

Posterior Pituitary Gland

盧子文醫師
(GSM: 46-05211)

高醫附設中和紀念醫院
highker@gap.kmu.edu.tw

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學習目標

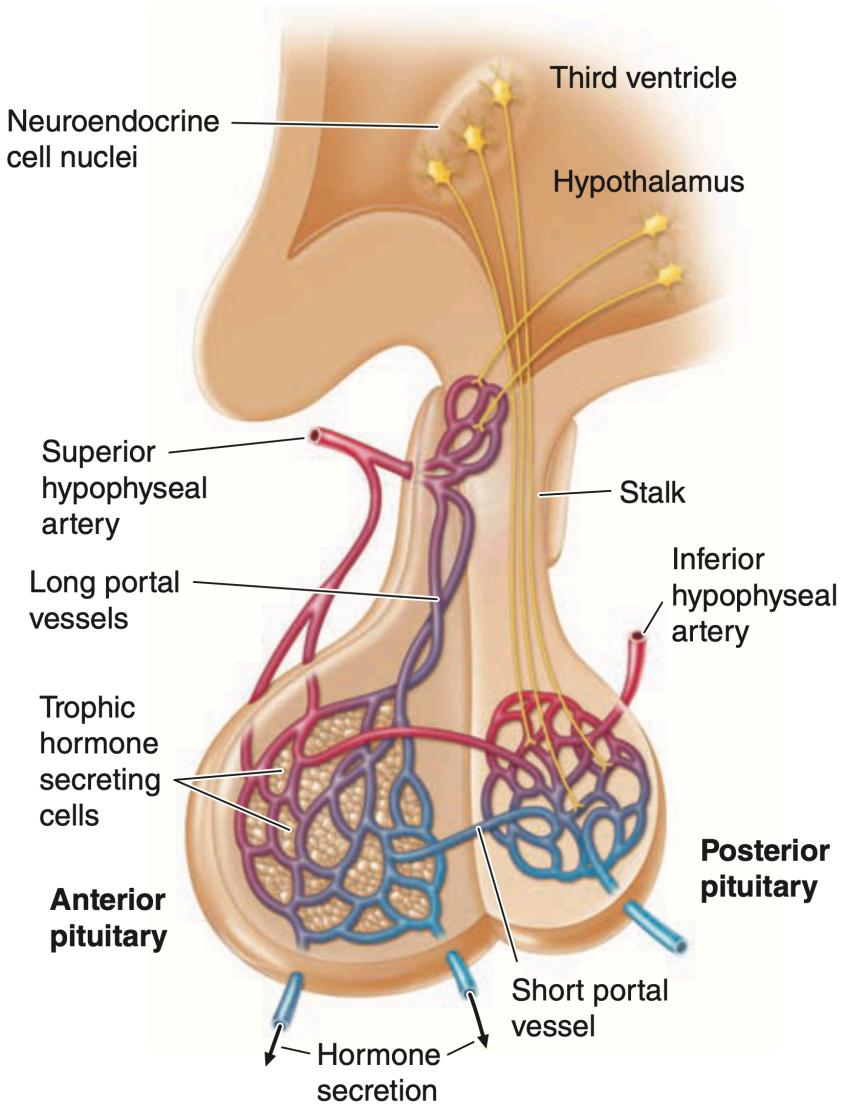
- Anatomy
- Posterior pituitary hormones
 - Arginine vasopressin(AVP)
 - Oxitocin
- Diabetes insipidus(DI)
- The Syndrome of Inappropriate Antidiuresis Hormones(SIADH)

Posterior pituitary gland (Neurohypophysis)

Posterior pituitary gland

- Structure and Development:
 - The posterior pituitary is neural tissue and consists only of the distal axons of the hypothalamic magnocellular neurons that make up the neurohypophysis.
 - These neurons' cell bodies are located in the hypothalamus' paraventricular(PVN) and supraoptic nuclei(SON).
- Neuroepithelial Cell Maturation:
 - During embryogenesis, neuroepithelial cells lining the third ventricle mature into magnocellular neurons. These cells migrate to form the supraoptic nuclei(SON) and the paraventricular nuclei(PVN).
- Neurotransmitters and Neuronal Activity:
 - Glutamate is the major stimulatory neurotransmitter in the neurohypophysis. **Gamma-aminobutyric acid (GABA)** provides major inhibitory input.

- Blood Supply
 - direct blood supply from the **inferior hypophyseal arteries**, branches of the posterior communicating and internal carotid arteries.
- Hormones Synthesized:
 - The main hormones produced by the posterior pituitary are **oxytocin and vasopressin**. Most magnocellular neurons are specific to one hormone, though a small number (~3%) can produce both.
- Neuronal Distribution and Function:
 - The supraoptic nucleus mainly produces vasopressin, while the more complex paraventricular nucleus synthesizes other peptides like corticotropin-releasing hormone(CRH), thyrotropin-releasing hormone(TRH), somatostatin, and opioids.

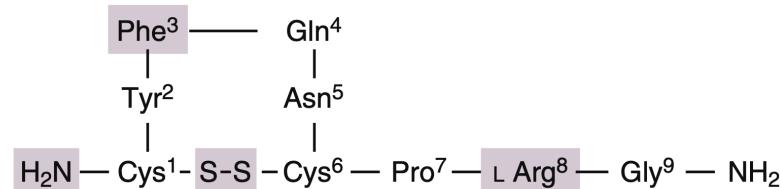


Ectopic Posterior Pituitary

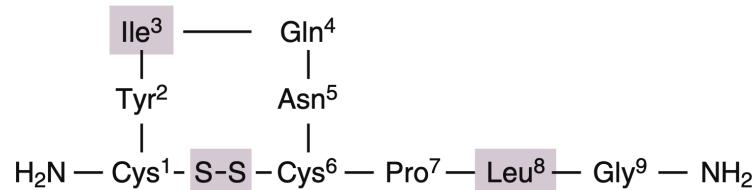
- MRI:
 - T1-weighted bright signal in the posterior pituitary
 - abnormal anatomy of the posterior pituitary when the “bright spot” was recognized in the base of the hypothalamus.
- Cases with malformations are more likely to have diabetes insipidus or other osmotic dysfunction than simple ectopic posterior pituitary
- Children with these pituitary abnormalities often present with growth retardation and deficiencies in the anterior pituitary rather than the posterior pituitary.
 - Deficiency of adrenocorticotropic hormone (ACTH) is common

Structures of AVP, Oxytocin, DDAVP

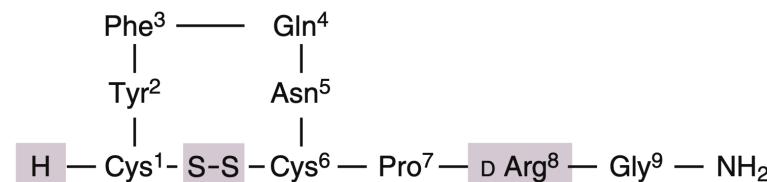
A Arginine vasopressin



B Oxytocin



C Desmopressin



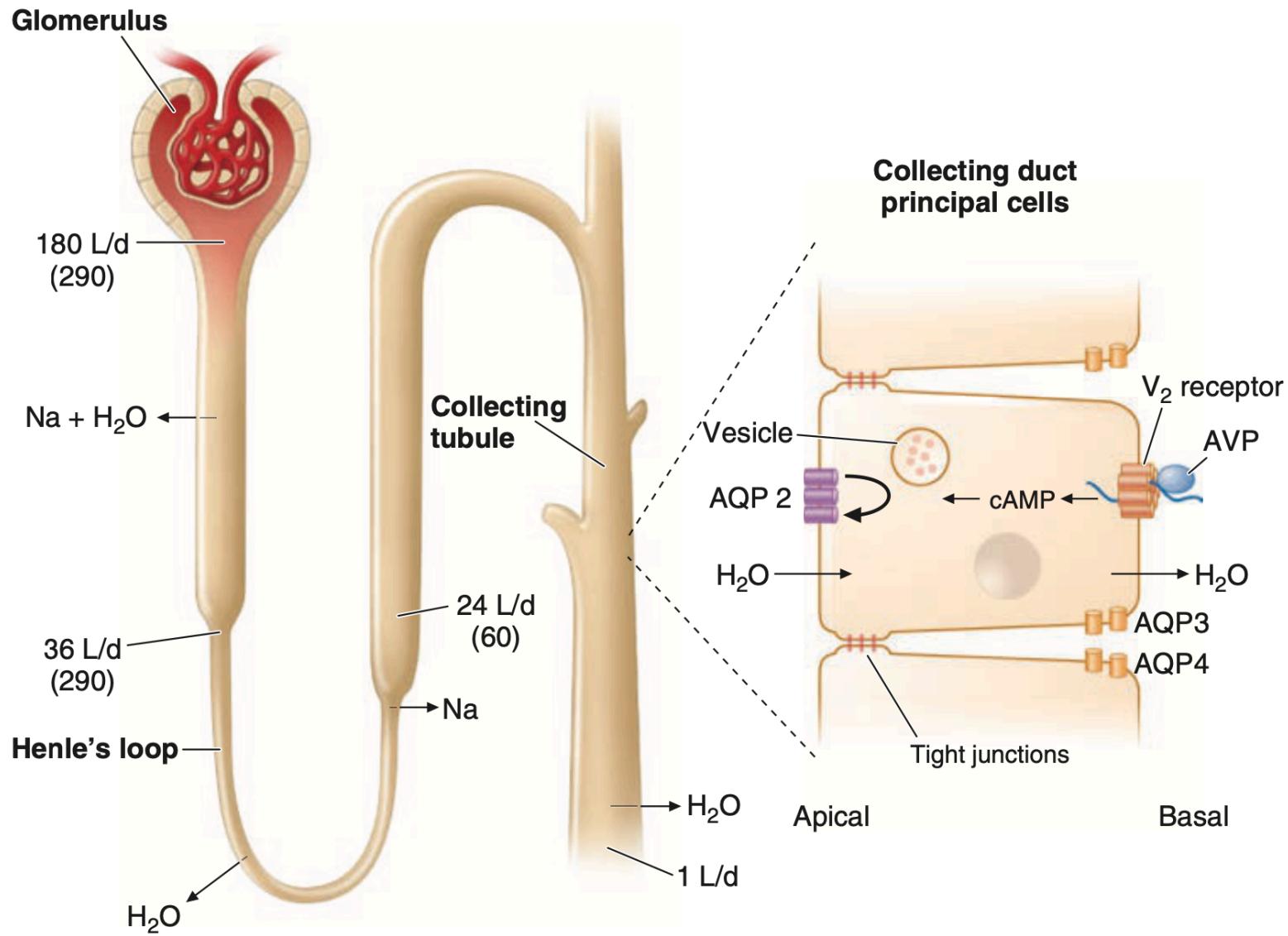
- **Fig. 10.1** Comparison of the chemical structures of arginine vasopressin (A), oxytocin (B), and desmopressin (C). The differences are illustrated by the shaded areas. Oxytocin differs from vasopressin in position 3 (Ile for Phe) and position 8 (Leu for Arg). Desmopressin differs from arginine vasopressin in that the terminal cystine is deaminated and the arginine in position 8 is a D-isomer rather than an L-isomer. (From A.G. Robinson, University of California at Los Angeles, used with permission.)

AVP physiology

- The physiologic regulation of vasopressin synthesis and secretion involves two systems: osmotic and pressure/volume.
- Functions of these two systems are so distinct that historically it was thought there were two hormones, an antidiuretic hormone and a vasopressor hormone. Hence the two names that are used interchangeably for (8-arginine) **vasopressin**
- V_{1a} receptors: on blood vessels; Glycogenolysis.
- V_2 receptors:
 - on renal collecting duct epithelia
 - stimulate factor VIII and von Willebrand factor production(vWF)
- V_{1b} receptors:
 - stimulate ACTH secretion from the anterior pituitary
 - in numerous peripheral tissues and areas of the brain.

- The most important physiologic action of AVP is to reduce water excretion by promoting concentration of urine.
- In the absence of AVP, these cells are impermeable to water and reabsorb little.
 - In this condition, the rate of urine output can be as high as 0.2 mL/kg per min and the specific gravity and osmolarity as low as ~1.000 and 50 mosmol/L
- When AVP is secreted, it binds to V2 receptors on the basal surface of principal cells causing water channels composed of aquaporin-2(AQP2) to be inserted into the apical surface of the cell.

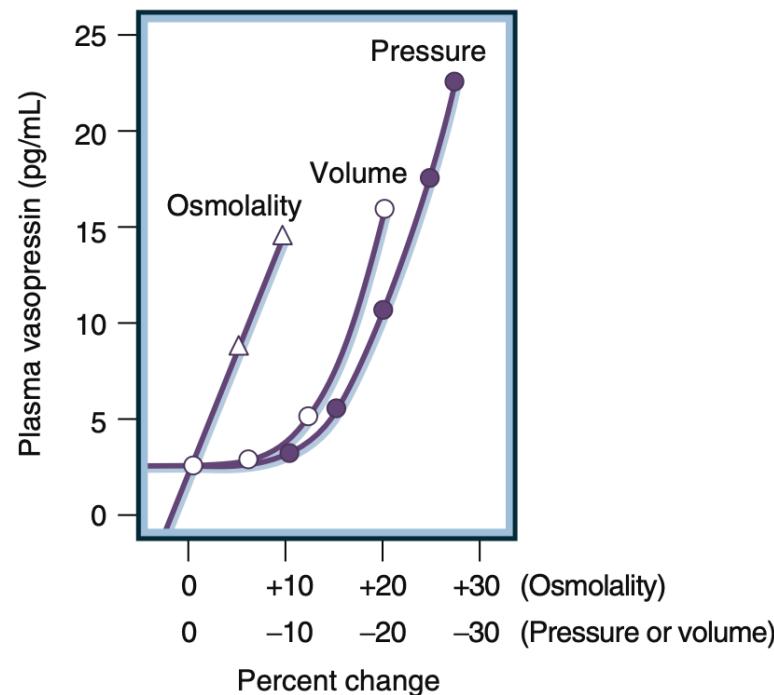
- The maximum anti-diuresis achievable in healthy humans occurs at plasma AVP levels in the range of 1 to 3 pg/mL and results in a urine osmolarity as high as 1200 mosmol/L and a rate of output as low as 0.35 mL/ min.
- At high concentrations, AVP also causes contraction of smooth muscle in blood vessels in the skin and gastro-intestinal tract, induces glycogenolysis in the liver, and potentiates adreno-corticotrophic hormone (ACTH) release by corticotropin-releasing factor(CRF).
 - via V_{1a} or V_{1b} receptors
 - 臨床上Low GI bleeding或angioplastia的病人會用DDAVP來止血(血管收縮+促進凝血因子釋放)
- 半衰期 $t_{1/2}$: 10–30 min.
- degradation in the liver and kidneys.



Volume and Pressure Regulation

- Location of Receptors
 - High-pressure arterial baroreceptors are located in the carotid sinus and aortic arch
 - Low-pressure volume receptors are located in the atria and pulmonary venous system.
- Signal Transmission:
 - afferent signals from these receptors are transmitted to the brainstem through cranial nerves 9 and 10
 - Baroreceptors and volume receptors normally inhibit magnocellular neurons, and decreases in this tonic inhibition result in the release of vasopressin.

- Vasopressin action on V_{1a} receptors induces arterial and venous constriction, contracting vessels around the existing plasma volume to effectively increase plasma volume and reestablish inhibition of vasopressin secretion.
- While vasopressin acts at the kidney to retain water and help replace volume, **the primary hormonal regulation of volume control is the Renin-Angiotensin-Aldosterone System (RAAS)**, which stimulates sodium reabsorption in the kidney.



Thirst

- Thirst and fluid intake are regulated primarily by an osmostat that is situated in the anteromedial hypothalamus and is able to detect very small changes in the plasma concentration of sodium and its anions.
- The thirst osmostat appears to be “set” about 3% higher than the AVP osmostat.
- This arrangement ensures that thirst, polydipsia, and dilution of body fluids do not occur until plasma osmolarity/ sodium exceeds the defensive capacity of the antidiuretic mechanism.

Oxitocin

- Oxytocin is also a nonapeptide that differs from AVP only at positions 3 and 8
- relatively little antidiuretic effect
- act mainly on mammary ducts to facilitate milk
- may help initiate or facilitate labor by stimulating contraction of uterine smooth muscle

Diabetes Insipidus

Diabetes Insipidus

- Excretion of large volumes of urine (diabetes), hypotonic, dilute
 - The 24-h urine volume exceeds 40 mL/ kg body weight
 - The 24-h urine osmolarity is <280 mosm/L.
- Tasteless (insipid).
- Diabetes mellitus: hypertonic and sweet urine
- clinical symptoms : increase in fluid intake (polydipsia)
- Four abnormal pathophysiologic processes:
 1. Primary polydipsia, caused by excess fluid intake
 2. Hypothalamic or **central diabetes insipidus(CDI)**, caused by diminished synthesis or secretion of vasopressin
 3. Diabetes insipidus of pregnancy(gestational DI), caused by increased enzymatic metabolism of vasopressin
 4. **Nephrogenic diabetes insipidus(NDI)**, caused by renal resistance to vasopressin

TABLE 381-1 Causes of Diabetes Insipidus

Pituitary diabetes insipidus	Gestational diabetes insipidus
Acquired	Pregnancy (second and third trimesters)
Head trauma (closed and penetrating) including pituitary surgery	
Neoplasms	Nephrogenic diabetes insipidus
Primary	Acquired
Craniopharyngioma	Drugs
Pituitary adenoma (suprasellar)	Lithium
Dysgerminoma	Demeocycline
Meningioma	Methoxyflurane
Metastatic (lung, breast)	Amphotericin B
Hematologic (lymphoma, leukemia)	Aminoglycosides
Granulomas	Cisplatin
Sarcoidosis	Rifampin
Histiocytosis	Foscarnet
Xanthoma disseminatum	Metabolic
Infectious	Hypercalcemia, hypercalciuria
Chronic meningitis	Hypokalemia
Viral encephalitis	Obstruction (ureter or urethra)
Toxoplasmosis	Vascular
Inflammatory	Sickle cell disease and trait
Lymphocytic infundibuloneurohypophysitis	Ischemia (acute tubular necrosis)
Granulomatosis with polyangiitis (Wegener's)	Granulomas
Lupus erythematosus	Sarcoidosis
Scleroderma	Neoplasms
Chemical toxins	Sarcoma
Tetrodotoxin	Infiltration
Snake venom	Amyloidosis
Vascular	Idiopathic
Sheehan's syndrome	Genetic
Aneurysm (internal carotid)	X-linked recessive (<i>AVP receptor-2 gene</i>)
Aortocoronary bypass	Autosomal recessive (<i>AQP2 gene</i>)
Hypoxic encephalopathy	Autosomal dominant (<i>AQP2 gene</i>)
Idiopathic	Primary polydipsia
Congenital malformations	Acquired
Septo-optic dysplasia	Psychogenic
Midline craniofacial defects	Schizophrenia
Holoprosencephaly	Obsessive compulsive disorder
Hypogenesis, ectopia of pituitary	Dipsogenic (abnormal thirst)
Genetic	Granulomas (sarcoidosis)
Autosomal dominant (<i>AVP-neurophysin gene</i>)	Infectious (tuberculous meningitis)
Autosomal recessive	Head trauma (closed and penetrating)
Type A (<i>AVP-neurophysin gene</i>)	Demyelination (multiple sclerosis)
Type B (<i>AVP-neurophysin gene</i>)	Drugs
Type C (<i>Wolfram's [4p-WFS1] gene</i>)	Idiopathic
X-linked recessive (Xq28)	Iatrogenic

Abbreviation: AVP, arginine vasopressin.

Diabetes Insipidus Due to Excess Fluid Intake (Primary Polydipsia)

- Primary polydipsia is associated with a wide variety of organic structural brain lesions, including sarcoidosis of the hypothalamus and craniopharyngioma.
- It can also be produced by drugs that cause a dry mouth or by any peripheral disorder causing an elevation of renin and/or angiotensin
- the disorder can be associated with psychiatric syndromes or be habitual throughout a lifetime.

Central Diabetes Insipidus(CDI)

- Genes mutation
 - Autosomal dominant (AVP-neurophysin gene)
 - Autosomal recessive
 - Type A (AVP-neurophysin gene)
 - Type B (AVP-neurophysin gene)
 - Type C (Wolfram's [4p-WFS1] gene)
 - X-linked recessive (Xq28)
- Neurosurgical intervention with transsphenoidal or transcranial surgery causes CDI in as many as 50% to 60% of patients
 - Most of whom will recover, with only a small number having permanent diabetes insipidus.
- Craniopharyngioma is particularly associated with CDI, particularly after extensive suprasellar surgery

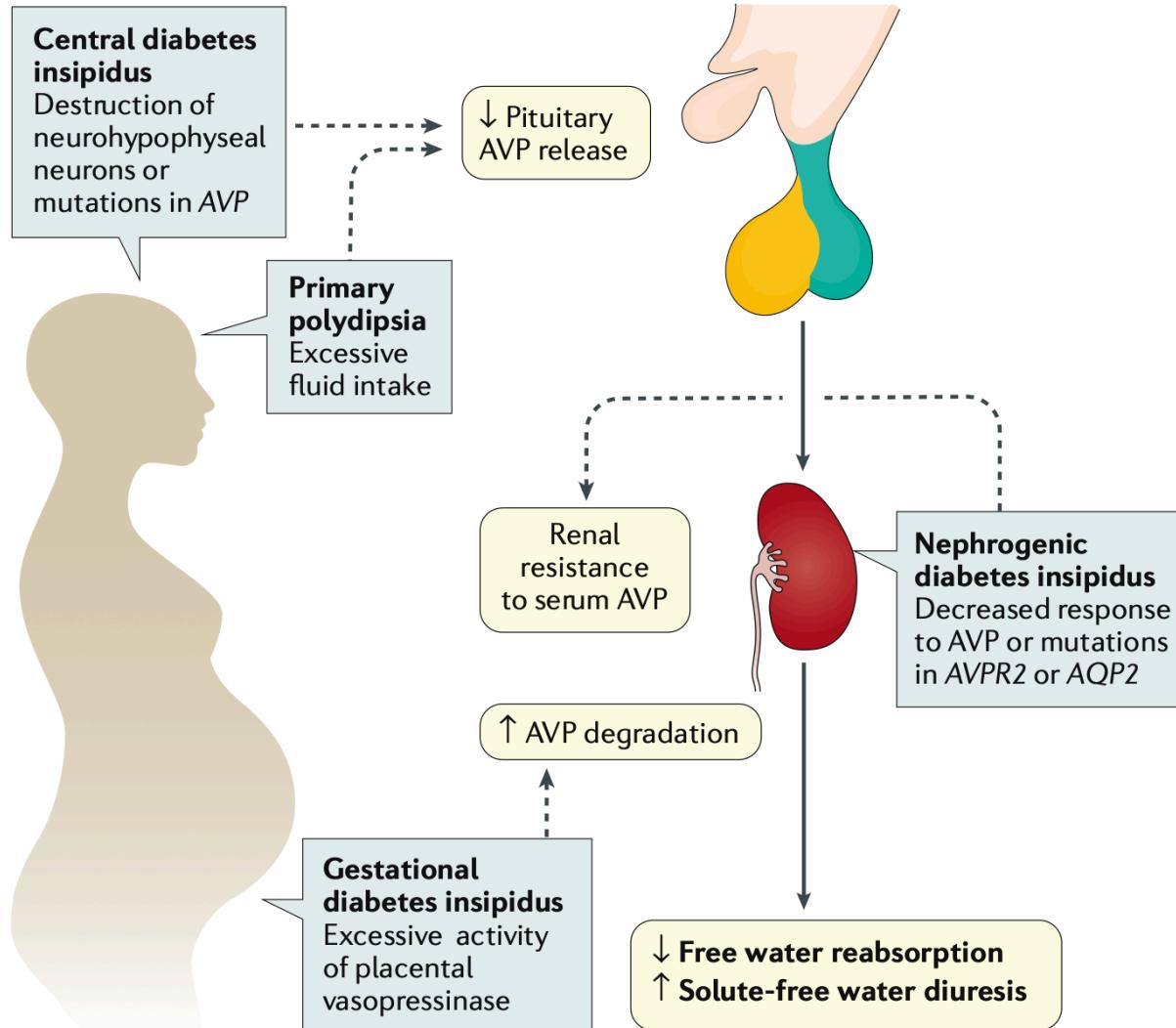
Nephrogenic diabetes insipidus(NDI)

- usually present in infancy, with vomiting, failure to thrive, and polyuria.
- caused by a drug such as lithium, a disorder such as hypokalemia, or a genetic mutation
- The most common genetic form is transmitted in a semirecessive X-linked manner and is due to mutations in the gene on chromosome Xq28 that encodes the V2 receptor.
- caused by mutations of the gene on chromosome 20 that encodes the aquaporin-2 water channels

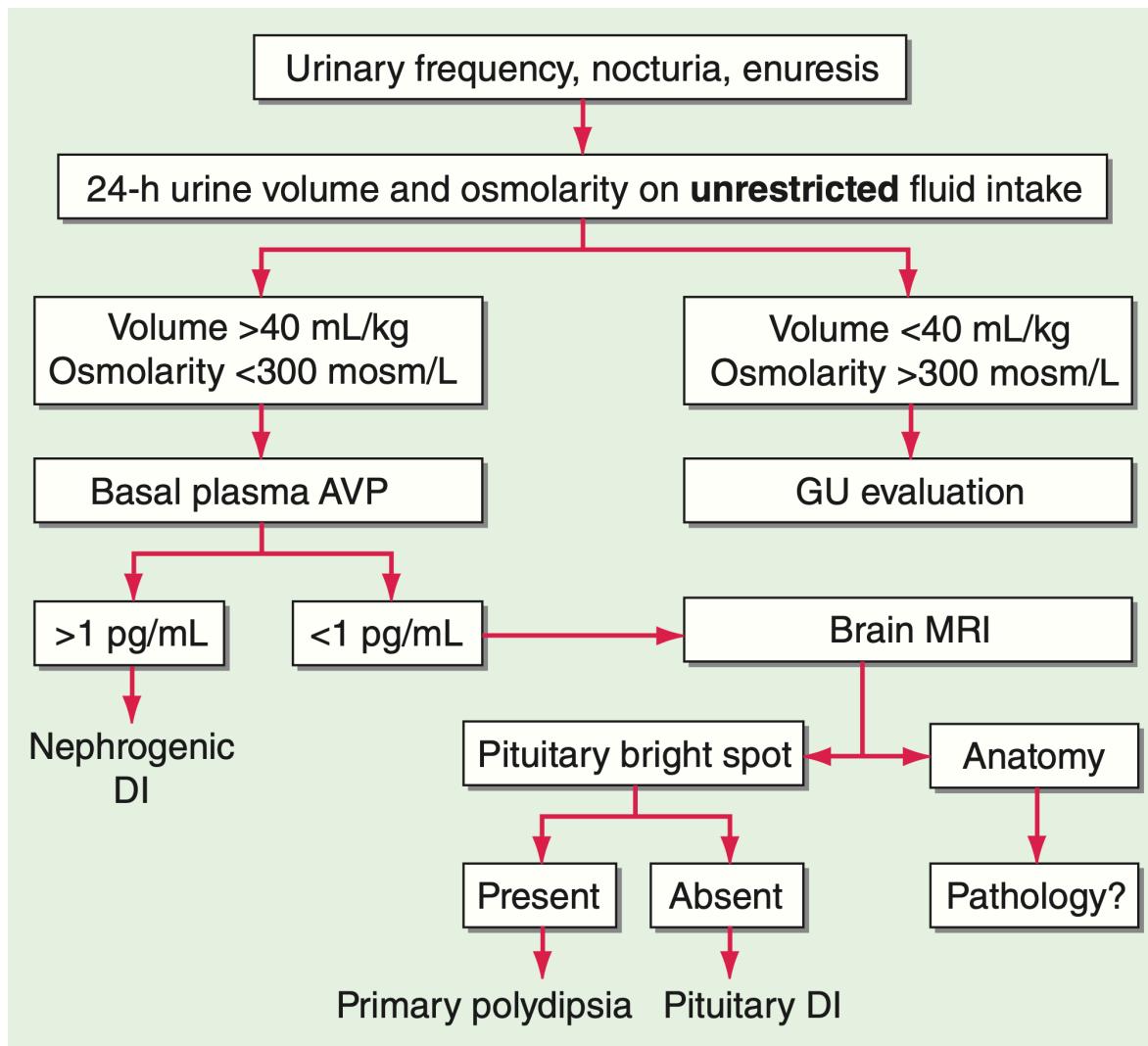
Diabetes Insipidus of Pregnancy(Gestational DI)

- Caused by a deficiency of antidiuretic hormone (AVP) due to an increased rate of degradation by an N-terminal aminopeptidase produced in the placenta.
- The signs and symptoms appear during pregnancy and usually remit several weeks after delivery.
- Patients with Sheehan syndrome may exhibit asymptomatic partial diabetes insipidus but rarely develop overt diabetes insipidus.

Pathophysiology of DI

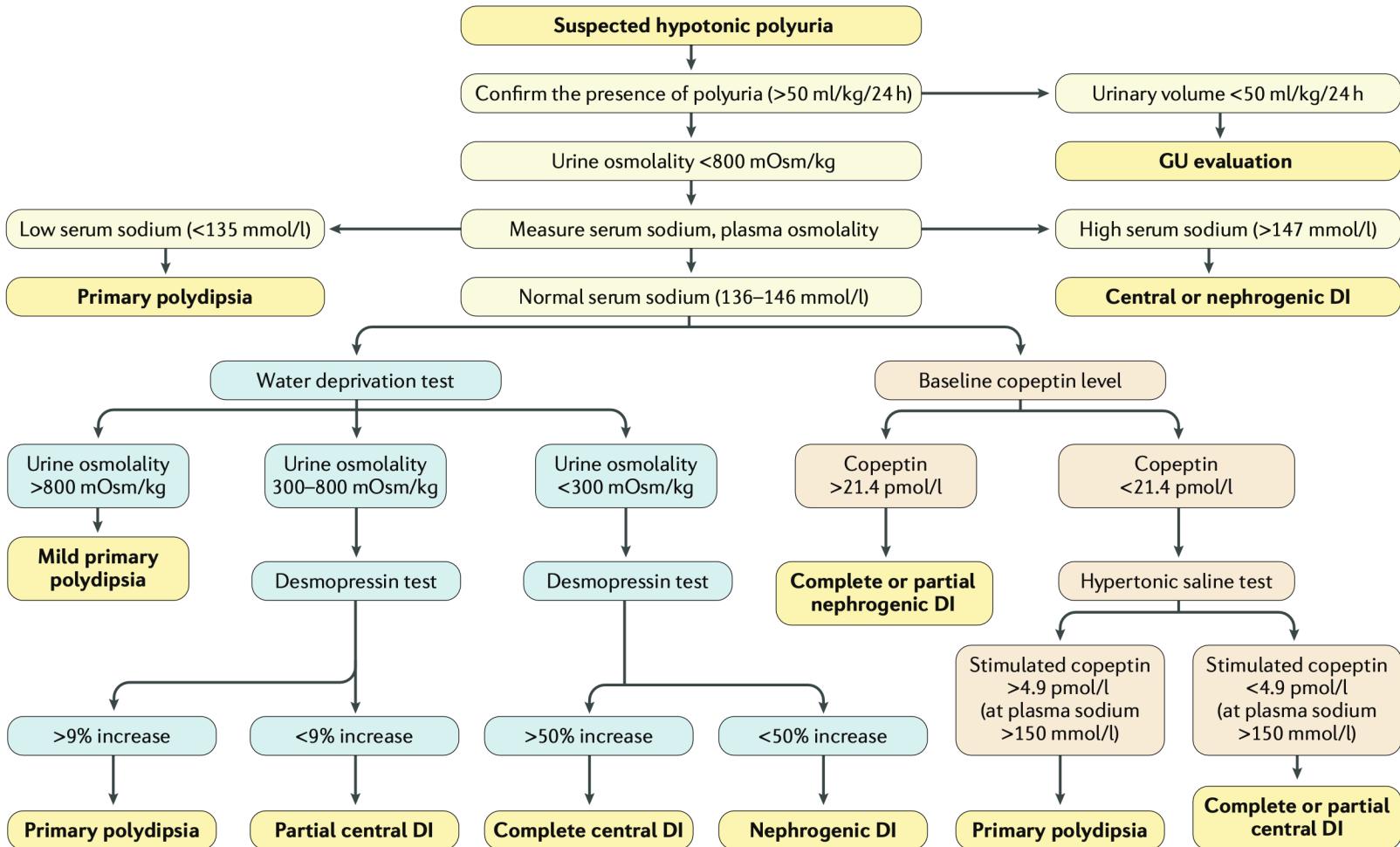


Approach to the Differential Diagnosis of Polyuric States



- polyuria(A 24-hour urine volume >50 mL/kg)
 - a random urine osmolality above 700 mOsm/kg excludes diabetes insipidus and makes the diagnosis of primary polydipsia certain.
 - Presenting serum sodium concentration is almost always normal in diabetes insipidus
- → A 24-h urine on unrestricted fluid intake
- → Check urine osmolarity
 - <280 mosm/L and the volume >50 mL/kg/day
→ the patient has DI → Water deprivation test

Modified algorithm for differential diagnosis of polyuria–polydipsia syndrome



Water deprivation test

1. The test should be started in the morning
2. Hourly measurements of body weight, plasma osmolality/Na concentration and urine volume and osmolality
3. The patient is maintained on a complete fluid restriction until urinary osmolality reach a plateau (an hourly increase of less than 30 mmol/kg for at least 3 successive hours)
 - DDAVP 0.03 ug/kg SC or IV → repeat the measurement of urine osmolality 1 to 2 h later
4. Urine didn't concentrate (osmolality > 300 mosmo/1g, specific gravity > 1.010) before body weight decrease by 5% or plasma sodium/osmolality exceed the upper limit of normal → primary polydipsia and a partial defect in AVP secretion or action are largely excluded

A. Purpose: Differential diagnosis of polyuria

B. Procedure:

項目 時間	體重	血壓	抽血		尿量	尿液(2管)	
	kg	mmHg	Sodium	Osmol	ml	Urine Sp.Gr	Urine Osmol
08:00 am	v	v	v	v	v	v	v
09:00 am					v	v	v
10:00 am	v	v	v	v	v	v	v
11:00 am					v	v	v
一直測....							
到 n 時間 (0 min)	v	v	v	v	v	v	v

禁食 +
禁水

n 時間 (0 min) 定義 :

連續兩次 urine osmolality 差異 ≤ 10%，且病人體重下降 2%。

或連續兩次 urine osmolality 差異 <30 mOsmol/kg。

或 Urine osmolality 達到 600-700 mOsmol/kg。

或 Plasma osmolality 達到 295-300 mOsmol/kg

(0 min): DDAVP (2 μg) 0.5 ml sc

60 min					v		v
120 min	v	v	v	v	v	v	v

95% of initial body weight = _____

注意事項

1. 8am 前可以進食，8 am~4 pm (整個 test 當中) 需要禁食 + 禁水
2. 若病人排尿有困難，可以使用單導或是尿管。
3. 12 noon 紀錄完了之後，再打 DDAVP (2 µg) 0.5 ml sc (0.5 vial)
4. 嚴重尿崩症患者可能因過度限水而導致脫水，甚至因血液中滲透壓過高而發生意識變化，尤其在體重下降達 3-5% 者，因此過程中需留意病人體重變化及臨床症狀之有無，若有明顯意識變化或是血壓降低，請立即停止 test 且給予點滴補充水分且通知總醫師。
5. 若限水前血液滲透壓已高達 300 mOsm/Kg 以上，則停止禁水，可直接給予 DDAVP 測其反應。
6. 若病人體重下降 3%，orthostatic hypotension，則停止禁水，可直接給予 DDVAP 測其反應
7. 實驗後應立即補充足夠液體以防止脫水。

C. Interpretation

Reference	Urine osmolality (mOsm/kg)			
	Williams Textbook 13th ed	Arch Dis Child 1998;79:84-89	After dehydration	After DDAVP
Normal			>750	>750
Central DI	No elevation	至少上升 50%，常上升 200-400%	<300	>750
Nephrogenic DI	No elevation	Little or no increase	<300	<300
Partial CDI	Mild elevation, but no more than 800-1200 mOsm/kg	At least > 10%	300-750	<750
Primary polydipsia		No increase		
Partial NDI				

References:

1. Robinson AG, et al. Williams Textbook of Endocrinology 13e, Chap. 10, p. 305-306
2. Manktelow BN, et al. Arch Dis Child Fetal Neonatal Ed. 2010 Mar;95:F95-8

Uosmo increase after vasopression

Type	Δ Uosmo
Normal	<9%
Complete CDI	>50%
Partial CDI	9%~50%
Primary polydipsia	<9%

Water deprivation test can't differentiate primary polydipsia, partial CDI and partial NDI

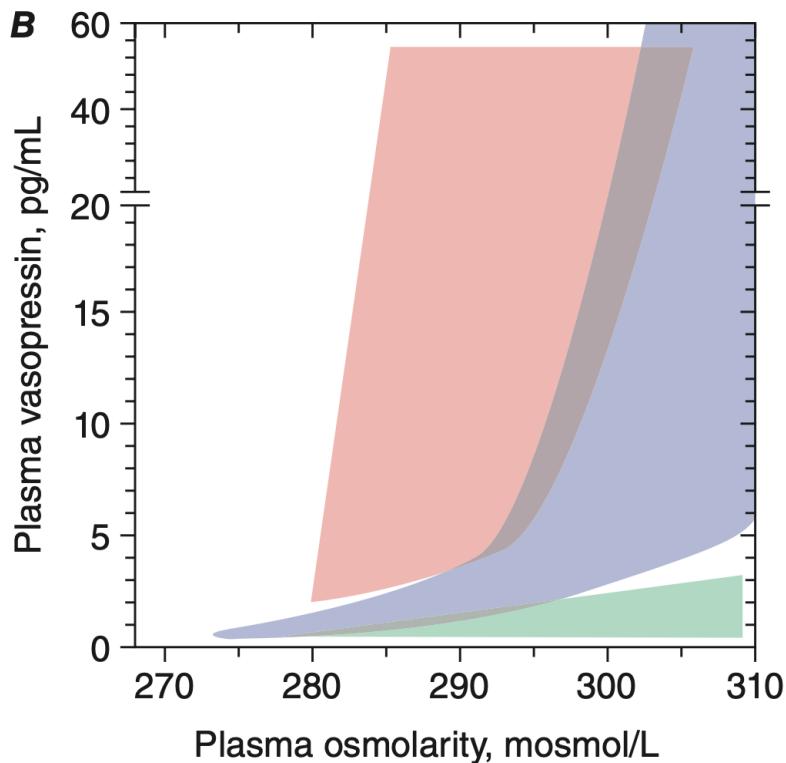
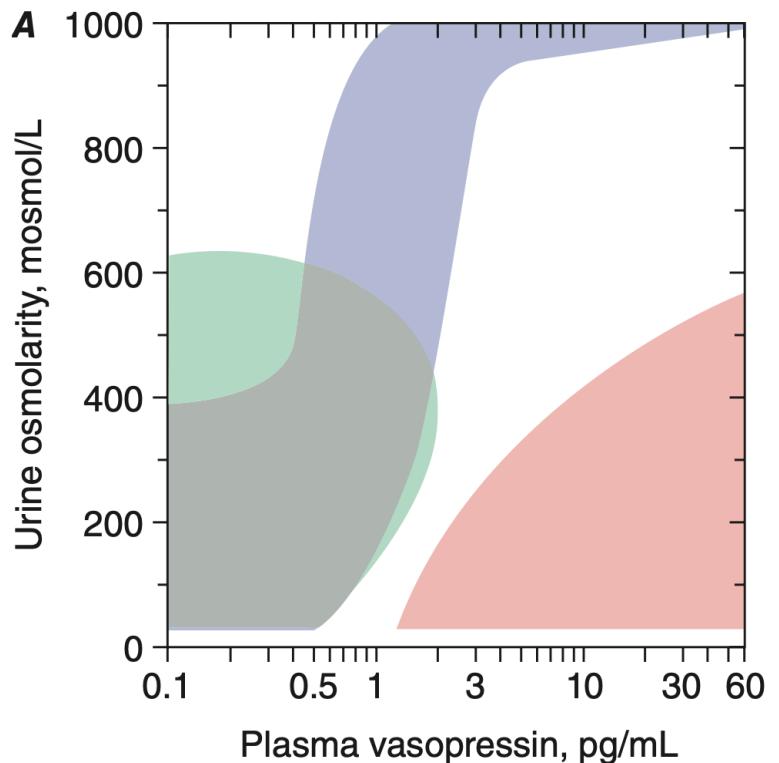
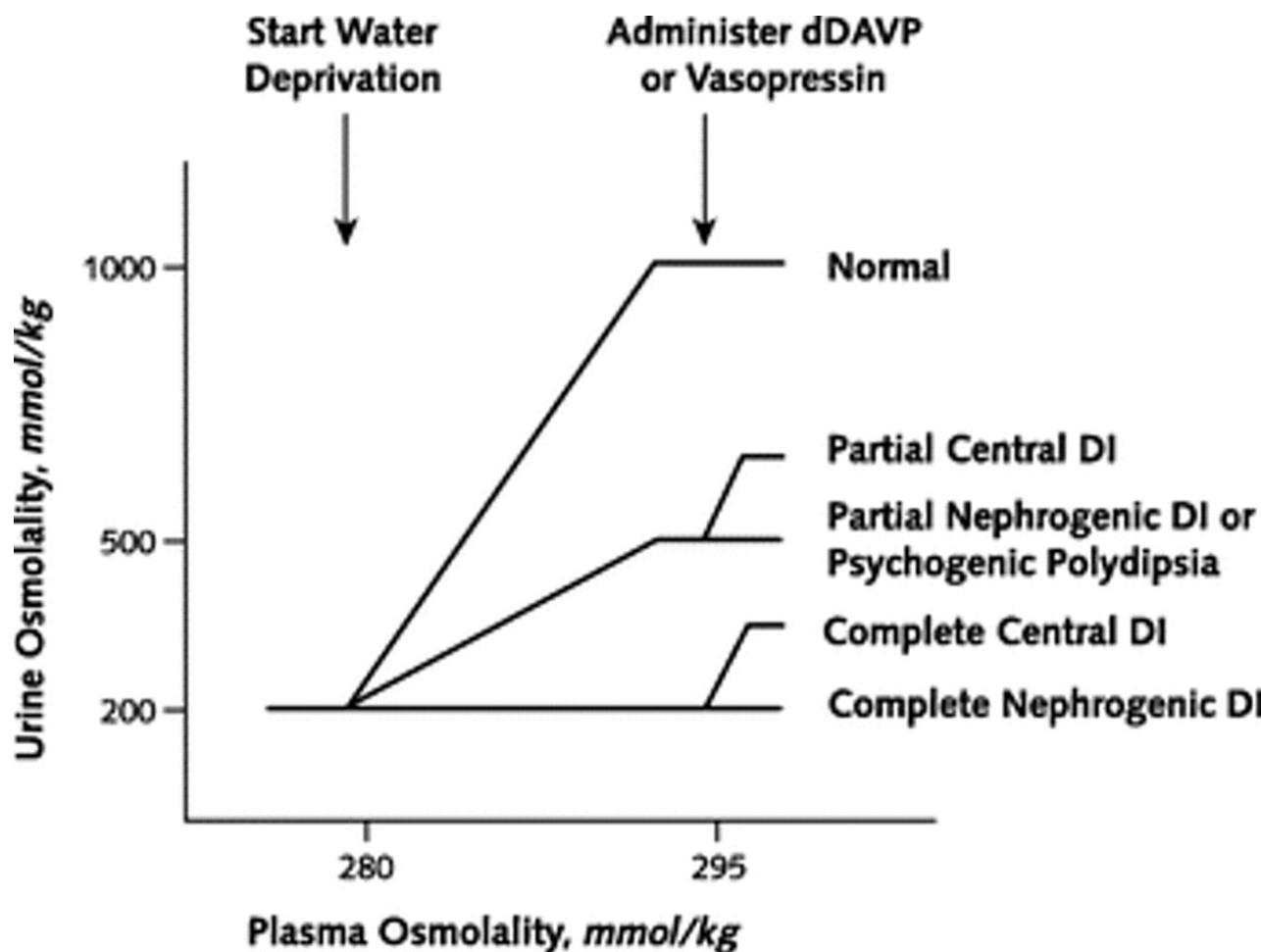
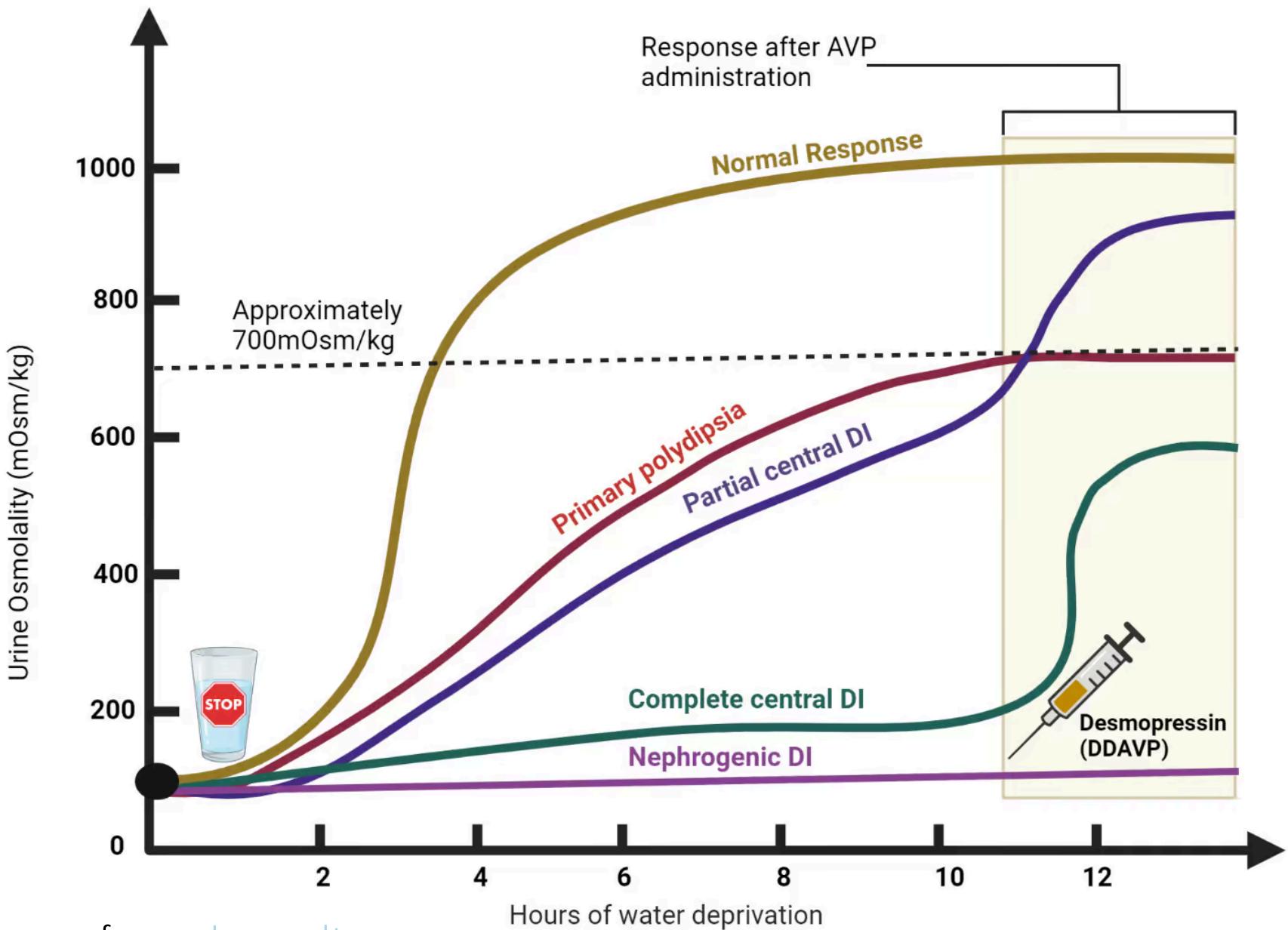
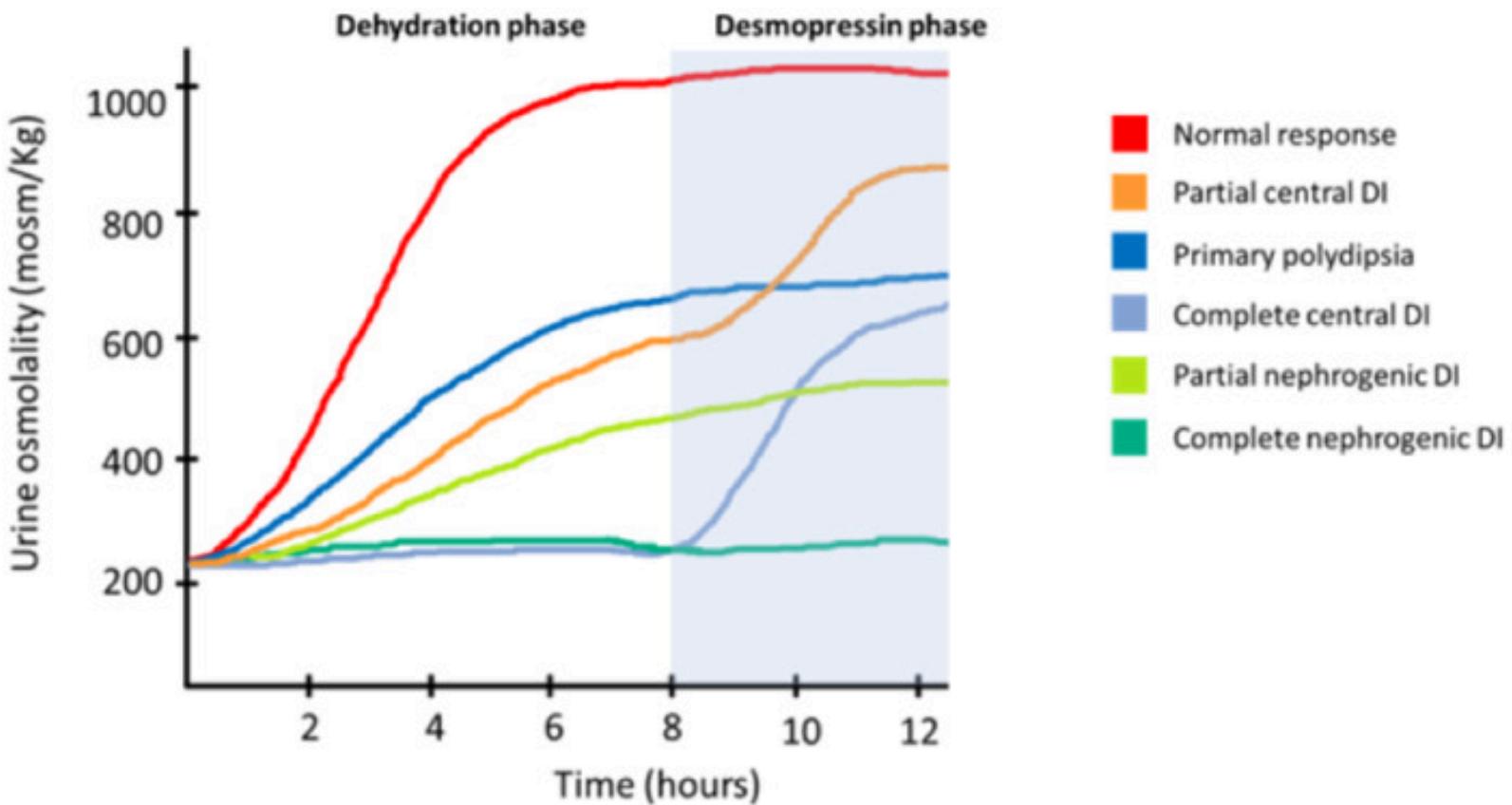


FIGURE 381-3 Relationship of plasma arginine vasopressin (AVP) to urine osmolarity (A**) and plasma osmolarity (**B**) before and during fluid deprivation–hypertonic saline infusion test in patients who are normal or have primary polydipsia (blue zones), pituitary diabetes insipidus (green zones), or nephrogenic diabetes insipidus (pink zones).**



REF: Ann Intern Med 7 February 2006;144 186-194 "Nephrogenic Diabetres Insipidus"





Gubbi S, Hannah-Shmouni F, Koch CA, et al. Diagnostic Testing for Diabetes Insipidus.

Treatment of Central DI

- DDAVP (Desamino-D-arginine-8 vasopressin)
 - Selectively at V2 receptor
 - More resistance to degrade than AVP→3-4 folds longer duration
 - Dose
 - IV/SC: 0.25 to 1 mcg every 12 to 24 hours
 - Nasal spray: Initial: 5 to 10 mcg once daily at bedtime; Usual maintenance dose: 5 to 20 mcg once or twice daily; suggested maximum dose: 40 mcg/day.
 - Oral: Initial: 0.05 to 0.2 mg once daily; Usual maintenance dose: 0.1 to 0.8 mg/day in 2 to 3 equally divided doses; suggested maximum dose: 1.2 mg/day

Treatment of Central DI

- Chlorpropamide:
 - may involve potentiation of the effect of small amounts of AVP or direct activation of the V2 receptor
 - Antidiuretic effect can be enhanced by thiazide diuretic

Treatment of Nephrogenic DI

- Nephrogenic diabetes insipidus does not respond to desmopressin therapy
- occasionally partial defects have limited response to high doses of desmopressin
- In congenital NDI, therapy aimed at reducing symptomatic polyuria is addressed primarily by inducing plasma volume contraction via **a low sodium diet and a thiazide diuretic.**
- Drug-induced nephrogenic diabetes insipidus should be treated by stopping the offending agent if possible.

Treatment of Primary polydipsia

- Treatment of primary polydipsia entails reduction of excessive fluid intakes, best done in a graded fashion to allow patients to slowly achieve a level of intake that reduced urine volume below polyuric levels (50 mL/kg BW).
- Measures to reduce mouth dryness (e.g., ice chips, hard candy to stimulate salivary flow) are useful adjuncts to reduce thirst.
- Pharmacologic therapies have been tried but without consistent evidence of success.

Treatment of Diabetes Insipidus in Pregnancy

- Once diagnosis of gestational DI is confirmed, treatment with desmopressin is indicated, regardless of whether DI is permanent or transient
- Desmopressin has 2% to 25% the oxytocic activity of lysine vasopressin or arginine vasopressin, and can be used with minimal stimulation of the oxytocin receptors in the uterus
- Desmopressin is not destroyed by the cysteine aminopeptidase (oxytocinase) of pregnancy and is reported to be safe for both the mother and the child.

Syndrome of Inappropriate Antidiuresis (SIAD)

Syndrome of Inappropriate Antidiuresis (SIAD)

- the hallmark of SIAD is hypoosmolality
- Also called the syndrome of inappropriate antidiuretic hormone (SIADH)

Clinical characteristics

- **hypo-osmolemic hyponatremia** and impaired urinary dilution in the absence of hypovolemia, hypotension, or other nonosmotic stimuli to AVP secretion.
- Water intoxication: mild headache, confusion, anorexia, nausea, vomiting coma and convulsion

Etiology

- The cause of SIAD is a failure to maximally dilute the urine and mount a water diuresis when total water intake exceeds urinary and insensible water loss.
- In most cases, the defect in urinary dilution is due to an abnormality in AVP secretion and is commonly referred to as the syndrome of inappropriate antidiuretic hormone (SIADH).
- Tumor:
 - 1st: bronchogenic carcinoma of the lung, small cell carcinoma of the lung
 - 2nd: Head and neck cancers
- Drugs:
 - Stimulated release of AVP (nicotine, phenothiazines, tricyclics)
 - Direct renal effects(DDAVP, oxytocin, prostaglandin synthesis inhibitors)
 - 3,4-methylenedioxymeth- amphetamine, "ecstasy"毒品

TABLE 10.2 Common Causes of the Syndrome of Inappropriate Antidiuretic Hormone (SIADH) Secretion

Tumors

- Pulmonary/mediastinal (bronchogenic carcinoma, mesothelioma, thymoma)
- Nonchest (duodenal carcinoma, pancreatic carcinoma, ureteral/prostate carcinoma, uterine carcinoma, nasopharyngeal carcinoma, leukemia)

Central Nervous System Disorders

- Mass lesions (tumors, brain abscesses, subdural hematoma)
- Inflammatory diseases (encephalitis, meningitis, systemic lupus erythematosus, acute intermittent porphyria, multiple sclerosis)
- Degenerative/demyelinative diseases (Guillain-Barré syndrome, spinal cord lesions)
- Miscellaneous (subarachnoid hemorrhage, head trauma, acute psychosis, delirium tremens, pituitary stalk section, transsphenoidal adenectomy, hydrocephalus)

Drug Related

- Stimulated release of AVP (nicotine, phenothiazines, tricyclics)
- Direct renal effects or potentiation of AVP antidiuretic effects (dDAVP, oxytocin, prostaglandin synthesis inhibitors)
- Mixed or uncertain actions (ACE inhibitors, carbamazepine and oxcarbazepine, chlorpropamide, clofibrate, clozapine, cyclophosphamide, 3,4-methylenedioxymethamphetamine [ecstasy], omeprazole; serotonin reuptake inhibitors, vincristine)

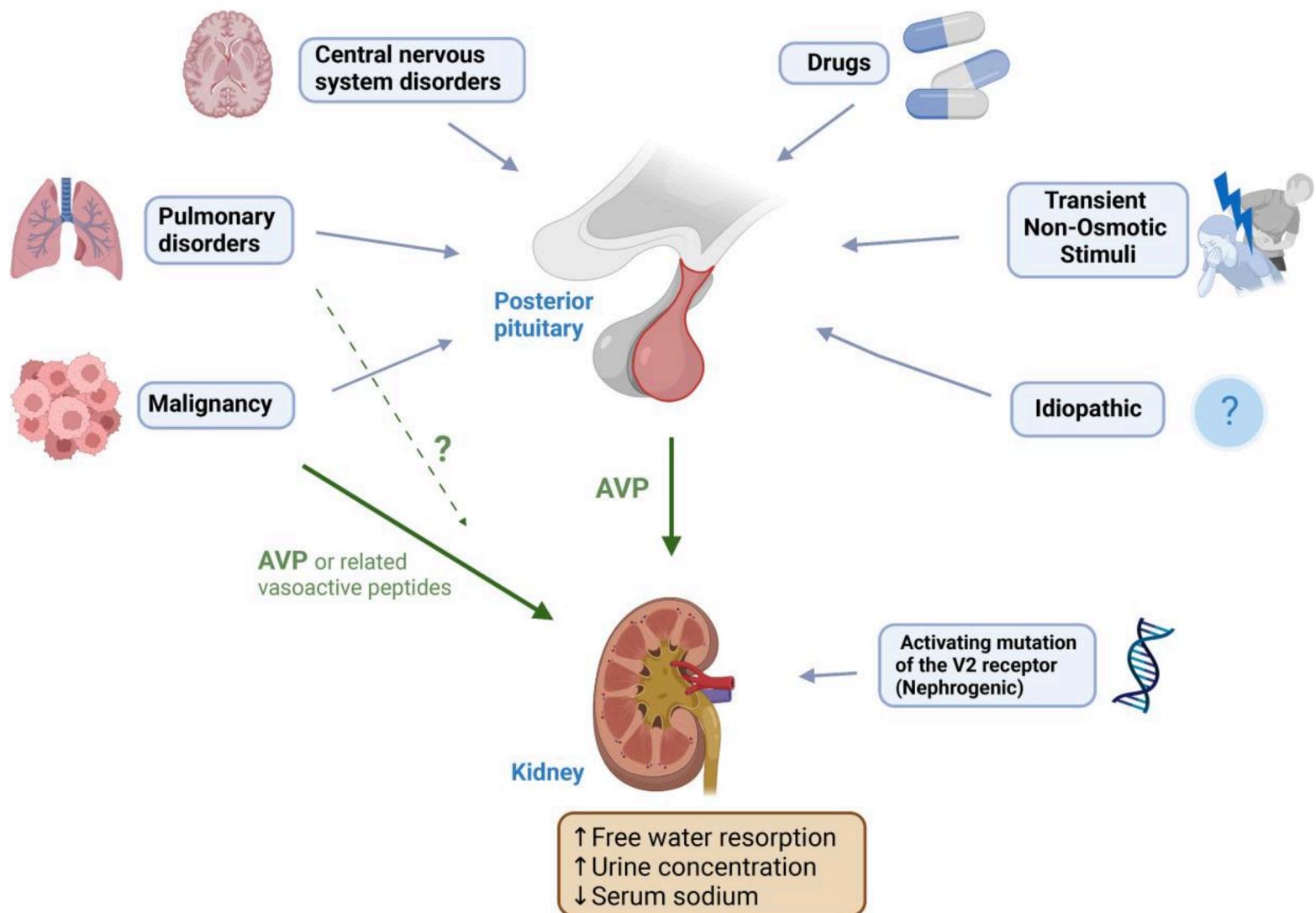
Pulmonary

- Infections (tuberculosis, acute bacterial and viral pneumonia, aspergillosis, empyema)
- Mechanical/ventilatory causes (acute respiratory failure, COPD, positive-pressure ventilation)

Other Causes

- Acquired immunodeficiency syndrome (AIDS) and AIDS-related complex
- Prolonged strenuous exercise (marathon, triathlon, ultramarathon, hot-weather hiking)
- Senile atrophy
- Idiopathic

ACE, Angiotensin-converting enzyme; AVP, arginine vasopressin; COPD, chronic obstructive pulmonary disease; dDAVP, desmopressin.



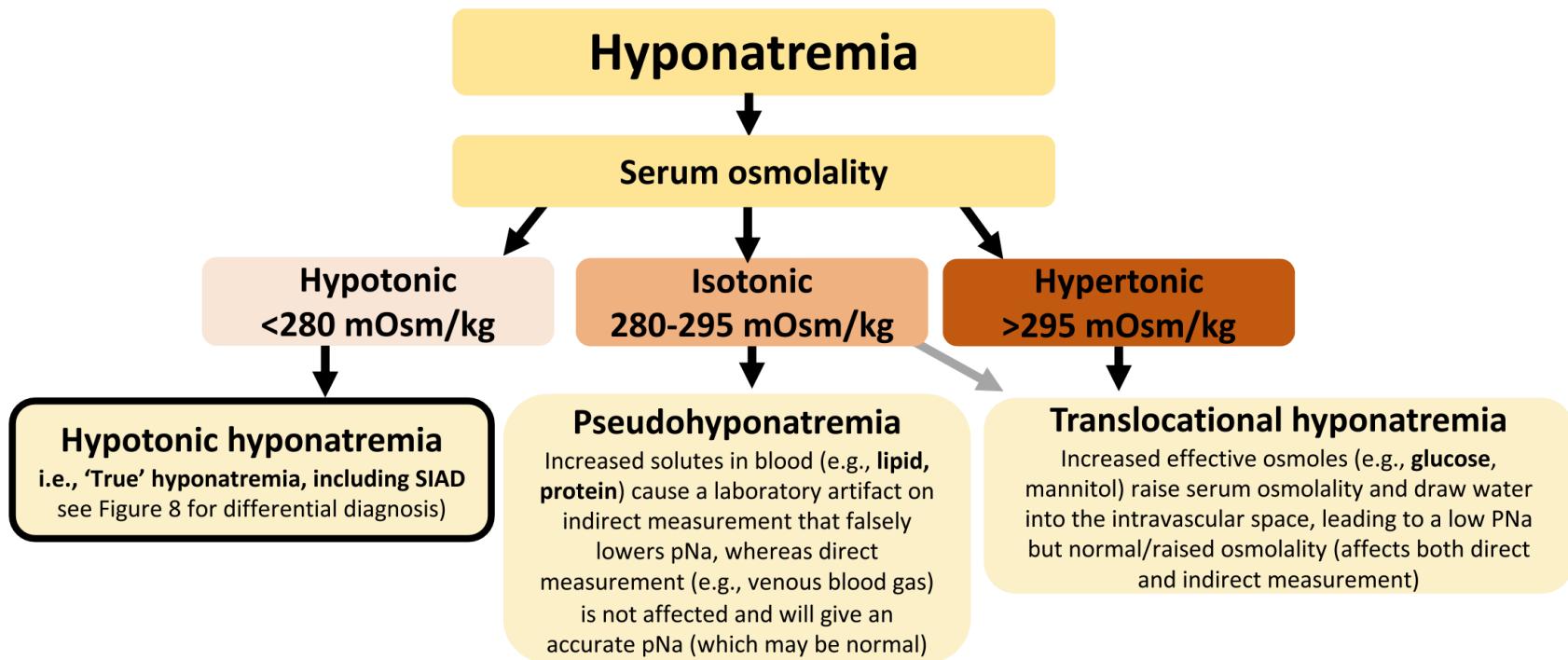
Criteria for diagnosis of syndrome of inappropriate diuresis

set forth by Schwartz and Bartter in 1967

- Low serum osmolality: $\text{pOsm} < 275 \text{ mOsmol/kgH}_2\text{O}$)
- Inappropriate urine concentration: urine osmolality $> 100 \text{ mOsmol/kg H}_2\text{O}$
- Clinical euvoolemia (absence of signs of hypovolemia or hypervolemia)
- Elevated urinary sodium excretion $> 30 \text{ mmol/L}$ with normal salt and water intake
- Absence of other potential causes of euvolemic hypoosmolality (glucocorticoid insufficiency, severe hypothyroidism)
- Normal renal functionc and absence of diuretic use (particularly thiazide diuretics)

Differential Diagnosis

Start from **hypo-osmolemic hyponatremia**



Differential Diagnosis

- SIAD must be differentiated from other types of hypo-osmolemic hyponatremia associated with impaired urinary dilution.
 - Hypervolemic hyponatremia (type I): generalized edema due to severe congestive heart failure or cirrhosis, elevated Plasma renin activity (PRA) and aldosterone.
 - Hypovolemic hyponatremia (type II): loss of sodium and water due to severe vomiting, diarrhea, or primary adrenal insufficiency, with an elevation in PRA.
 - Euvolemic hyponatremia (type III)
 - Severe deficiency in cortisol or thyroxine
 - SIAD

TABLE 381-3 Differential Diagnosis of Hyponatremia Based on Clinical Assessment of Extracellular Fluid Volume (ECFV)

CLINICAL FINDINGS	TYPE I, HYPERVOLEMIC	TYPE II, HYPOVOLEMIC	TYPE III, EUVOLEMIC	SIADH AND SIAD EUVOLEMIC
History				
CHF, cirrhosis, or nephrosis	Yes	No	No	No
Salt and water loss	No	Yes	No	No
ACTH-cortisol deficiency and/or nausea and vomiting	No	No	Yes	No
Physical examination				
Generalized edema, ascites	Yes	No	No	No
Postural hypotension	Maybe	Maybe	Maybe ^a	No
Laboratory				
BUN, creatinine	High-normal	High-normal	Low-normal	Low-normal
Uric acid	High-normal	High-normal	Low-normal	Low-normal
Serum potassium	Low-normal	Low-normal ^b	Normal ^c	Normal
Serum urate	High	High	Low	Low
Serum albumin	Low-normal	High-normal	Normal	Normal
Serum cortisol	Normal-high	Normal-high ^d	Low ^e	Normal
Plasma renin activity	High	High	Low ^f	Low
Urinary sodium (meq per unit of time) ^g	Low	Low ^h	High ⁱ	High ⁱ

^aPostural hypotension may occur in secondary (ACTH-dependent) adrenal insufficiency even though extracellular fluid volume and aldosterone are usually normal. ^bSerum potassium may be high if hypovolemia is due to aldosterone deficiency. ^cSerum potassium may be low if vomiting causes alkalosis. ^dSerum cortisol is low if hypovolemia is due to primary adrenal insufficiency (Addison's disease). ^eSerum cortisol will be normal or high if the cause is nausea and vomiting rather than secondary (ACTH-dependent) adrenal insufficiency. ^fPlasma renin activity may be high if the cause is secondary (ACTH) adrenal insufficiency. ^gUrinary sodium should be expressed as the rate of excretion rather than the concentration. In a hyponatremic adult, an excretion rate >25 meq/d (or 25 μeq/mg of creatinine) could be considered high. ^hThe rate of urinary sodium excretion may be high if the hypovolemia is due to diuretic abuse, primary adrenal insufficiency, or other causes of renal sodium wasting. ⁱThe rate of urinary sodium excretion may be low if intake is curtailed by symptoms or treatment.

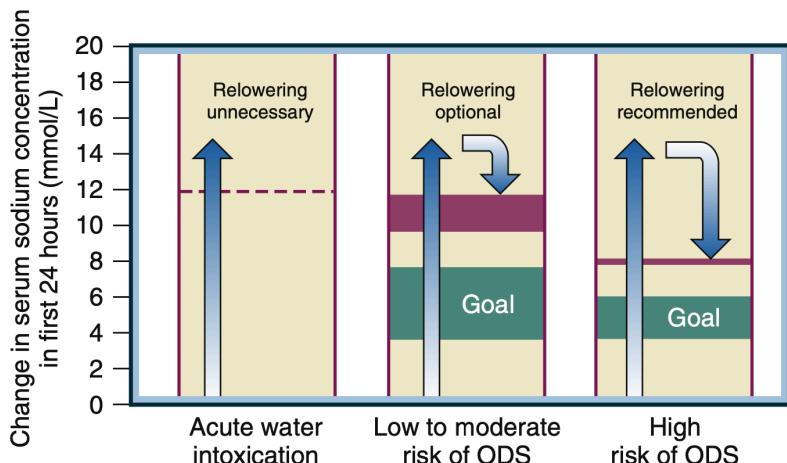
Abbreviations: ACTH, adrenocorticotrophic hormone; BUN, blood urea nitrogen; CHF, congestive heart failure; SIAD, syndrome of inappropriate antidiuresis; SIADH, syndrome of inappropriate antidiuretic hormone.

Treatment of SIAD

- Correction of hyponatremia is associated with markedly improved neurologic outcomes in patients with severely symptomatic hyponatremia.
- If the hyponatremia is mild and largely asymptomatic, restricting total water intake to ~30 mL/kg per day less than urine output for several days
- If the hyponatremia is severe and symptomatic, the goal should be to partially correct it by intravenous infusion of hypertonic (3%) saline or administration of an AVP antagonist such as tolvaptan or conivaptan

Treatment of SIAD

- For all therapies, careful attention should be paid to recommendations for goals and limits of correction of the serum $[Na^+]$ to reduce the risk of the osmotic demyelination syndrome (ODS).
- Hypertonic Saline(3% NaCl ($[Na^+] = 513 \text{ mmol/L}$))
 - Patient's weight (kg) \times desired correction rate (mEq/L/hr) = infusion rate of 3% NaCl (mL/hr)
 - usually Rate $< 0.05 \text{ mL/kg/min}$
 - Serum sodium monitor every hour → stop when serum sodium by 12 mmol/L or to 130 mmol/L
 - If the hyponatremia has been corrected too rapidly → central pontine myelinolysis
- Isotonic Saline($[Na^+] = 154 \text{ mmol/L}$)
 - clinical signs of hypovolemia or in whom a spot urine $[Na^+] < 20$ to 30 mEq/L.
- Fluid Restriction
 - fluids < 500 to 1000 mL/24 hours.



- Fig. 10.7** Recommended goals (green) and limits (red) for correction of hyponatremia based on risk of producing ODS and recommendations for relowering of serum sodium concentration ($[Na^+]$) to goals for patients presenting with serum $[Na^+]$ lower than 120 mmol/L who exceed the recommended limits of correction in the first 24 hours. ODS, osmotic demyelination syndrome. (From Verbalis JG, Goldsmith SR, Greenberg A, et al. Diagnosis, evaluation, and treatment of hyponatremia: expert panel recommendations. *Am J Med.* 2013;126:S1–S42.)

TABLE 10.3

General Recommendations for Use of Fluid Restriction and Predictors of the Increased Likelihood of Failure of Fluid Restriction

General Recommendations

- Restrict *all* intake that is consumed by drinking, not just water.
- Aim for a fluid restriction that is 500 mL/day *below* the 24-hour urine volume.
- Do not* restrict sodium or protein intake unless indicated.

Predictors of the Likely Failure of Fluid Restriction

- High urine osmolality ($\geq 500 \text{ mOsm/kg H}_2\text{O}$).
- Sum of the urine $[Na^+]$ and $[K^+]$ concentrations exceeds the serum $[Na^+]$ concentration.
- 24-hour urine volume $< 1500 \text{ mL/day}$.
- Increase in serum $[Na^+]$ concentration $< 2 \text{ mmol/L/day}$ in 24–48 hours on a fluid restriction of $\leq 1 \text{ L/day}$.

Treatment of SIAD

- Arginine Vasopressin Receptor Antagonists
 - Tolvaptan: oral vasopressin V2 receptor antagonist → blocks AVP action in the kidney
- Urea
- Sodium-Glucose Cotransporter 2 Inhibitors(SGLT2i)
 - in the proximal renal tubule: 90% of renal glucose resorption and 65% of sodium resorption
- Oral Sodium Chloride (Salt Tablets)
- Loop Diuretics
- Demeclocycline
- Lithium
- Apelin Analogues

Syndrome of Inappropriate Antidiuresis (SIAD):

Tolvaptan:

Urea:

SGLT2i:

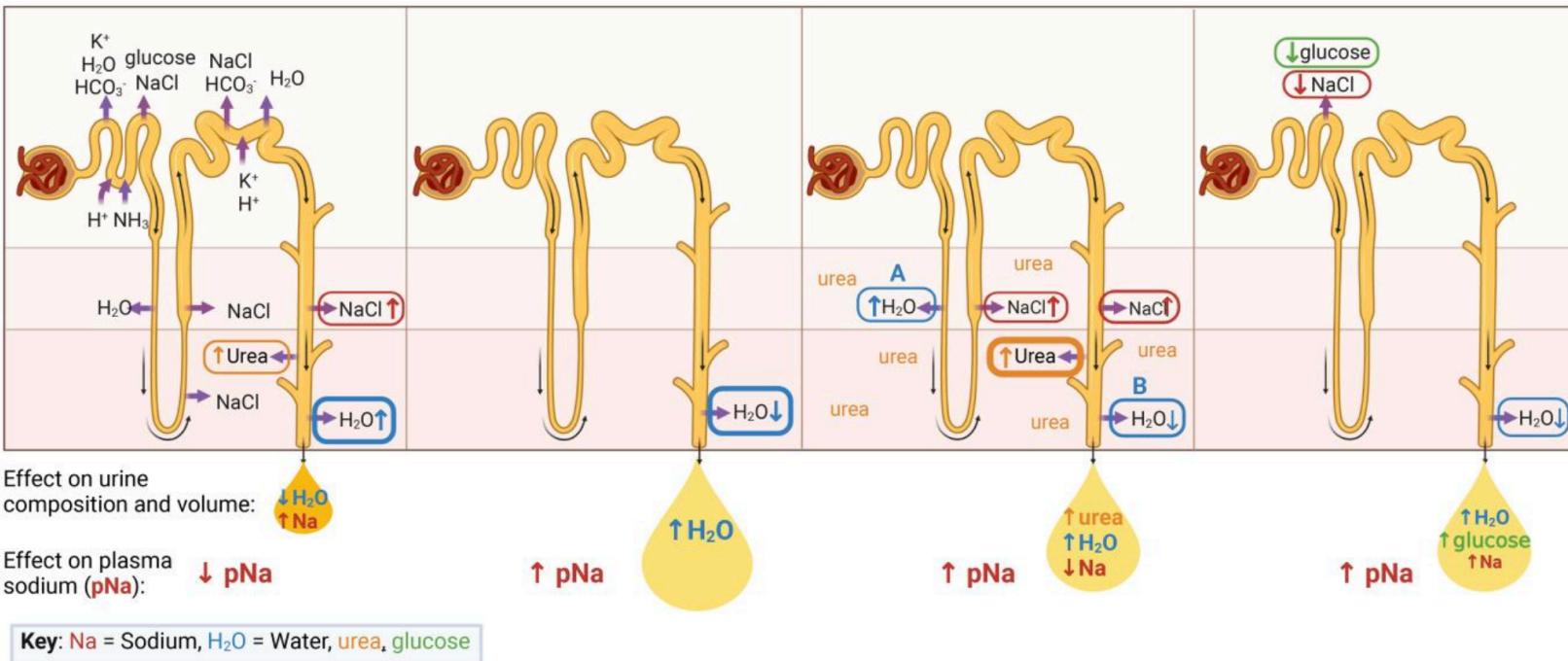


Figure 11. Renal physiology in SIAD, and mechanisms of action of tolvaptan, urea, and SGLT2i at the nephron. **SIAD:** Nonosmotic increase in circulating AVP leads to increased water resorption in the collecting duct via aquaporins, plus reduced sodium resorption in the proximal convoluted tubule, ascending limb, and distal convoluted tubule, resulting in concentrated urine production and decreased serum sodium concentration (see Fig. 5). AVP also promotes water retention by upregulating expression of UT-A1s to increase reabsorption of urea, augmenting medullary interstitial osmolality and hence urinary concentrating ability. **Tolvaptan:** blockade of AVP V2 receptor leads to reduced water resorption in the context of reduced aquaporins, resulting in a free water diuresis leading to a rise in serum sodium. **Urea:** Administration of urea leads to increased concentration of urea both in the filtrate and the renal interstitium. This leads to A, increased water resorption in the descending limb due to the osmotic effect of urea, initially leading to an elevated sodium concentration in the filtrate in the descending limb. This leads to increased sodium resorption by passive diffusion in the ascending limb, reducing sodium loss. Later, the osmotic draw of urea in the filtrate leads to B, reduced water resorption in the collecting duct, resulting in an osmotic diuresis and rise in serum sodium. **SGLT2i:** SGLT2i inhibitors act at the sodium-glucose cotransporter in the proximal tubule to reduce resorption of glucose and sodium. The primary effect is glycosuria (even in those without diabetes mellitus), accompanied by increased water excretion due to an osmotic diuresis. There is a transient increase in sodium excretion as well; however, the net effect on plasma sodium level is to increment when used in hyponatremia. AVP, arginine vasopressin; SIAD, syndrome of inappropriate diuresis; SGLT2i, sodium-glucose cotransporter 2 inhibitor. Original figure created with biorender.com, with reference to Decaux 1980 regarding urea physiology (306).

Management

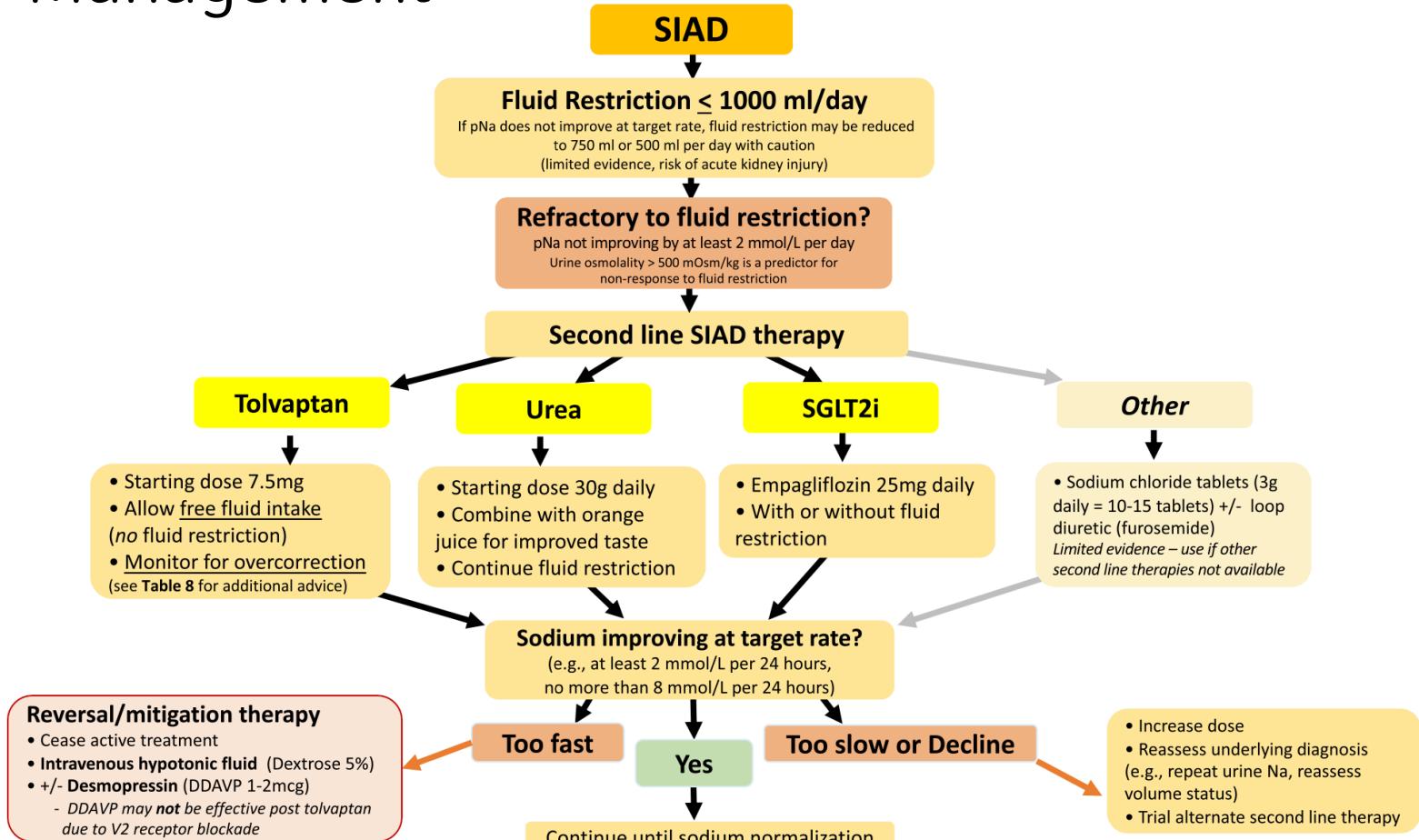


Figure 10. An approach to management of syndrome of inappropriate antidiuresis (SIAD), based on current limited evidence base. pNa, plasma sodium concentration.

Take Home Message

- 臨床上SIADH比DI常見，但是DI考題比較多
- AVP的生理機轉與體液調控
- DI的分類與鑑別診斷
 - Water deprivation test
- SIAD的診斷與治療
 - flowchart of hyponatremia

References

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Thanks for your attention!

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