PRIMER

Diabetes insipidus

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Abstract | Diabetes insipidus (DI) is a disorder characterized by excretion of large amounts of hypotonic urine. Central DI results from a deficiency of the hormone arginine vasopressin (AVP) in the pituitary gland or the hypothalamus, whereas nephrogenic DI results from resistance to AVP in the kidneys. Central and nephrogenic DI are usually acquired, but genetic causes must be evaluated, especially if symptoms occur in early childhood. Central or nephrogenic DI must be differentiated from primary polydipsia, which involves excessive intake of large amounts of water despite normal AVP secretion and action. Primary polydipsia is most common in psychiatric patients and health enthusiasts but the polydipsia in a small subgroup of patients seems to be due to an abnormally low thirst threshold, a condition termed dipsogenic DI. Distinguishing between the different types of DI can be challenging and is done either by a water deprivation test or by hypertonic saline stimulation together with copeptin (or AVP) measurement. Furthermore, a detailed medical history, physical examination and imaging studies are needed

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polyuria, despite intact AVP secretion and an appropri-
ate antidiuretic renal response. Gestational DI results

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Posterior Pituitary

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CHAPTER OUTLINE

KEY POINTS

- The posterior pituitary is composed of neural tissue and consists of distal axon terminals of the hypothalamic magnocellular arginine vasopressin (AVP) and oxytocin neurons that constitute the neurohypophysis.
- Regulation of neurohypophyseal hormone synthesis occurs at the level of transcription. Stimuli for the secretion of AVP or oxytocin also induce transcription and increase the hormone messenger ribonucleic acid (mRNA) content in the magnocellular neurons.
- Physiologic regulation of AVP synthesis and secretion involves two systems: osmotic and pressure/volume. Each is controlled by separate neural inputs to the neurohypophysis and has transduction cascade that results in insertion of aquapo water channels into the apical membrane of principal ce the renal collecting duct.
- Diabetes insipidus (DI) is a disorder of a large volume of (diabetes) that is hypotonic (dilute) and tasteless (insipic leading to polyuria and polydipsia. It can be caused by c AVP secretion, increased AVP catabolism, or decreased A effect in the kidneys.
- The syndrome of inappropriate antidiuresis (SIAD) occur plasma levels of AVP are elevated at times when physiol AVP secretion from the posterior pituitary would norma be osmotically suppressed, leading to water retention a

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Diagnosis and Management of Central Diabetes Insipidus in Adults

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Diagnostic Testing for Diabetes Insipidus

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- Diabetes insipidus (DI) is a form of polyuria–polydipsia syndrome and is characterized by hypotonic polyuria (excessive urination; >50 ml/kg body weight/24 h) and polydipsia (excessive drinking; >3 l/day) After exclusion of disorders of osmotic diuresis (such as uncontrolled diabetes mellitus)
- A large patient survey showed that >80% of patients with CDI preferred a name change, with the clear wish to not use the term diabetes in the name.
- Recently, an international working group published a position statement to rename central DI to **vasopressin (AVP) deficiency** and nephrogenic DI to **vasopressin (AVP) resistance.**

Causes of Hypothalamic/Central Diabetes Insipidus

- **Neurosurgical interventions**, such as transsphenoidal or transcranial .

  50–60% of patients develop CDI post-surgery, but most recover, a small number permanent CDI

  Craniotomies, particularly for large tumors, are more likely to result in permanent CDI.

- If there is a **complete stalk section,** a pattern known as **triphasic** DI:
- Initial Phase (DI): Occurs within the first 24 hours after surgery, caused by axon shock that disrupts AVP signaling
- Antidiuretic Phase: occures 5-7 days post-surgery, uncontrolled AVP release leads to hyponatremia, exacerbated by improper IV fluid
- Final Phase (Permanent CDI): Damaged neurons undergo **gliosis**, leading to permanent CDI
- **Isolated Second Phase Hyponatremia:** in 10% to 25% of patients after pituitary surgery without preceding or subsequent phases of DI.
- This phase typically presents 7-10 days post-surgery and resolves after a few days.
- Symptoms include headache, nausea, vomiting, or seizures due to water retention.

- **Sellar Masses and CDI:**
- **Pituitary adenomas** almost never cause CDI
- if a patient presents with a pituitary mass and symptom of CDI it is likely caused by something other than a pituitary adenoma.
  - sellar mass is more likely to have a **non-pituitary tumor** or a **granulomatous disorder** than a pituitary adenoma.
  - **Craniopharyngiomas** are particularly associated with CDI, especially after extensive suprasellar surgery.
- **Other Tumors Causing CDI:**
- Germinomas, pinealomas, Meningioma and metastatic tumors (usually from breast or lung cancer)
- Metastases are twice as likely to involve the posterior pituitary compared to the anterior pituitary due to its direct arterial blood supply.
- Most tumors in the hypothalamic-pituitary area causing CDI are slow-growing so A rapidly growing mass in this region should raise suspicion of a metastatic tumor.

- **Granulomatous Diseases and CDI**
- **Sarcoidosis** and **histiocytosis** are the most common granulomatous diseases linked to CDI.
  - These conditions often have systemic manifestations, making the diagnosis easier.
  - MRI Findings: Hypothalamic involvement, absence of the posterior pituitary bright spot on T1-weighted images, and pituitary stalk widening.
  - Although there are reports of CDI resolution with treatment, **permanent** DI is more typical once the disease is established.
- **Lymphocytic Infundibuloneurohypophysitis (LIN):** with a thickened pituitary stalk and loss of the bright spot on T1 MRI
  - Lymphocytic **adenohypophysitis** presents classically in **females around the time of pregnancy**, whereas **infundibuloneurohypophysitis** occurs in **either sex.**
  - Personal or family history of autoimmune disorders
  - Chronic inflammation of parasellar structures (e.g., hypertrophic pachymeningitis,)
  - Presence of anti-rabphilin 3A antibodies
  - Infundibuloneurohypophysitis occurring in **middle-aged to elderly males** in association with Ig G4-related systemic disease has been reported.

• BOX 8.1 Diseases Associated With Enlarged Infundibular Stalk

1. Germinoma
2. Craniopharyngioma
3. Metastases to the hypothalamus and long portal vessels (e.g., carcinoma of the breast or lung)
4. Granulomatosis diseases
   a. Langerhans cell histiocytosis
   b. Sarcoidosis
   c. Granulomatosis with polyangiitis (GPA)
   d. Non–Langerhans cell histiocytosis (e.g., Erdheim-Chester disease)
5. Tuberculosis
6. Lymphocytic infundibulo-hypophysitis

- **IgG4-related Hypophysitis:**
  - Often involves other organs (e.g., pancreas, other endocrine glands).
  - Diagnosed through elevated serum IgG4 levels and biopsy with characteristic histology.
  - Treatment: Responds well to steroids or immunosuppressive therapy.
- **Idiopathic CDI** without a known cause, but research suggests many cases may have an autoimmune basis.
  - Antibodies targeting AVP cells have been found in several patients with idiopathic CDI.
  - Up to 30% of patients also have autoimmune endocrine diseases, which is higher in type 1 DM
- **CDI in Subarachnoid Hemorrhage (SAH)**
- Incidence: ~15% of patients SAH
  - CDI typically resolves in patients who survive the initial injury.
  - Permanent CDI is rare but can occur following surgical clipping of anterior communicating artery aneurysms.
- Adipsic CDI (ADI): vascular damage to osmoreceptors in the anterior hypothalamus, leading to adipsia

- **CDI in Traumatic Brain Injury (TBI)**
- Prevalence: 15-20% of patients with moderate or severe TBI develop CDI shortly after injury.
  - If not managed carefully, patients can develop hypernatremia due to impaired thirst or cognitive decline.
  - Persistent CDI and hypernatremia often indicate **poor outcomes,** correlating with rising intracranial pressure
  - Occasionally Triphasic Response in TBI:
- Close fluid monitoring during the second phase (SIADH) to avoid cerebral edema and raised intracranial pressure.
  - Administer **intermittent** parenteral desmopressin.
- **Cortisol Deficiency and CDI in TBI patients**
- may also experience anterior pituitary dysfunction, leading to ACTH and cortisol deficiency
  - Cortisol deficiency can mask CDI symptoms even without AVP.
  - If CDI resolves spontaneously, consider adrenal insufficiency as a potential cause
- **Other Rare Causes of CDI:**
- Pituitary **abscess/ lymphoma and leukemia** more common in **non-lymphocytic leukemia**
- MRI in leukemia can show infiltration or an infundibular mass, but often appear normal, even when leukemic cells are found in CSF

Mechanisms/pathophysiology
Acquired central DI.

Despite numerous lesions that could cause central DI, many patients do not develop the condition.beacause:

1:AVP synthesis occurs in the hypothalamus and not in the posterior pituitary gland,. Thus, lesions in the sella turcica that damage only the posterior pituitary **leave the cell bodies intact** and therefore do not usually cause central DI;for example, enlarging large pituitary macroadenomas allowing sufficient time for the site of AVP release to shift more superiorly to the pituitary stalk

development of DI from a pituitary adenoma is so uncommon that its presence should lead to consideration of alternative diagnoses, such as craniopharyngioma or more rapidly enlarging sellar or suprasellar masses (such as metastatic lesions or acute haemorrhage), which do not allow sufficient time for a shift in the site of AVP release.

2.The **AVP-producing neurons** in the hypothalamus have a large reserve capacity, needing **80–90% destruction** before DI symptoms occur.Even severe lesions must extensively damage these neurons to cause DI.

3. Similar to all neurons, the probability of retrograde neuronal degeneration occurring **depends on how close the axotomy is to the cell body** of the magnocellular neuron. transection of the pituitary stalk at the level of the diaphragm sellae (**low stalk transection**) caused only **transient central DI**, whereas transection at the level of the infundibulum (**high stalk transection**) caused **permanent central** DI in most patients

Adipsic Diabetes Insipidus (ADI)

- rare but dangerous combines CDI with adipsia due to damage to hypothalamic **osmoreceptors**.
- Osmoreceptors in the **anterior hypothalamus** regulate thirst and AVP release.
- Most CDI patients have intact osmoreceptors, preventing hypernatremic dehydration unless Diminished consciousness or Limited access to water.
- ADI occurs when damage extends to both the neurohypophysis and osmoreceptors
- **Surgical Causes of ADI**
- ADI can result from extensive surgery for:
  - Hypothalamo-pituitary tumors (e.g., large **craniopharyngiomas**).
  - after s gical clipping of anterior communicating artery aneurysms, which damage osmoreceptors while sparing baroreceptors.
- In craniopharyngioma surgery, both osmotic and baroreceptor-regulated AVP release may be lost.
- **Clinical Complications of ADI** can be associated with a **hypothalamic syndrome:**
  - Hyperphagia
  - Sleep apnea
  - Thermoregulation issues
  - Seizures

- **Genetic Causes of CDI**
- **Familial CDI:**
  - Typically presents with polydipsia and polyuria during **childhood or adolescence.**
  - Unlike NDI, which manifests at birth, familial CDI may be **asymptomatic in infancy.**
- Genetic Defects:occur in the neurophysin or signal peptide regions of the AVP pre-prohormone.
- **autosomal dominant** phenotype despite heterozygous mutations.
- MRI Findings: Variability exists among family members, but most consistent finding is the progressive loss of bright spot on T1-weighted images.
- **Wolfram Syndrome (DIDMOAD)**
  - Rare autosomal-**recessive** disorder characterized by DI, DM, Optic Atrophy, and Deafness (DIDMOAD).
  - Caused by mutations in the Wolframin protein involved in protein folding, β-cell proliferation, and calcium homeostasis.
  - its dysfunction leads to widespread endocrine and CNS disorders.
  - DI typically occurs later in the disease progression

- **CDI in Brain Death**
- Reported in 50% to 90% of patients with brain death, likely due to rising intracranial pressure and hypothalamic damage.
- **Management in Organ Donors:**
  - Treatment of CDI is now considered standard care in organ donors who develop CDI, ensuring optimal conditions for organ preservation.

Primary Polydipsia

- Causes of Primary Polydipsia
- **Organic Brain Lesions**: Conditions like **sarcoidosis of the hypothalamus** and **craniopharyngioma** can impair thirst regulation.

In conditions like **hypothalamic sarcoidosis**, increased water intake is more likely due to enhanced thirst rather than impaired AVP secretion.

- **Drug-Induced:** Medications causing dry mouth or affecting the renin-angiotensin system can trigger increased thirst.
- **Psychiatric Disorders:** Common in psychiatric patients, with up to 42% exhibiting polydipsia, often without an organic cause.
- **Habitual Polydipsia:** Increasingly seen in health-conscious individuals who alter drinking habits for perceived well-being benefits.

Primary Polydipsia

1.Common in patients with **neurodevelopmental** disorders (e.g., autism, intellectual disability) and **psychotic disorders** (e.g., schizophrenia, schizoaffective disorder, bipolar disorder and psychotic depression)

- Occurs in 11-20% of chronic schizophrenia patients.
- Linked to episodes of hyponatraemia, especially during psychotic relapses, termed Psychosis Intermittent Hyponatraemia-Polydipsia (PIP) syndrome
  - **Behavioral Patterns:**
    - especially schizophrenia, **rarely report thirst** but often provide **delusional reasons** for excessive water intake (e.g., to reduce anxiety or feel better).
    - Patients may exhibit compulsive drinking behaviors, such as always carrying a cup, drinking from toilets,
    - associated with other stereotypical behaviors (e.g., smoking, pacing), and they **typically do not drink at night, unlike patients with DI.**
  - In PIP patients, hyponatremia must be distinguished from that caused by psychotropic medications(e.g., antipsychotics, carbamazepine), antihypertensive drugs (e.g., thiazides), or diabetic medications(e.g., chlorpropamide).
  - The **impaired water excretion** caused by antipsychotic drugs is typically **stable** and **more marked** than that in patients with PIP.

Risk factors
Primary polydipsia

- **2. Compulsive Water Drinking (CWD):**
- Seen in non-psychotic Axis I psychiatric disorders.
- Rarely leads to hyponatraemia without external factors (e.g., thiazide diuretics).
- Increasing prevalence in the general population, particularly among **women**, due to lifestyle trends promoting hydration.
  - often associated with **excessive thirst** and **psychosomatic** disorders(e.g., depression, anxiety, obsessive-compulsive disorder, anorexia nervosa).

Risk factors
Primary polydipsia

3. Dipsogenic DI:

- Dipsogenic DI results from a low thirst threshold.
    - is associated with **increased thirst** and is thought to have **systemic** rather than psychological causes.
    - overlap between CWD without psychiatric illness and dipsogenic DI is unclear, as they lack distinguishing features.
    - Definitive Diagnosis of dipsogenic DI requires assessment of the osmotic threshold for thirst.

Diabetes Insipidus of Pregnancy

- Thirst and fluid intake are common, but polyuria may indicate DI
- **Two forms of transient DI in pregnancy** are linked to the placental oxytocinase which degrades (AVP)
- **Type 1: AVP-Resistant DI of Pregnancy**
- Abnormally high oxytocinase activity degrades AVP,
- Associated with conditions like preeclampsia, acute fatty liver, and coagulopathies.
- Affected patients have decreased metabolism of AVPase by the liver.
- Symptoms usually emerge in **late second or early third trimester.**
- More common in multiple pregnancies but does not affect future pregnancies.
- **Type 2: Accelerated Metabolism of AVP**
- Occurs in patients with borderline AVP function (e.g., mild nephrogenic DI or partial hypothalamic/ neurohypophyseal DI).
- Increased AVP degradation overwhelms the neurohypophysis.
- Symptoms appear **early** in pregnancy but do not hinder labor or lactation.
- **Sheehan syndrome** have been reported to have asymptomatic partial DI but rarely develop overt DI.

Nephrogenic Diabetes Insipidus

- **Genetic Causes of NDI**
- Genetic forms usually manifest in infancy with vomiting, failure to thrive, and polyuria.
- NDI can be caused by mutations in either the V2 receptor or the aquaporin 2 (AQP2) water channels.
- **1. V2 Receptor Mutations**
- Over 90% of genetic NDI cases are **X-linked recessive,** mainly affecting **males**.
- 200+ mutations of the V2 receptor are known, with three main categories:
  - Type 1: Impaired AVP binding.
  - Type 2: Defective receptor transport (most common).
  - Type 3: Unstable receptors that are degraded.
- 10% of V2 receptor mutations occur de novo.
- Female carriers are typically asymptomatic, but some may exhibit reduced urine concentration in response to AVP.
- **2. Aquaporin 2 Mutations**
- **Autosomal-recessive mutations of** the AQP2 gene should be suspected when both males and females are affected, especially in cases of consanguinity.

- **Acquired NDI in Adults**
- most common cause being **lithium** therapy.
- **hypokalemia**, **hypercalcemia**, and the **resolution of urinary tract obstruction.**
- Lithium disrupts urea transporters and significantly reduces aquaporin 2 levels by up to 95%, impairing water reabsorption.
  - Lithium-induced aquaporin defects are slow to correct and may be permanent.
- **Demeclocycline** and other drugs can also cause NDI

Diagnostic Steps

- 1.**Confirm Polyuria**: first step is to rule out urinary **frequency** caused by conditions like bladder wall defects, infection, or prostate disease, which can mimic polyuria.
- Diagnostic Criteria for Polyuria:
  - A 24-hour urine volume > 50 mL/kg body weight confirms polyuria
  - Exclude other causes like diabetes mellitus, hypercalcemia, hypokalemia, and chronic renal failure through biochemical tests.
- **2.Urine Osmolality and Serum Sodium**
- **Urine Osmolality:**
  - A urine osmolality > 800 mOsm/kg rules out DI and supports a diagnosis of primary polydipsia.
  - Low urine osmolality is common in polyuric states but requires further testing for accurate diagnosis.
- **Serum Sodium:**
- Presenting serum sodium concentration is almost always normal in DI
- results at the higher part of the reference range are more suggestive of DI
- whereas sodium levels below the normal range are suggestive of primary polydipsia

- **3. Diagnostic Challenges**
- **Water Deprivation Test**
  - **Dehydration Phase**:
    - A elevation plasma osmolality in a functioning osmoregulatory system will secrete AVP, concentrating urine (>**800 mOsm/kg).**
    - a plasma osmolality of over **295** mOsm/kg H2 O is needed to stimulate sufficient AVP to maximally concentrate the urine.
    - In primary polydipsia, urine concentrates normally
    - In CDI or NDI, urine remains dilute despite dehydration
  - **Desmopressin Challenge**:
  - If upon **thirsting**, urinary osmolality **remains** <**300 mOsm/kg** , after desmopressin injection, urinary osmolality:
  - not increase by >50% **complete nephrogenic DI** is diagnosed
  - increase is >50% **Complete central DI** is diagnosed
- In **partial central DI and primary polydipsia,** urinary osmolality increases to **300–800** mOsm/kg, with an increase of >**9% (in partial central DI)** and <**9% (in primary polydipsia)** after desmopressin injection.
- overall diagnostic accuracy is 70%, and accuracy is only 41% in patients with primary polydipsia

Diagnostic Challenges in Severe Polyuria

1. **Prolonged Polyuria and Misdiagnosis**:
   - In **PP and chronic polyuria**, **hypoosmolality** suppresses **AVP secretion** and **aquaporin 2** production.As a result, urine may not concentrate during water deprivation, leading to a **false diagnosis** of **partial DI** despite normal AVP function.
2. **Partial CDI Confusion**:
   - In **partial CDI**, **upregulated V2 receptors** may allow for urine concentration with relatively low AVP levels.
3. **NDI Diagnostic Overlap**:
   - In **NDI**, elevated AVP levels from dehydration may overcome renal resistance, increasing urine osmolality and mimicking **partial CDI**.

Challenges with Plasma AVP Measurement:
Plasma AVP testing is **logistically challenging** and requires **specialized handling**, making it impractical for most clinical labs.

Introduction of Copeptin:

- **Copeptin** serves as a **biological surrogate** for plasma AVP.
- It is derived from the C-terminal part of the AVP precursor proAVP and is co-secreted with AVP in equal amounts in response to similar stimuli.
- Copeptin is **more stable ex vivo**, allowing straightforward sample handling.

Diagnostic Utility:

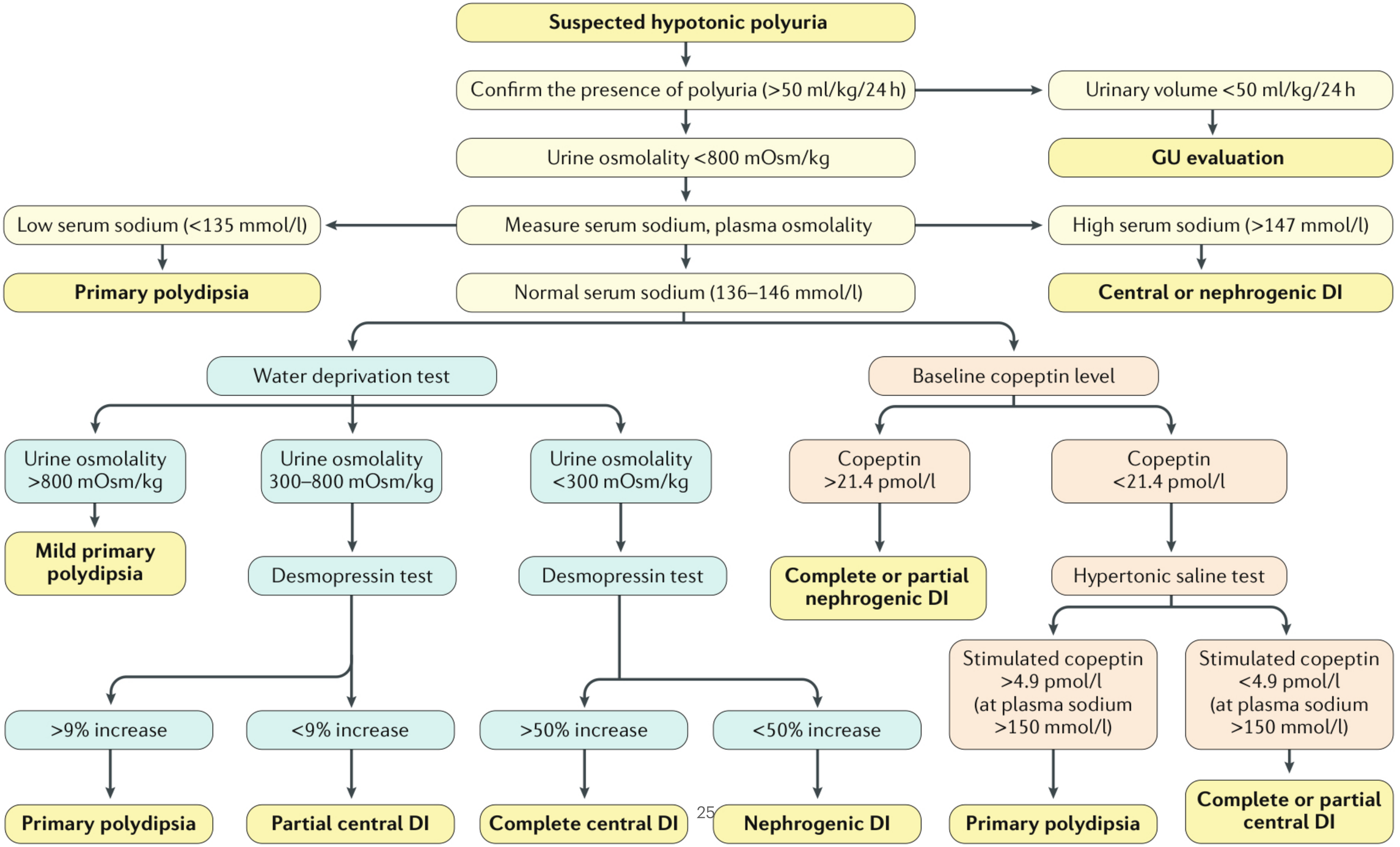
- A single copeptin concentration of **over 21.4 pmol/L** (without prior thirsting) can **differentiate Nephrogenic Diabetes Insipidus (NDI)** from other causes of polyuria, achieving **100% sensitivity and specificity**
- An osmotically stimulated copeptin level of >**4.9** pmol/L after infusion of 3% saline (aiming at a **sodium level ≥150** mmol/L) had an overall diagnostic accuracy of **96.5**% in distinguishing between patients with primary polydipsia and those with CDI, which was superior to the indirect water deprivation test, which had a diagnostic accuracy of only **76%**.can effectively distinguish between **Central Diabetes Insipidus (CDI)** and **primary polydipsia** with high accuracy.

Limitations of the Hypertonic Saline Infusion Test:

- Requires administration in **specialized centers**.
- Necessitates **close monitoring of sodium levels** to achieve diagnostic hyperosmolarity while avoiding sodium overstimulation.
- **Contraindicated** for pediatric, elderly patients, and those with neurological disorders due to risks associated with high sodium levels.

Alternative: Arginine Infusion for Copeptin Stimulation:

- A recent study demonstrated that **arginine infusion** offers an effective nonosmotic method to stimulate copeptin levels.
- A copeptin level of **3.8 pmol/L**, measured **60 minutes after the start of arginine infusion**, achieved a diagnostic accuracy of **93%** in distinguishing **Central Diabetes Insipidus (CDI)** from **primary polydipsia**.


Suspected hypotonic polyuria
Confirm the presence of polyuria (>50 ml/kg/24 h)
Urinary volume <50 ml/kg/24 h
GU evaluation
Urine osmolality <800 mOsm/kg
Low serum sodium (<135 mmol/l)
Measure serum sodium, plasma osmolality
High serum sodium (>147 mmol/l)
Primary polydipsia
Normal serum sodium (136–146 mmol/l)
Central or nephrogenic DI
Water deprivation test
Baseline copeptin level
Urine osmolality >800 mOsm/kg
Urine osmolality 300–800 mOsm/kg
Urine osmolality <300 mOsm/kg
Copeptin >21.4 pmol/l
Copeptin <21.4 pmol/l
Mild primary polydipsia
Desmopressin test
Desmopressin test
Complete or partial nephrogenic DI
Hypertonic saline test
>9% increase
<9% increase
>50% increase
<50% increase
Stimulated copeptin >4.9 pmol/l (at plasma sodium >150 mmol/l)
Stimulated copeptin <4.9 pmol/l (at plasma sodium >150 mmol/l)
Primary polydipsia
Partial central DI
Complete central DI
Nephrogenic DI
Primary polydipsia
Complete or partial central DI

Measurement of Thirst in Osmotic Studies and Its Diagnostic Value

Thirst measurement using a **visual analogue scale** has shown that **thirst onset** occurs at the **same osmotic threshold** as **AVP secretion**.

In CDI patients, during **water deprivation testing** or **hypertonic saline infusion**, thirst follows a **linear increase** with rising plasma osmolality.

Drinking leads to a **rapid suppression of thirst**

Thirst measurement is clinically valuable in two conditions:

1-Adipsia (ADI):

The **absence of osmoregulated thirst** during water deprivation is considered the **gold standard** for diagnosing ADI.

2-**Primary Polydipsia**:

Three key abnormalities are observed:

A **low osmotic threshold** for thirst, which is **disconnected from AVP release**.

Exaggerated thirst with increasing plasma osmolality.

Failure to suppress thirst after drinking,

Particularly, a failure to **reduce thirst by more than 50%** after drinking is a strong diagnostic **indicator of primary polydipsia.**

Imaging in the Diagnosis of Central Diabetes Insipidus (CDI)

Role of MRI in CDI:

- Once CDI is diagnosed, an **MRI of the hypothalamoneurohypophyseal** is indicated.
- On T1-weighted MRI, a posterior pituitary bright spot is AVP stored in neurosecretory granule
- The **bright spot** is present in over **80% of norma**l individuals but is **absent in most CDI patients**.
- In early familial CDI, the bright spot may persist when the condition is partial but disappears as **AVP deficiency** worsens.

Differentiating Other Conditions:

- **Primary polydipsia**: In primary polydipsia the bright spot **usually** is seen.
- **Nephrogenic DI (NDI)**: bright spot **may be absen**t due to **AVP depletion** caused by chronic dehydration
- bright spot can also be transiently lost in other disorders, such as **untreated diabetes mellitus** or the **transient DI of pregnancy**.
- presence or absence of the bright spot on MRI is not sufficient to establish a diagnosis in patients with DI.

Imaging the Hypothalamus:

- **Pituitary adenomas** do **not cause CDI**, but diseases of the **pituitary stalk** commonly do(box)
- A **thickened stalk** and absence of the bright spot often indicate **systemic disease**
- a **diameter of >2–3 mm** is generally considered to be pathological (for example, in hypophysitis, granulomatous disorders, tuberculosis, craniopharyngioma, germinoma or metastasis to the sella or suprasellar region)
- A **thickened stalk** with coexistent **anterior pituitary deficien**cy is especially suggestive of etiologic **systemic disease.**

Diagnostic Approach in the Absence of Structural Causes of CDI on MRI

1. **Germinoma** Consideration:
   - particularly in **children and young adults**,
   - Germinomas may not be detectable on initial MRI scans.
     - Markers such as **βhCG and AFP should be measured in both blood and CSF** if clinical suspicion is high.
     - in pure germinomas, these **markers are often negative, s**o it is essential to perform **repeat MRI scans every 3-6 months for the first 2 years of follow-up.**
2. Infundibulo-neurohypophysitis:

A **decrease in stalk thickness on follow-up** imaging is suggestive of infundibulo-neurohypophysitis.

Initially, there may be an **increase in stalk thickness,** but **if this persists over 2-3 years, a biopsy of t**he pituitary stalk is warranted to confirm the diagnosis.

3. Other Investigations:should be based on clinical suspicion:
   - If **histiocytosis** X is suspected, a **radiologic skeletal survey** should be conducted.
   - **Sarcoidosis** can be identified through **chest radiographs or CT scans s**howing typical changes, along with elevated **ACE** activity.
4. Autoimmune Causes of CDI:

some patients classified as having "**idiopathic**" CDI may **actually have antibodies to AVP neurons.**

There is also a high incidence of related autoimmune conditions, most commonly **thyroid** disease.

Prevention

- Currently, most forms of DI cannot be prevented.
- incidence of postoperative DI seems to be dependent mainly on hospital and surgeon case-load, suggesting that greater experience leads to lower rates of postoperative DI
- To date, the prevalence of postsurgical DI seems to be similar for endoscopic trans-sphenoidal surgery and microscopic trans-sphenoidal surgery of large pituitary adenomas
- P**erioperative hydrocortisone** treatment **influences the rate of postoperative DI** . Administration of hydrocortisone doses lower than the usual institution's standard protocols led to almost 50% lower incidence of DI, possibly owing to suppression of AVP release by hydrocortisone

Prevention

- Prevention of **lithium induced nephrogenic** DI is an important aspect of the treatment of affective disorders.
- In patients receiving long- term lithium treatment, nephrogenic DI seems to only be partially reversible after discontinuation of lithium
- Close monitoring of lithium treatment is recommended, including **annual measurement of the urinary volume per day** to make both the patient and the physician aware of the development of drug-induced nephrogenic DI.
- As gestational DI is rare and there is no straightforward diagnostic measure for this disorder, **screening in pregnancy is not helpful.**

Management

- general goals of treatment for all forms of DI include :**correcting pre-existing water deficits** and **reducing ongoing excessive water loss** through urination.
- specific therapy will depend on the type of DI and clinical circumstances
- Management of **primary polydipsia** entails different challenges and solutions because therapies are primarily based on **behavioural** interventions rather than biological and pharmacological interventions

Correction of body water deficits

- Untreated central and nephrogenic DI often leads to hyperosmolar dehydration.
- Total body water deficit = 0.6× premorbid weight × (1− 140⁄[Na +]) where [Na +] is the serum sodium concentration in millimoles per litre and weight is in kilograms.
- plasma osmolality should be lowered over the **first 24 h** of therapy by replacing **~50% of the calculated free water deficit**

Correction of body water deficits

- Physiologically, neurons increase intracellular osmolality by increasing the cellular content of organic osmolytes to protect against excessive osmotic shrinkage during prolonged hyperosmolality .these osmolytes cannot be immediately dissipated, so **correction** to a normal plasma osmolality **should be spread over the subsequent 24–72 h to avoid cerebral oedema** from osmotic water shifts into the brain during treatment
- treatment of **hyperosmolar dehydration** with **isotonic saline is dangerous** because it can result in worsened hypernatraemia.

Correction of body water deficits

- A child weighing 10 kg has an estimated 7 l of total body water. Administration of 1 l of isotonic saline (154 mmol Na +) with excretion of 1 l of hypotonic urine containing 10 mmol Na + will result in retention of 144 mmol Na + , and thus will increase serum sodium concentration by 20 mmol/l (144 mmol/7 l).
- **isotonic fluids** should only be administered for acute intravascular volume expansion in those with **hypovolaemic shock**, which is an exceptionally rare complication, as extracellular fluid volume is usually preserved with hyperosmolality.
- Patients with DI should be treated with **hypotonic** fluids, either milk or water consumed enterally or, if required**, 5% dextrose i**n water administered intravenously.
- administration of hypotonic fluids as an intravenous **bolus** is not recommended; instead, the **infusion rate should be adjusted to exceed the hourly urine output by an amount necessary to achieve the desired reduction in the calculated total body water deficit.**

Correction of body water deficits

- The aim is to provide just enough water to **safely normalize serum sodium concentration at a rate of <0.5 mmol/l/h (<10–12 mmol/l/day)** or even slower so as to prevent cerebral oedema
- **Frequent, careful monitorin**g of the clinical condition and biochemistry is crucial
- To enable fluid intake to be correctly regulated by thirst physiology, **oral consumption of fluids should begin as soon as feasible**.
- In most patients with DI, thirst remains intact and patients will drink sufficient fluid to maintain a fairly normal fluid balance.

Treatment of Polyuric Conditions
Central Diabetes Insipidus in Ambulatory Patients

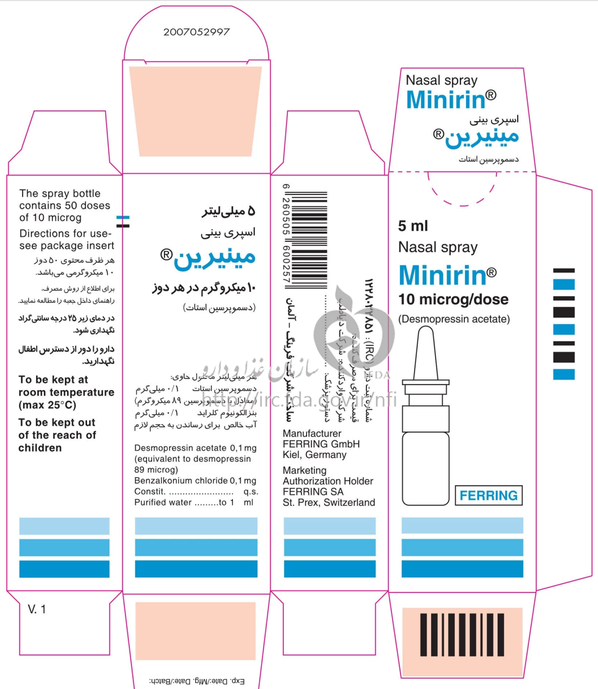
- central DI should be treated to reduce polyuria and polydipsia to levels that allow **maintenance of a normal lifestyle.**

- **Desmopressin (DDAVP) Therapy**:an agent nearly 2000 times more specific for antidiuresis than naturally l-arginine AVP.
- **Forms of administration**:
  Tablets (0.1 and 0.2 mg), **oral melt**, **intranasal spray**, and **parenteral solution**.
  Oral tablets are preferred by most patients, but must be taken **1 hour before or 2 hours after meals**

starting with a nasal spray initially is preferable because of greater of absorption and physiological effect, after which the patient can be switched to an oral preparation

Dose comparison of different formulations of desmopressin

	Melt	Tablets	Spray	Solution for injection
Dose comparison	60 mcg	100 mcg	2.5 mcg	N/A
	120 mcg	200 mcg	5 mcg	Less than 0.5 mcg
	240 mcg	400 mcg	10 mcg	Less than 1 mcg



Dosing:

Highly **variable** based on individual **AVP deficiency**:

Some patients with **partial** CDI may need only **one dose at night** to prevent nocturia.

Others with **complete** CDI may require **2-4 doses per day**.

Duration of action is **6 to 18 hours**, depending on the route of administration.

maximum dose of desmopressin required rarely exceeds **0.2 mg orally, 120 μg sublingually or 10 μg (one nasal spray) two or three times daily**

Once a **stable therapeutic response** is achieved with desmopressin, **further dose increases** (e.g., doubling the dose) result in only a **moderate increase in duration** of action, usually by a few hours.

complications desmopressin therapy

- **Hyponatraemia** is the major complication of desmopressin therapy — a 27% incidence of mild hyponatraemia (serum Na + 131–134 mmol/l) and a 15% incidence of more severe hyponatraemia (serum Na + ≤130 mmol/l)
- It occurs due to **social** or pleasure drinking, as desmopressin's continuous antidiuretic effect
- Hyponatremia is a particular risk in **infants** due to liquid-heavy diets (formula or breast milk)

Strategies to Reduce Hyponatremia Risk:

- Three desmopressin dosing schedules are employed to reduce this risk:
  1. **Omitting one full dose weekly** to allow water clearance through aquaresis.
  2. **Delaying a dose once or twice weekly** until the patient urinates 2-3 times, offering less disruption to daily life.
  3. **Delaying each dose** until urination begins, preferred by those sensitive to water retention effects.

complications

- desmopressin-induced hyponatraemia is usually **chronic (>48 h duration),** care in acutely treating patients to **avoid osmotic demyelination syndrome (ODS)**
- **Stopping desmopressin can lead to a rapid aquaresis**, causing hyponatremia to correct too quickly. This increases the risk of ODS.
- **Continued Desmopressin:** Some experts recommend continuing desmopressin therapy while slowly correcting hyponatremia using hypertonic hypertonic (3%) NaCl
- **Re-administration of Desmopressin**: Another approach is to re-administer desmopressin after a desired correction(**6–8 mmol/l)** of serum sodium has been achieved to stop ongoing water loss.
- **Gradual Correction**: To prevent ODS , limiting the rate of sodium level correction to less than 12 mmol/L in the first 24 hours and less than 18 mmol/L in the first 48 hours.

Central Diabetes Insipidus in Hospitalized Patients

Incidence Severe hypernatremia (plasma sodium ≥150 mmol/L) **in Hospitalized Patients**:

23% of neurosurgical patients, and

19% of non-neurosurgical emergency admissions.

This high incidence is often due to **delayed or omitted doses** of desmopressin , largely attributed to **clinician unawareness** of the urgency for **timely desmopressin administration**.

Delayed or omitted desmopressin has been directly linked to increased **morbidity and mortality**

Central Diabetes Insipidus in Neurosurgical Patients

- **Predictors of post-surgical CDI** include:
  Suprasellar tumor extension,
  Older age,
  Craniopharyngioma, and
  Presence of **CSF leaks** during surgery .

Diagnosis: CDI is diagnosed based on the classic triad of:**Polyuria**,**Hypernatremia**, and**Dilute urine**
Other potential causes such as **diabetes mellitus** and **mannitol therapy** should be excluded .

- **Postoperative polyuria** can result from the excretion of **retained fluids** after surgery rather than CDI,
- If CDI is suspected, **withholding intravenous fluids :**
- if the urine output decreases and the serum sodium is stable, the polyuria can be attributed to the excretion of physiologically retained fluid.
  - If, the serum sodium begins to rise while urine osmolality is low, the diagnosis of DI can be established

Central Diabetes Insipidus in Neurosurgical Patients

Treatment:

- ***Fluid replacement*** parenterally or orally is appropriate for **transient, mild cases of CDI**
- If the patient is awake and responds to thirst, then thirst is a sufficient guide for water replacement.
- if the patient cannot respond to thirst because of a decreased level of consciousness or from damage to the hypothalamic thirst centre fluid balance must be maintained using intravenous fluids.
- **most** patients,require **desmopressin** (0.5–2 μg) is given subcutaneously, intramuscularly, or intravenously.
- Urine output will be reduced in 1 to 2 hours, and the duration of effect is 6 to 24 hours.
- **Caution** is necessary to avoid excessive administration of **hypotonic fluids** after desmopressin, which could lead to **profound hyponatremia**
- Urine osmolality and serum sodium should be checked every 4–6 h during initial therapy and then daily
  - Because there is always the possibility of developing **Pituitary stalk damage** and can lead to a **triphasic response** Recurrent **polyuria** should be present before administering subsequent doses of desmopressin

updates

Postoperative diabetes insipidus: how to define and grade this complication?

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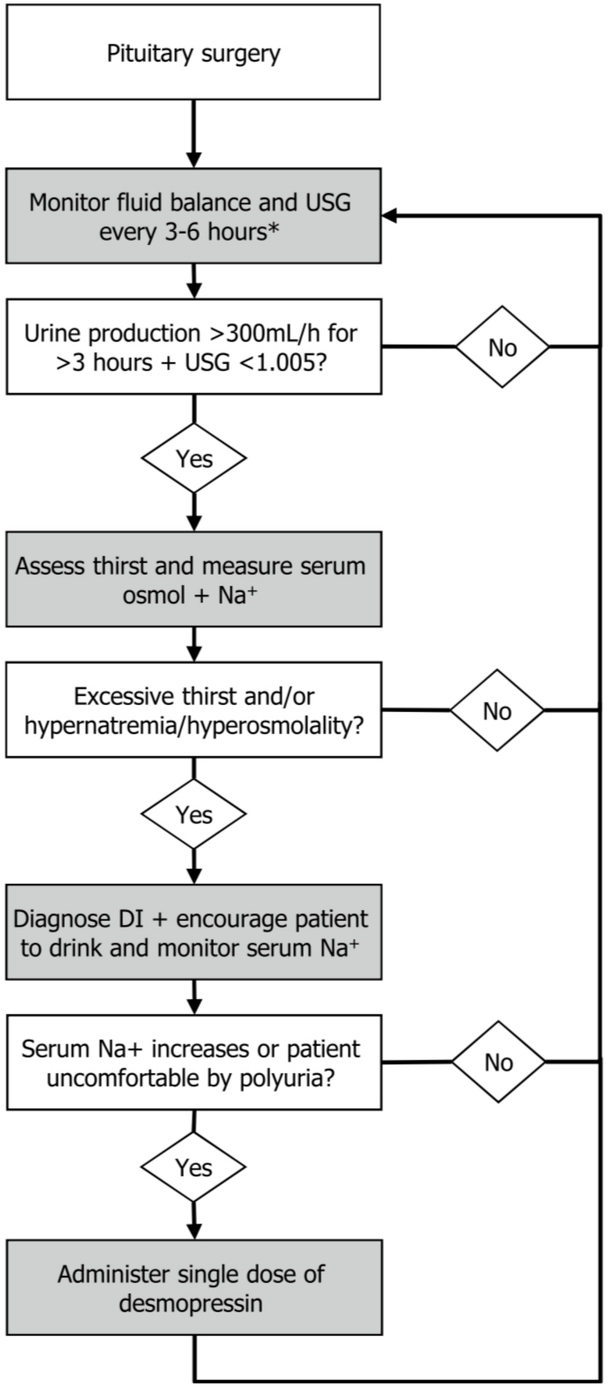
Proposed definition of postoperative Diabetes Insipidus. DI: Diabetes Insipidus, USG: Urine Specific Gravity, NRS: Numeric Rating Scale

Hypotonic polyuria:

- Urine production > 300 mL/h for 3 consecutive hours
  AND
- USG < 1.005

And at least one of the following:

- Excessive thirst (NRS ≥ 6 out of 10)
- Serum osmolality > 300 mosmol/kg
- Serum sodium > 145 nmol/L.



adipsic central DI

- It has high morbidity and mortality rates; **50% of ambulatory patients develop hypernatremi**a, and **20% face severe cases during hospital admission**s.

- Lack of normal thirst regulation makes ADI patients vulnerable to both **hypernatremia** (from dehydration) and **hyponatremia** (from over-treatment with desmopressin).

- Management includes a **fixed** oral desmopressin dose and prescribed fluid intake, along with regular serum sodium monitoring.

- Home devices for sodium monitoring help better manage fluid balance, and daily weight tracking can guide fluid intake.

- Severe dehydration in ADI may lead to thrombotic complications, including fatal pulmonary embolism.

- Associated hypothalamic issues, like sleep apnea, should also be managed to reduce morbidity.

DI Treatment in Pregnancy

- Desmopressin is the only recommended treatment for DI during pregnancy, being safe for both mother and child.

- It minimally stimulates oxytocin receptors and isn’t degraded by oxytocinase

- During delivery, oral desmopressin intake is safe, but physicians must avoid excessive intravenous fluids to prevent water intoxication.

- Post-delivery, patients may recover normal fluid and urine regulation as oxytocinase levels decrease.

Nephrogenic DI

- **Dietitians** play a critical role in managing patients with nephrogenic DI, especially in the first year of life.
- **Balancing Fluid and Nutrition:** Dietitians must ensure adequate fluid intake and caloric consumption to support normal growth and development while minimizing osmotic load.
- **Impact of Salt:** 1 gram of table salt increases obligatory urine output by 340 ml in patients with a urine osmolality of 100 mOsm/kg.
- **Estimating Dietary Osmolar Load:** The dietary osmolar load can be calculated by multiplying the millimolar amounts of sodium and potassium by two and adding the gram amount of protein multiplied by four.

Pharmacological therapy:

- **Mainstay of Treatment:** Adequate water intake is critical as most patients do not respond to desmopressin Goal: Reduce urine volume by decreasing GFR and enhancing proximal tubular sodium and water reabsorption.
- **Thiazide Diuretics:**
  - Core treatment to reduce urine output.
  - Shown to increase aquaporin 2 levels, independent of AVP action.
- **Potassium Supplementation**: Often required as hypokalemia worsens AVP resistance.
- **NSAIDs**: May enhance the effect of thiazides, but pose nephrotoxicity risks, requiring regular renal function monitoring.
- **COX-2 Inhibitors:** These may reduce water loss with fewer gastrointestinal side effects, though long-term safety data is limited.
- Common Cause Drug-Induced NDI:**Lithium** is a major :
- Treatment: **Discontinuation of the causative agent is ideal, followed by hydrochlorothiazide and amiloride** if NDI persists.
- Pharmacologic Chaperones (**Vaptans**): In autosomal-dominant NDI, where misfolded V2 receptors are trapped in the endoplasmic reticulum, vaptans may help fold and transport the receptors to the cell membrane. Once at the membrane, the receptors can respond to AVP, improving water retention.

Management Primary polydipsia

- Management of primary polydipsia **depends** on the patient's psychological profile and whether hyponatremia is present.
- **Water Intoxication:** most acute danger of primary polydipsia is episodic water intoxication, in psychotic patients with PIP.
- **AVPR2 Antagonists(vaptans):** These drugs can rapidly normalize serum sodium levels but require close monitoring to prevent dehydration and renal damage.
- **Clozapine**: Unlike other antipsychotics, clozapine **may be effective in normalizing sodium leve**ls in patients with PIP at risk of water intoxication.
- **Potential Benefit**s: Clozapine may be effective in normonatremic psychotic polydipsic patients as well

- **Gradual Reduction of Fluid Intake:** slowly decrease excessive fluid consumption, aiming to bring urine volume below polyuric levels (50 mL/kg body weight).
- **Adjunctive Measures**: Using ice chips or hard candy to reduce mouth dryness and stimulate salivary flow help alleviate excessive thirst.
- **Pharmacologic Approaches:** Though not consistently effective, **GLP-1 analogues** have recently shown promise in reducing fluid intake, urine output, and thirst perception.
- **Acetazolamide** may be promising: Case reports suggest acetazolamide could potentially reduce polydipsia, warranting further research.
- **CWD treatment:** Unlike psychotic disorders, CWD typically resolves with successful pharmacological treatment of the core psychiatric symptoms (such as depression and anxiety).
- **Desmopressin**: Generally **contraindicated** in primary polydipsia due to the risk of hyponatremia
- desmopressin may be effective in some patients with **dipsogenic** DI, particularly when combined with behavioral therapy for concurrent primary polydipsia.

Management of DI in Routine Surgical Procedures

- require only their usual dose of desmopressin. If oral desmopressin cannot be taken (NPO status), a parenteral dose can be given.

- In **NDI** should be a greater **emphasis on fluid replacement** to avoid dehydration and hypernatremia.

- **Panhypopituitarism**:
  - **Risk of Hyponatremia**: Patients with both DI and anterior pituitary deficiency may develop hyponatremia due to cortisol deficiency, which impairs water excretion

  - Those missing hydrocortisone doses are more susceptible to desmopressin-induced hyponatremia,


سپاس از توجه شما

Summary of the Indirect Water Deprivation Test

- **Preparation phase:**
- The test is performed either as an out-patient or preferably after admitting the patient to an in-patient ward in a controlled setting
- For those individuals with **milder** polyuria (50 – 70 ml/Kg/24 hours), the test can be initiated in the evening and the dehydration can be performed overnight as an out-patient. However, for those who experience **significant polyuria or nocturia, the test is better performed during the day so that the patient can be supervised**
- Test can begin either overnight (for out-patient testing) or at 08:00 am (for in-patient testing)
- No thirsting prior to the test. Smoking and caffeine intake are avoided
- Any electrolyte abnormalities (potassium, calcium) are corrected.
- Drugs that can affect urine output (diuretics, sodium-glucose co-transporter-2 inhibitors, glucocorticoids, non-steroidal anti-inflammatory drugs) must be held 24 hours prior to dehydration.
- Baseline weight, blood pressure and heart rate are measured prior to dehydration.
- Baseline plasma osmolality, serum sodium, urine osmolality (and plasma AVP or plasma copeptin where available) are obtained (these measures can be obtained on the morning prior to overnight dehydration in cases of out-patient water deprivation test).

Dehydration phase:

· This phase usually lasts for 8 hours (can last longer in certain cases)

· For out-patient testing, the duration (hours) of overnight dehydration can be determined using the formula: patient's weight (Kg) x 0.03 x 1000 (ml) / urine output (ml/hour).

· Patient is allowed to have nothing by mouth.

· Adequate supervision is necessary to watch for any undisclosed drinking (in case of in-patient testing).

· Weight, blood pressure and heart rate are measured every 1 hour (in case of in-patient testing).

· **Urine output, urine osmolality, serum sodium and plasma osmolality are measured every 2 hours (**for in-patient testing). Plasma copeptin is measured towards the end of the dehydration phase. (In case of out-patient overnight dehydration, serum/plasma and urine measures are obtained around 07:00 – 08:00 am the following morning)

Dehydration phase is discontinued if one of the following occurs:
Dehydration is completed for 8 hours (not applicable for those who might need longer periods of dehydration)

Two consecutive urine osmolality measures do not differ by >10% and loss of 2% body weight.

The total body weight reduces by more than 3%

Serum sodium increases to above upper limit of normal (preferably >150 mmol/L).

Orthostatic hypotension or orthostatic symptoms.

Intractable thirst (or if patient admits to drinking water overnight in case of out-patient testing).

Desmopressin phase:

· An injection of 2 µg desmopressin is administered either through intravenous or intramuscular route (use of oral or intranasal desmopressin is not preferred due to unpredictable absorption)

· The patient is allowed to eat and drink, even up to 1.5 – 2 times the volume of urine passed during the dehydration phase

· Urine output, urine osmolality, serum sodium and plasma osmolality are measured hourly for 1 – 2 hours after desmopressin administration.

Quality of life

- **Limited QOL Studie**s: Formal assessment of QOL in patients with central DI is limited, with only two studies focusing specifically on this condition.
- **Impact of Treatment:** Isolated and treated central DI is generally associated with a fairly normal QOL, especially when oral desmopressin is prescribed.
- **Nagasaki Diabetes Insipidus Questionnaire:** This 12-question questionnaire provides a reliable measure of QOL in central DI patients, focusing on symptoms and treatment satisfaction.
- **Benefits of Desmopressin:** Desmopressin treatment has been shown to improve QOL by reducing polyuria, thirst, and limitations in daily life.
- **Weight Loss:** Some patients may experience weight loss due to reduced polydipsia, leading to further improvements in QOL.
- **Nocturia and Incontinence**: Desmopressin can improve QOL in patients with nocturia and incontinence associated with CWD, dipsogenic DI, or partial central DI.
- **Clozapine and Psychiatric Disorders:** Clozapine may improve QOL in psychotic patients with PIP by allowing for discharge from long-term inpatient facilities.

Postoperative diabetes insipidus

- following assessment scheme for **polyuria (> 300 mL for > 3 consecutive hours)**, which follows a step-wise approach:
- (1)Assessment of urine specific gravity in each urine portion (see Table 1)
- (2) If **USG is < 1005**, assess the presence of unquenchable thirst, preferably with the NRS and measure serum osmolality and/or serum sodium concentration.
- (3) In case of unquenchable thirst and/or an increased serum sodium concentration (> 145): diagnose postoperative DI, and treat accordingly
- (4)Repeat the assessment as stated above every 3 h until the urine production normalizes.
- **Treatment of postoperative DI**
- Step 1: (**Mild**) Postoperative DI can initially be treated with **adequate water intake;** compensating the excretion with equivalent intake. Patients should be encouraged to drink according to thirst to compensate for the fluid loss and pre- vent hypernatremia.
- Step 2: fluid balance and electrolyte status should be monitored **every 3 h** to assess if the fluid loss is adequately compensated.
- Step 3: When the fluid loss exceeds the patient's ability to drink or causes discomfort, incidental **desmopressin**, should be administered. In our center, we administer desmopressin orally in 50 to 100 μg doses, but nasal, subcutaneous, and intravenous preparations are also available.
- nasal administration is not appropriate in the postoperative period due to nasal con- gestion causing absorption impairment. After administration of desmopressin, the fluid balance and electrolyte status of the patient should be monitored **every 3 h.** Attention should be given to fluctuating severity and the possibility of the development of SIADH.

Hypertonic Encephalopathy:

Causes and Mechanism: Hypertonic encephalopathy is rare in DI but can occur in adipsic patients or those with inadequate fluid intake. Hypernatremia leads to cellular dehydration and is linked to loss of hypotonic fluids or excessive intake of hypertonic fluids. The brain generates **idiogenic osmoles** to reduce cellular shrinkage from hypernatremia, but rapid fluid replacement can increase the risk of cerebral edema.

Management of Hypernatremia:

Mild Hypernatremia (145-149 mmol/L): Encourage oral water intake to manage mild cases. If the patient is dehydrated or has cognitive impairment, intravenous fluids may be needed.

Severe Hypernatremia (>149 mmol/L): Requires intravenous infusion of dextrose (5% D5W) or nasogastric water, along with parenteral desmopressin (dDAVP) to reduce renal water loss.

Fluid Replacement Guidelines: Careful adjustment of the infusion rate is recommended to ensure a slow reduction in plasma sodium concentration (no more than 0.5 mmol/L per hour or 10 mmol/L in 24 hours) to avoid cerebral edema. Although rapid correction in adults is not strongly associated with morbidity, caution remains important.

Complications:

Thrombosis and Rhabdomyolysis: Hypernatremia increases hematocrit, leading to a higher risk of deep venous thrombosis and pulmonary embolism, particularly in adipsic diabetes insipidus (ADI). **Prophylaxis**with low-molecular-weight heparin is recommended.

Regular Monitoring: Continuous monitoring of plasma electrolytes is essential, especially when hypotonic fluids like dextrose are administered to prevent overcorrection.