Diabetes Insipidus

AVP deficiency and AVP resistance · Dilute urine while the serum concentrates

< 300 / > 290
urine osm / serum osm

THE 2022 RENAMING: LEARN BOTH SETS OF WORDS

Central DI is now arginine vasopressin deficiency (AVP-D). Nephrogenic DI is now AVP resistance (AVP-R). The change was endorsed by the Endocrine Society, the European Society of Endocrinology, the Pituitary Society and others, and it exists for a safety reason: **"diabetes" made staff think of diabetes mellitus**, and patients have been harmed by insulin given for the wrong disease or, worse, by **desmopressin being withheld or stopped** on a ward that assumed the label meant something else. Charts and colleagues will use both names for years, so recognize both.

STEP 1: IS IT REALLY DI? *most polyuria referred as DI is something else*

CONFIRM TRUE POLYURIA

More than 3 L/day, or 50 mL/kg/day. Separate it from **frequency** (small volumes, usually urinary tract or prostatic) by actually measuring a 24 hour volume. Frequency is far commoner and needs no endocrine workup.

EXCLUDE OSMOTIC DIURESIS FIRST

Check the glucose. Then consider **mannitol, high-protein feeds, post-obstructive diuresis, recovering AKI** and a high urea. In osmotic diuresis the urine is **not** dilute: urine osmolality sits **above 300**, which separates it immediately from DI.

THE SIGNATURE

Urine osmolality < 300 with serum osmolality > 290 or a high-normal sodium. **A raised serum sodium alongside dilute urine effectively makes the diagnosis** and no provocation test is needed: the patient has already failed the water deprivation test in real life.

STEP 2: WHICH OF THE THREE? *the polyuria-polydipsia triad*

Condition	Serum Na	Urine osm after DDAVP	What it means
AVP deficiency *formerly central DI*	**High** or high-normal	**Rises > 50%**	The pituitary cannot make ADH but the kidney still answers it. **Replace the hormone.**
AVP resistance *formerly nephrogenic DI*	**High** or high-normal	**Little or no rise**	Hormone is present; the kidney cannot respond. **Giving desmopressin will not work.** Remove the cause.
Primary polydipsia	**Low-normal**	Concentrates (may be blunted by washout of the medullary gradient)	Drinking drives the polyuria. **The low-normal sodium is the giveaway**: restricting water corrects it, and desmopressin here causes dangerous hyponatremia.

STEP 3: COPEPTIN HAS REPLACED THE WATER DEPRIVATION TEST *where the assay is available*

WHY THE CHANGE

Copeptin is cleaved from the same precursor as ADH in equal amounts and is stable enough to measure, so it is a usable surrogate for a hormone that is not. **The classic indirect water deprivation test misclassified a substantial minority of patients**, which is why stimulated copeptin has taken over as the reference standard.

HOW IT IS DONE

Hypertonic saline-stimulated copeptin is the most accurate test, around 96%. Saline is infused until the **sodium exceeds 149 mmol/L**, then copeptin is measured: **below 4.9 pmol/L indicates AVP deficiency, above it indicates primary polydipsia** Fenske, 2018. **Arginine stimulation is better tolerated but less accurate.** The saline test needs close sodium monitoring and is not a bedside test.

FIND THE CAUSE *the subtype dictates where to look*

Subtype	Causes, most common first
AVP deficiency *central*	**Pituitary or hypothalamic surgery is the commonest**, then **head trauma**, craniopharyngioma and other tumors, and **infiltrative disease** (sarcoidosis, Langerhans cell histiocytosis, hypophysitis, including checkpoint-inhibitor hypophysitis). Also **Sheehan syndrome** and brain death. **Image the pituitary in any new case**: loss of the normal posterior pituitary bright spot on T1 supports the diagnosis.
AVP resistance *nephrogenic*	**Lithium is by far the commonest** and can persist after the drug is stopped. Then **hypercalcemia** and **hypokalemia** (both correctable, so check them early), chronic kidney disease, post-obstructive uropathy, demeclocycline and amphotericin. **Congenital forms** (AVPR2 or aquaporin-2 mutations) present in infancy.

TREAT BY SUBTYPE *and give water in both*

Subtype	Treatment	Watch for
AVP deficiency	**Desmopressin.** 1 to 2 mcg IV or SC q12h, or 10 to 20 mcg intranasally BID, or 0.1 to 0.4 mg PO, titrated to urine output.	**Build in a deliberate escape window** each day where the urine is allowed to run dilute. Without it the patient accumulates water and becomes **hyponatremic**, which is the commonest iatrogenic harm in treated AVP-D.
AVP resistance	**Remove the cause first** (lithium, calcium, potassium). Then a **low-solute, low-sodium diet** plus a **thiazide**, with **amiloride** specifically for lithium-induced disease. An NSAID can be added under supervision.	**The thiazide paradox:** mild volume depletion increases proximal reabsorption, so less water reaches the collecting duct and urine output falls. **Amiloride blocks lithium entry through ENaC**, which is why it is the targeted choice.
Both	**Free access to water is the single most important measure.** Correct any hypernatremia deliberately.	**Free water deficit = TBW × (Na/140 − 1).** Correct at **≤ 10 mEq/L per 24 h** if chronic, to avoid cerebral edema, and **replace ongoing urine losses on top of the deficit** or the sodium will plateau.

THE POST-PITUITARY TRIPHASIC RESPONSE: THE TRAP THAT KILLS

After pituitary surgery roughly a quarter of patients follow three phases: **DI for the first few days, then a SIADH-like hyponatremic phase around days 5 to 10** as stored hormone leaks from the dying posterior pituitary, then **permanent DI. Continuing desmopressin into the middle phase causes severe, sometimes fatal hyponatremia.** When the urine output falls and the sodium starts dropping, stop the desmopressin rather than reaching for more. These patients also need **glucocorticoid cover**: unreplaced cortisol deficiency both mimics SIADH and can mask DI until steroid is given.

PEARLS & PITFALLS

- **Check the glucose before anything else.** Osmotic diuresis is commoner than DI and the urine is not dilute.
- **A high sodium with dilute urine is the diagnosis.** Do not deprive a patient who has already proven it.
- **Desmopressin distinguishes deficiency from resistance**: the kidney either answers or it cannot.
- **A low-normal sodium points to primary polydipsia**, where desmopressin is dangerous rather than diagnostic.
- **Lithium is the commonest cause of AVP resistance**, and amiloride is the targeted treatment.
- **Never let a DI patient be nil by mouth without an IV plan.** Losing water access is how sodium reaches 170.

References: Working Group for Renaming Diabetes Insipidus, 2022 joint statement (Endocrine Society, ESE, Pituitary Society and others) · Fenske et al, copeptin-based diagnosis of diabetes insipidus, NEJM 2018 · Refardt et al, arginine or hypertonic saline-stimulated copeptin, NEJM 2023 · international consensus on congenital AVP resistance, Nat Rev Nephrol 2024.