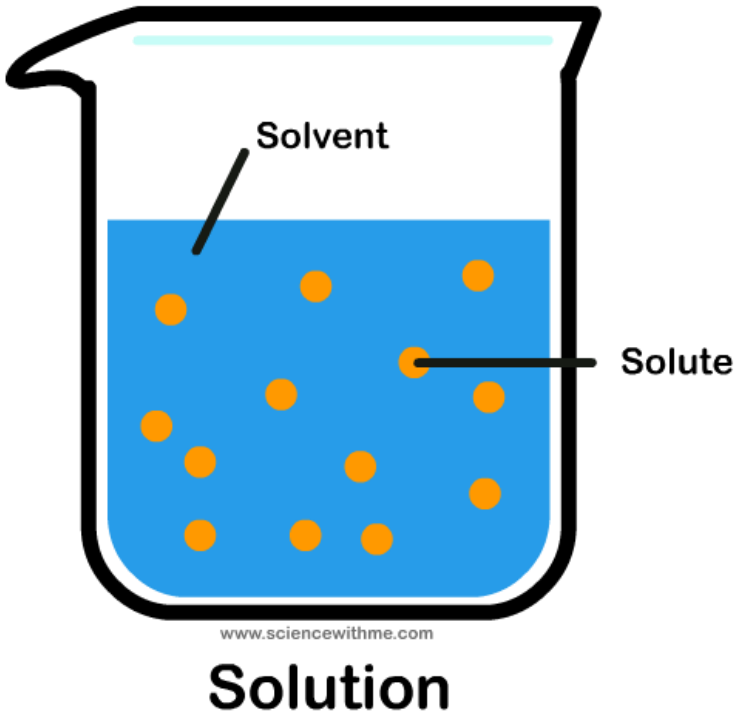
A. Check urine electrolytes

B. Give DDAVP

C. Check urine osmolality

D. Administer water deprivation test

Urine osmolality



$$\text{Urine osmolality (mOsm/kg)} = \frac{\text{Osmoles}}{\text{Urine Volume (L)}}$$

Term	Definition	Unit	Measurement Basis
Osmolality	Number of solute particles per **kilogram** of solvent	mOsm/kg H_2O	Based on **mass**
Osmolarity	Number of solute particles per **liter** of solution	mOsm/L	Based on **volume**

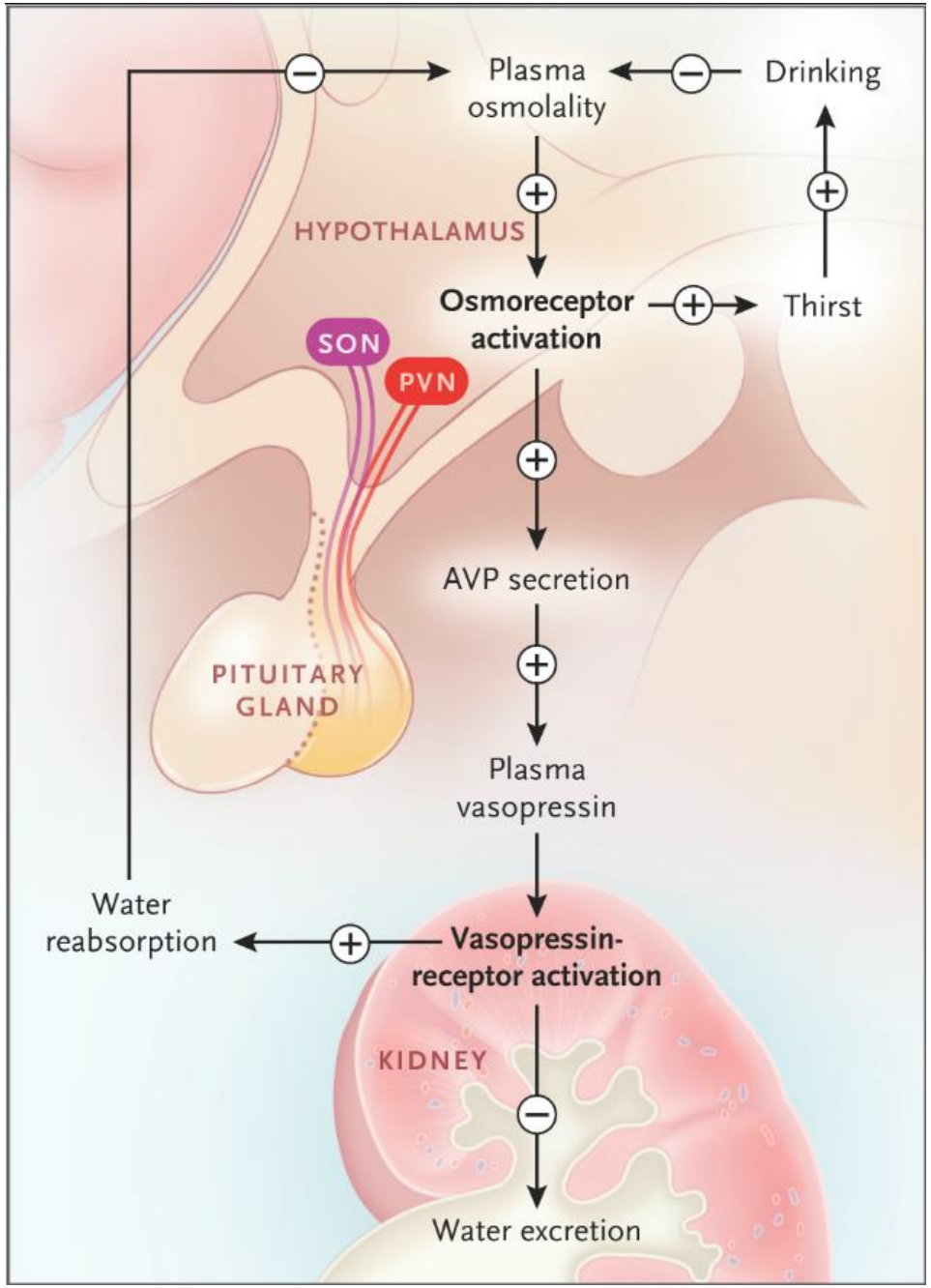
Homeostasis

Serum osmolality is tightly regulated (~285–295 mOsm/kg)

Water intake (via drinking, metabolism) and **solute load** (diet, catabolism) must be matched by output

The **kidney adjusts urine osmolality** (typically 50–1200 mOsm/kg) to maintain balance

- **If water intake is high → dilute urine** (↓ urine osm)
- **If water intake is low or solute load is high → concentrated urine** (↑ urine osm)



Knepper, Mark A., Tae-Hwan Kwon, and Soren Nielsen. "Molecular physiology of water balance." *New England Journal of Medicine* 372.14 (2015): 1349-1358.

How do I estimate the urine volume produced in a day? (assuming no other intake/losses)

800 mOsm
of NaCl

A. It depends on **serum osmolality**

B. It depends on **total body water**

C. It depends on **urine osmolality**

D. It depends on **GFR**

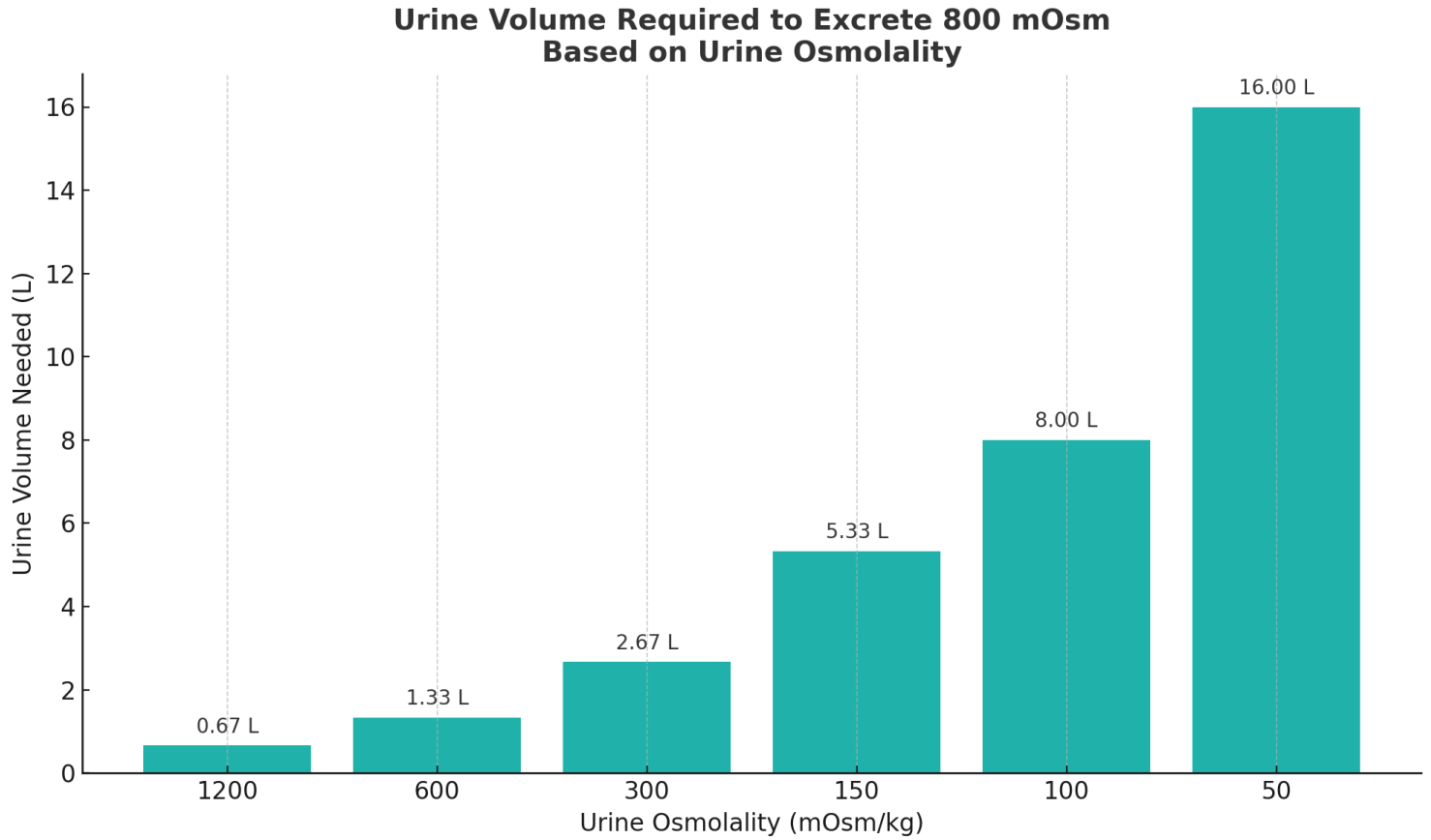
E. It depends on **ADH secretion rate**

What goes in must come out

$$\text{Urine Volume (L)} = \frac{\text{Osmoles}}{\text{Urine Osmolality (mOsm/Kg)}}$$

800 mOsm of NaCl

To maintain serum osmolality



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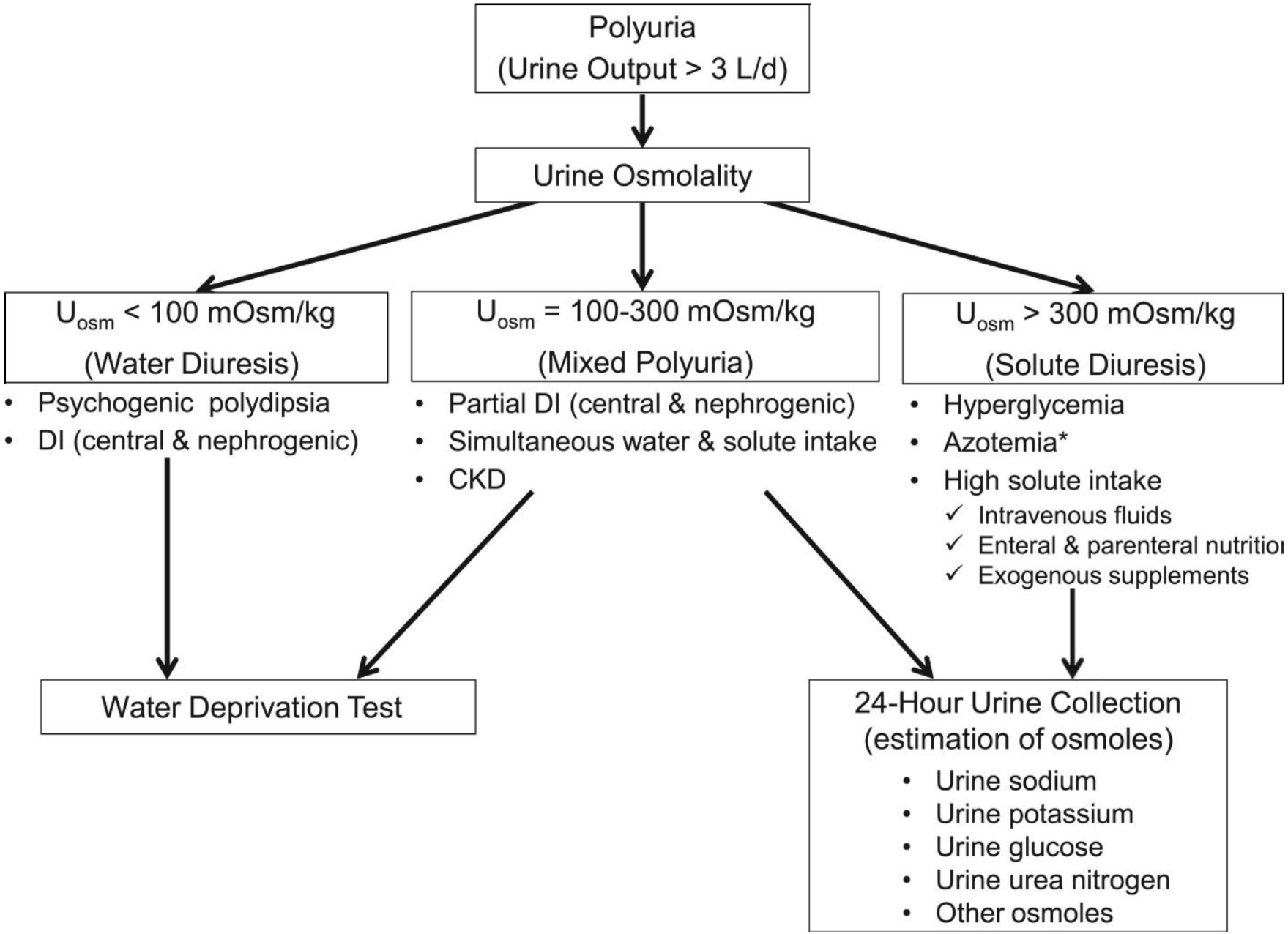

Bhasin, Bhavna, and Juan Carlos Q. Velez. "Evaluation of polyuria: the roles of solute loading and water diuresis." *AJKD 2016*

Back to our patient

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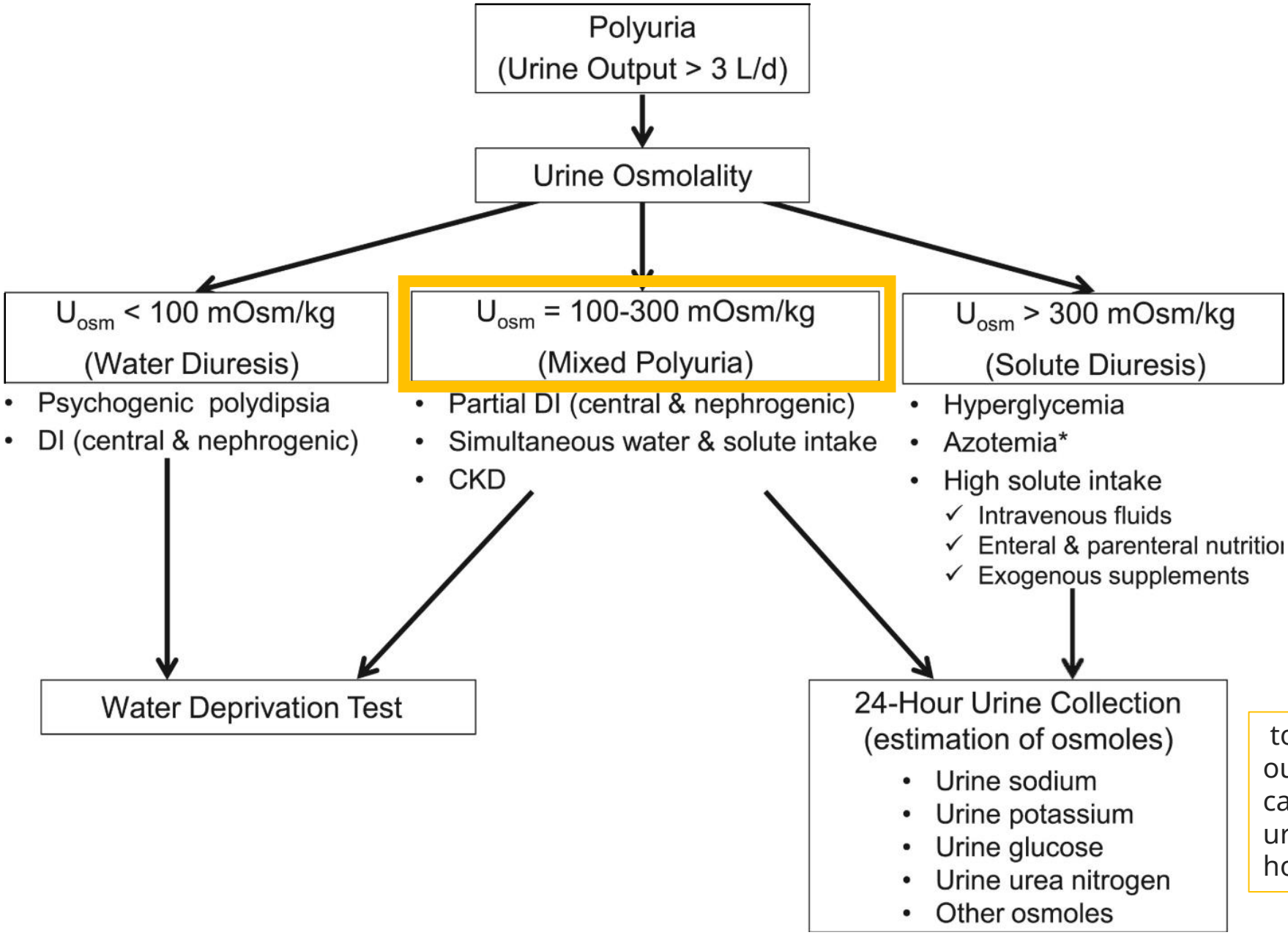
Daily UOP (by Foley) confirmed to be 4-6L

Labs notable for low potassium despite IV/PO repletion

UOsm 294 mOsm/Kg [reference range: 150 - 1,150 mOsm/kg H20]



total daily osmolar output can be calculated as the urine osmolality x 24-hour urine volume

Bhasin, Bhavna, and Juan Carlos Q. Velez. "Evaluation of polyuria: the roles of solute loading and water diuresis." *AJKD 2016*

Causes of polyuria in inpatient setting

- Volume resuscitation
- Hyperglycemia
- Post-ATN
- Diuretics, SGLT2i
- Post-obstruction
- High protein feeds
- Mannitol
- Renal salt wasting due to cisplatin or cerebral salt wasting

Work up

DDAVP trial

Uosm pre DDAVP: **295**
DDAVP 2mcg IV given @ 11.45am
Post DDAVP
Uosm @ 12.15pm: **351**
Uosm @ 12.47pm: **354**
Uosm @ 1.15pm: **357**
Uosm @ 1.45pm: **344**

Indicative of partial arginine vasopressin deficiency (partial central diabetes insipidus), though cause of this is unclear

24h UOP (7am - 7am): 4275ml
Pre DDAVP - total osmolar load for past 24h = ~**1180 mOsm**

Labs: K 3.3, phos 1.6, Mg 1.7

Causes of polyuria

- ~~Volume resuscitation~~
- ~~Hyperglycemia~~
- ~~Post-ATN~~
- ~~Diuretics, SGLT2i~~
- ~~Post-obstruction~~
- ~~High protein feeds~~
- ~~Mannitol~~
- ~~Renal salt wasting due to cisplatin or cerebral salt wasting~~

Transient Diabetes Insipidus After Discontinuation of Vasopressin in Neurological Intensive Care Unit Patients: Case Series and Literature Review

Michael A. Bohl[1], James Forseth[2], Peter Nakaji[1]

World Neurosurgery, 2017, 97, 479-488

ONLINE CLINICAL INVESTIGATIONS

Diabetes Insipidus After Discontinuation of Vasopressin Infusion for Treatment of Shock

Ferenchick, Hannah MD[1]; Cemalovic, Nail MD[1]; Ferguson, Nadia PharmD[2]; Dicpinigaitis, Peter V. MD[1]

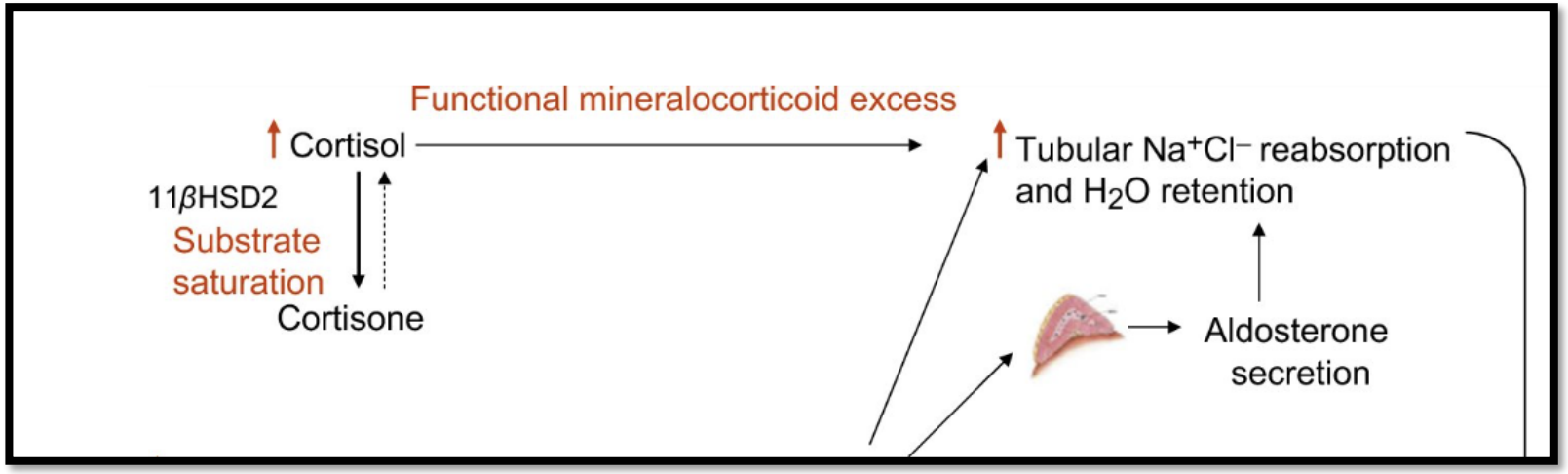
Author Information

Critical Care Medicine 47(12):p e1008-e1013, December 2019. | **DOI:** 10.1097/CCM.0000000000004045

- Historically seen in patients post neurosurgery
- In more recent times (especially COVID era, for reasons yet unclear) many case reports in patients without any clear predisposing factor
  - Length of vasopressin exposure in chronically critically ill Covid patients
- In CCM paper -- >1300 patients on vaso, no NSGY patients, 2 developed DI
  - Pts included – septic or cardiogenic shock
- Typically, close temporal association with vaso cessation
- Often self-limited
- May be more common than previously thought, but missed due to transient nature of injury + limited familiarity with the diagnosis

Hypokalemia in polyuria

- With malignancy associated ectopic ACTH, production of glucocorticoids/mineralocorticoids escalates rapidly
- Thus, classical signs of Cushing's syndrome on exam often absent
- Hypokalemia + metabolic acidosis most common (only 1:3 have both)
  - 2/2 excessive cortisol binding mineralocorticoid receptor
  - Should consider in tumors that are rapidly metastasizing/expanding



Sharma, Susmeeta T., and Lynnette K. Nieman. "Cushing's syndrome: all variants, detection, and treatment." *Endocrinology and Metabolism Clinics* 40.2 (2011): 379-391.

Cushing's and Polyuria

- Complex mechanistically – impaired urinary concentration is key

- Note that hypoK itself increases AVP-R (chicken vs egg)
- Tissue catabolism thought to drive urea diuresis

- Mineralocorticoid effect
  - Downregulate aquaporin (AQP2) in apical membrane of CD
    - Thus reducing water reabsorption --> polyuria

- Glucocorticoid effect
  - Downregulate urea transporters --> impair urine concentration --> decrease UOsm / polyuria
  - Glucocorticoids suppress ADH secretion --> polyuria

AVP and Cortisol

- DI is often "masked" in patients with AI
- Precise mechanism has been unclear
  - Glucocorticoid DEFICIENCY --> increase plasma AVP levels in rats
  - Water permeability of CD increases after adrenalectomy in AVP-D rats
- Case reports of IV high dose hydrocortisone (glucocorticoid EXCESS) --> polyuria / reduced AVP
- Clearly, close regulation between glucocorticoid / mineralocorticoid excess or deficiency and AVP production
  - We are only beginning to understand the mechanism

Hypokalemia

Polyuria

Case Reports > Pituitary. 2009;12(3):280-3. doi: 10.1007/s11102-008-0100-z.

Cushing's syndrome due to ectopic ACTH production by (neuroendocrine) prostate carcinoma

R A Alwani [1], S J C M M Neggers, M van der Klift, M G A Baggen, G J L H van Leenders, M O van Aken, A J van der Lely, W W de Herder, R A Feelders

Primary polydipsia

Diagnosis

- AM cortisol: 96.3 --> 187.0 (ref range: normal AM values: 5-25 ug/dL)

- ACTH: 782 (profoundly elevated)
- 24h urine cortisol: ~7k (profoundly elevated)

- Liver biopsy – high grade neuroendocrine tumor (transformation of androgen deprivation therapy resistant prostate cancer)
- Biopsy did NOT stain positive for ACTH
    - Immunohistochemical staining for ACTH commonly does not reflect biological behavior of a tumor
    - Started on steroidogenesis inhibitor (ketoconazole --> osilodrosat)

Ectopic ACTH production by metastatic prostate cancer

Follow up

- Seen by Endocrine
- Started on ketoconazole briefly then transitioned to osilodrostat
- Added spironolactone for persistent hypokalemia

- Unfortunately, he later had complication of GI bleed, by septic shock and passed peacefully with family at bedside

Take home points

- Polyuria can be due to water diuresis or solute diuresis

- In hospitalized patients (especially those with cancer), considering sources of ectopic ACTH is important in patients with hypokalemia or polyuria (important to recognize that these can present atypically/acutely)

REFERENCES

Bhasin, Bhavna, and Juan Carlos Q. Velez. "Evaluation of polyuria: the roles of solute loading and water diuresis." *American Journal of Kidney Diseases* 67.3 (2016): 507-511.

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Vokoun, Chad W., et al. "Case 1-2023: A 49-Year-Old Man with Hypokalemia and Paranoia." *New England Journal of Medicine* 388.2 (2023): 165-175.