polyuria and nephrogenic DI

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Definition of Polyuria

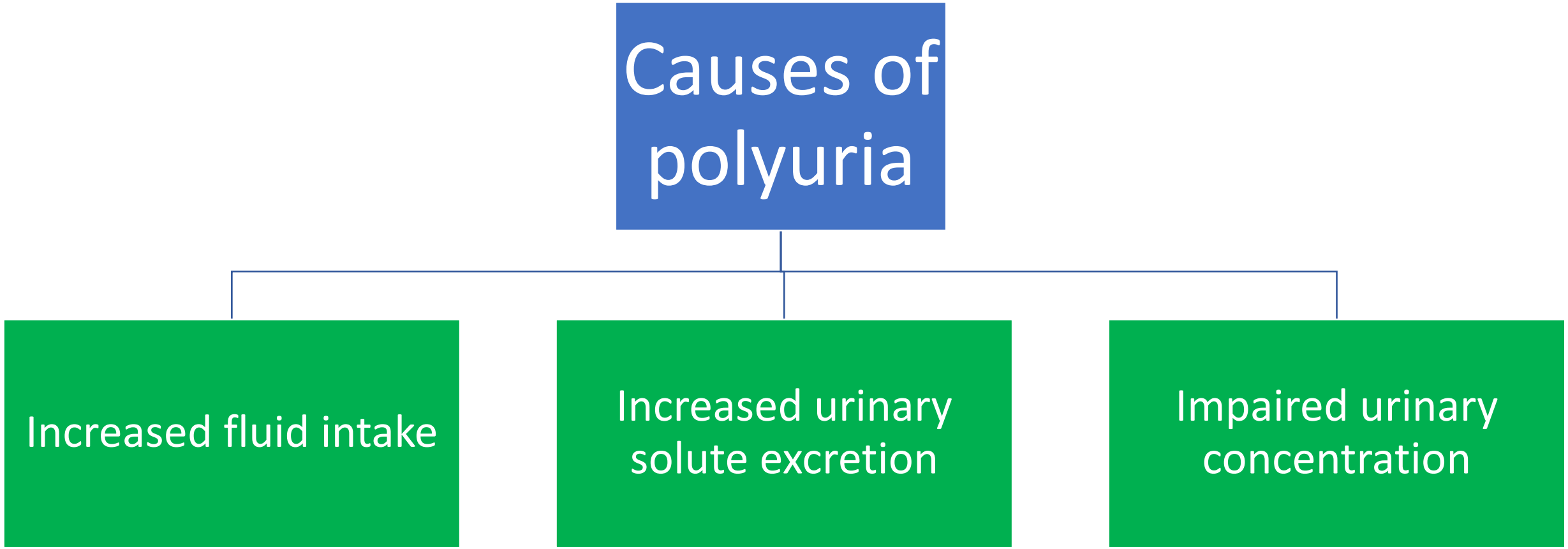
urine output > 2 L/m2/day in children, and 3L/day in adults.

It must be differentiated from the more common complaints of frequency or nocturia, which are not associated with an increase in the total urine output.

$$\text{DuBois Formula: BSA } (m^2) = \sqrt{\frac{\text{Height (cm)} \times \text{Weight (kg)}}{3{,}600}}$$

Or

$$BSA(m^2) = \frac{(4 \times B.wt) + 7}{wt + 90}$$


Causes of polyuria
Increased fluid intake
Increased urinary solute excretion
Impaired urinary concentration

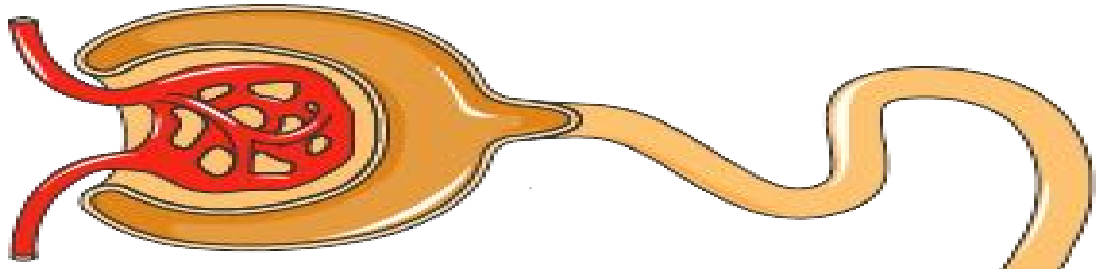
Increased fluid intake	Increased urinary solute excretion
Compulsive water drinking (*primary polydipsia*)	▪ osmotic diuresis 1- *DM* 2- *Mannitol treatment* ▪ Salt loose 1- Adrenal insufficiency 2- Aldosterone resistance 3- Cerebral salt wasting 4- Diuretic therapy

Impaired urinary concentration

- Insufficient ADH action (Diabetes insipidus)
  1- Central (neurogenic) DI
  2- Nephrogenic DI

- Renal disorders
  1- RTA
  2- Bartter syndrome
  3- Gitelman syndrome

180 L /day
of plasma



About 80 % of this is passively reabsorbed in the(PT),
through H20 channels **(AQP1)** , (Na by Na/k ATPase ,Hco3, P) .

H20

↑ M. Tonicity
(1200 mOsm/kg)

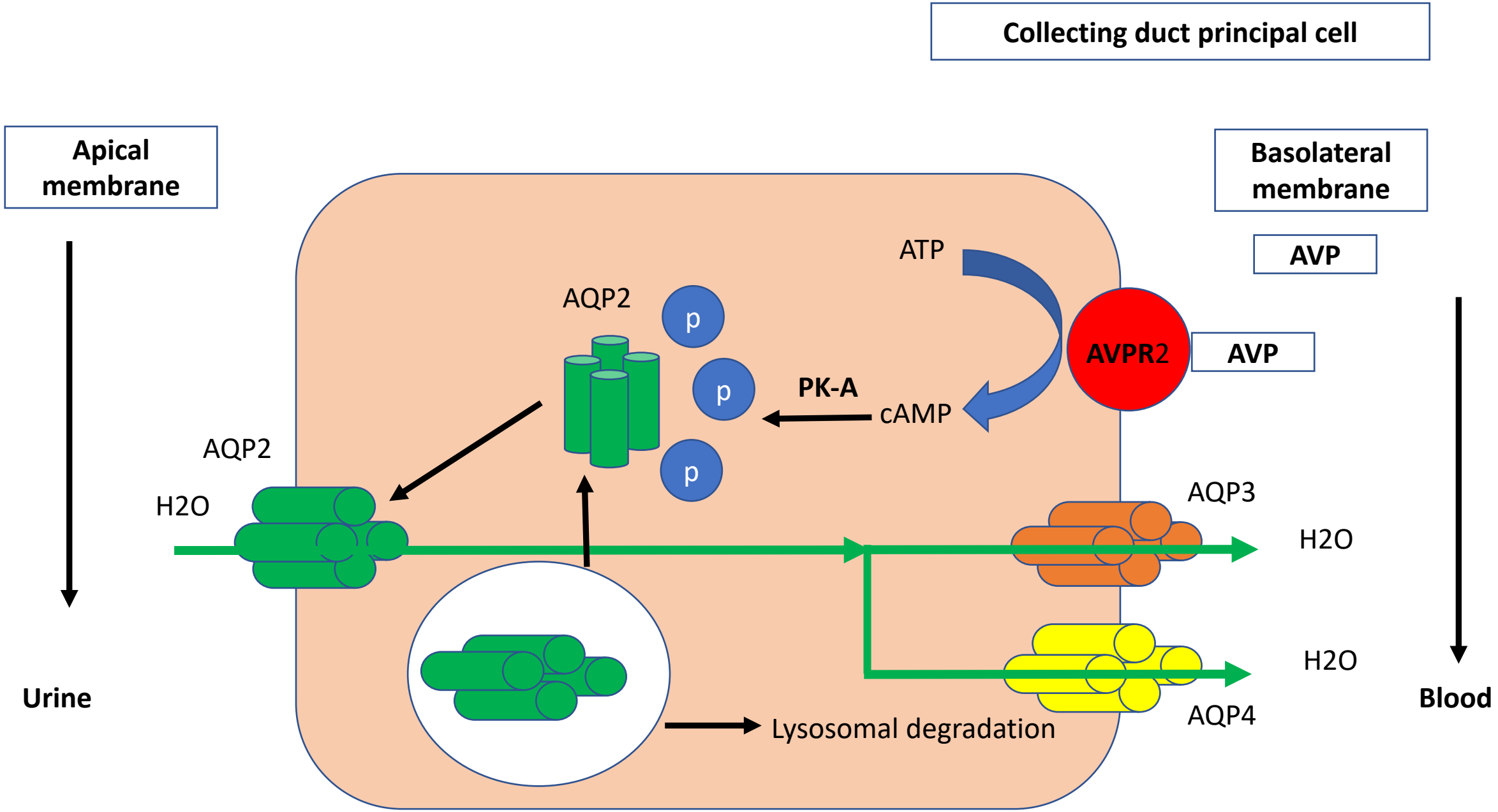
TAL is
impermeable to
H2o but
permeable to Na

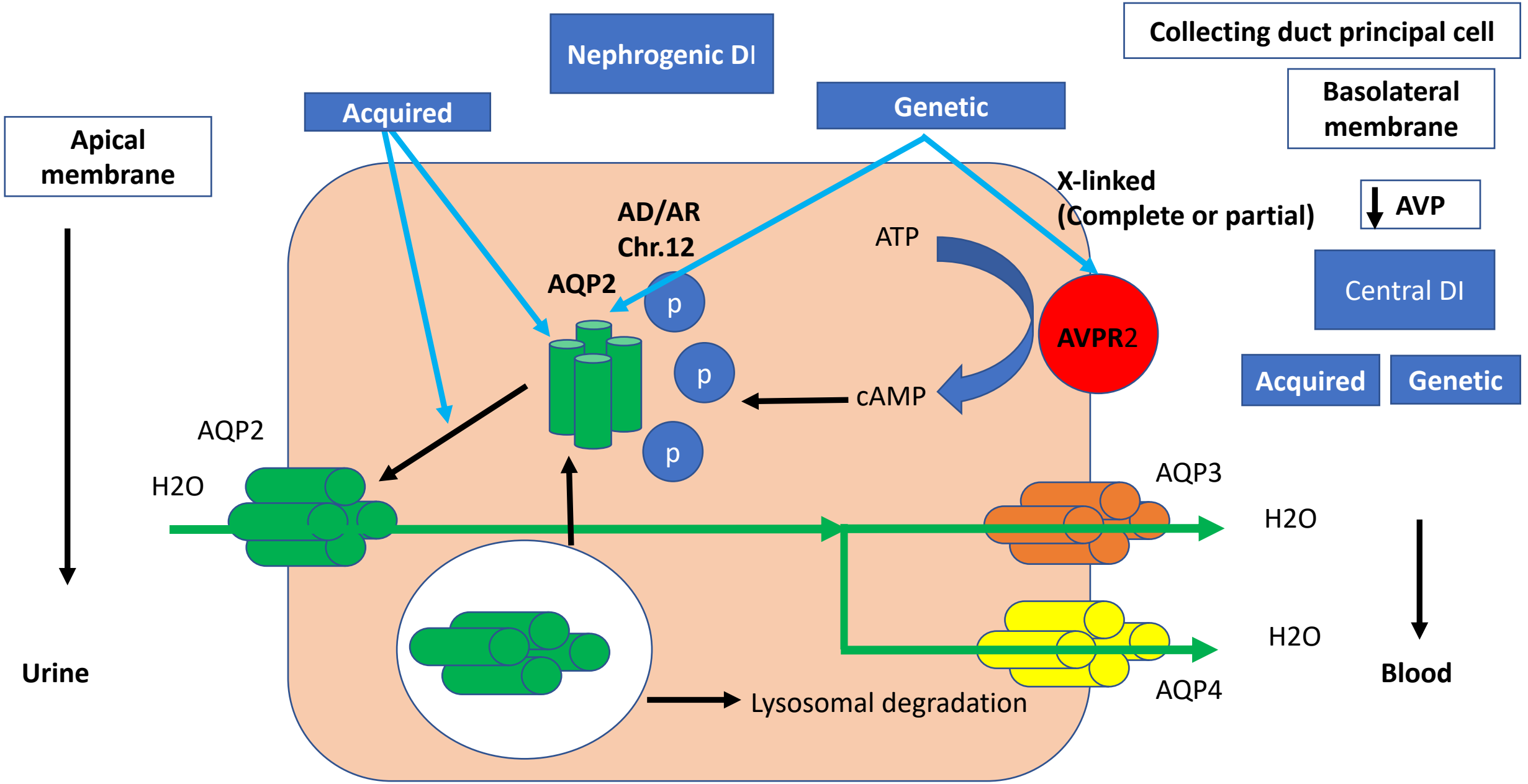
↑ M. Tonicity
(1200 mOSm/kg)

H20

permeable
to H20

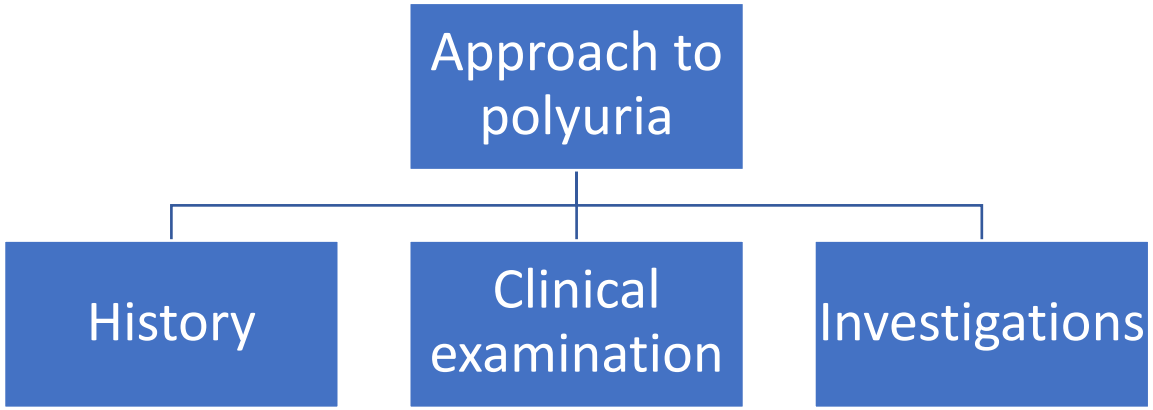
(ADH)
(AQP2)


Collecting duct principal cell
Apical membrane
Basolateral membrane
AVP
ATP
AQP2
p
p
p
PK-A
cAMP
AVPR2
AVP
AQP2
H2O
AQP3
H2O
H2O
AQP4
Lysosomal degradation
Urine
Blood


Collecting duct principal cell
Nephrogenic DI
Acquired
Genetic
Basolateral membrane
Apical membrane
X-linked (Complete or partial)
AVP
AD/AR Chr.12
AQP2
ATP
p
p
p
AVPR2
Central DI
cAMP
Acquired
Genetic
AQP2
H2O
AQP3
H2O
H2O
AQP4
Urine
Blood
Lysosomal degradation

DI

Central DI	Nephrogenic DI
▪ Genetic AR/AD / wolfram syndrome ▪ Malformation septo-optic dysplasia, Holoprosencephaly , Anencephaly, Agenesis of corpus callosum ▪ Acquired Head trauma , tumor, infection , surgery ▪ Idiopathic	▪ Genetic XL (AVPR2) defect AR/AD (AQP2) defect ▪ Acquired Hypokalemia, hypercalcemia , obstructive uropathy, nephrocalcinosis, lithium, Amphotericin B



- Age of onset
- Meningitis / increased ICT
- Head trauma / neurosurgery
- Drug intake
- Psychological troubles
- Repeated attacks of fever and dehydration

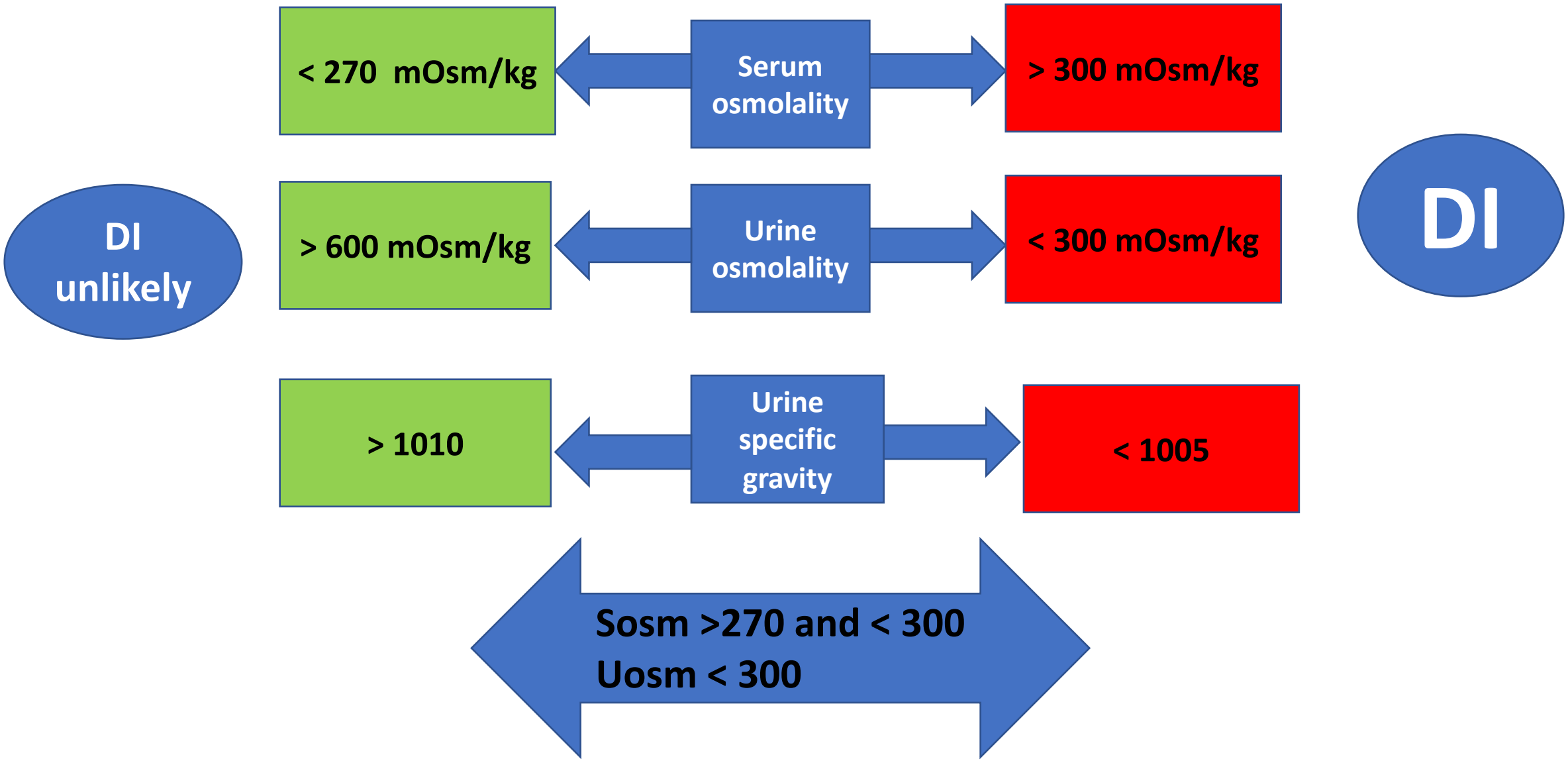
- Anthropometric measures
- Signs of dehydration
- MR / neurological deficits / midline defects***(central DI)***
- Genital ambiguity ***(CAH)***
- Rash / seborrhea / ear discharge ***(histocytosis)***
- Hyperpigmentation ***(Adrenal insufficiency)***
- Acidotic breathing***(RTA)***
- Rickets ***(RTA,CKD)***
- Muscle weakness ***(Hypokalemia)***

Clinical features (primary, X-linked nephrogenic DI)

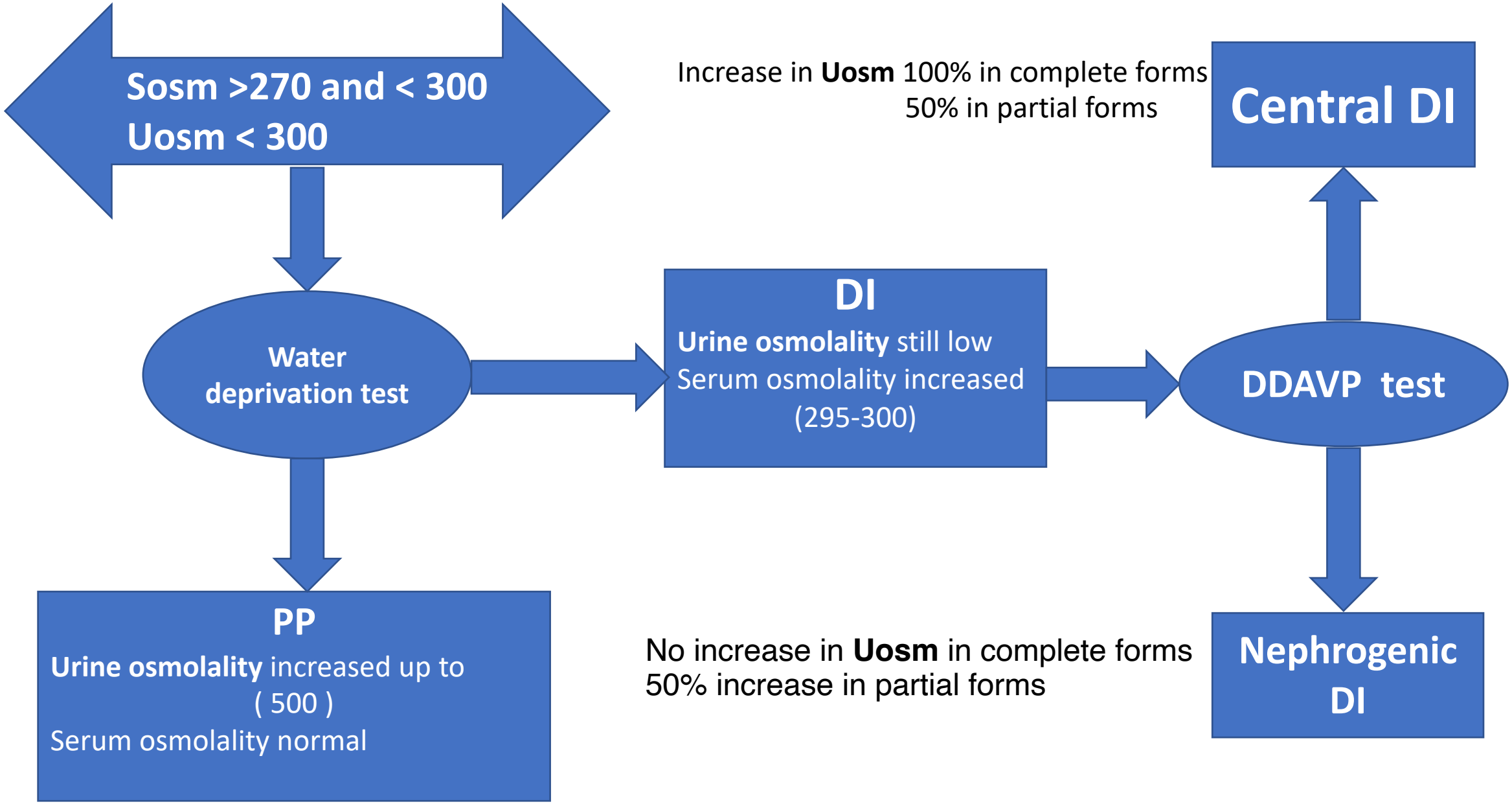
- Present in infancy (*no prenatal symptoms, no polyhydramnions*).
- *Polyuria and polydipsia* with episodes of hypernatraemic dehydration.
- Episodes of *pyrexia*, irritability, and vomiting.
- *Failure to thrive* (patients are only interested in drinking, but not eating).
- *Females* Usually present at a later age with milder symptoms or are asymptomatic.
- *Developmental delay/learning problems* .
- Megaureter and megacystis (due to high urine volume).

Investigations

- CBC
- Electrolytes
- KFT
- LFT
- ABG
- Blood glucose
- Urinalysis and urine specific gravity
- Paired urine/plasma osmolality
- US (kidney & UB)
- MRI Brain
- Genetic study


DI unlikely
< 270 mOsm/kg
Serum osmolality
> 300 mOsm/kg
DI
> 600 mOsm/kg
Urine osmolality
< 300 mOsm/kg
> 1010
Urine specific gravity
< 1005
Sosm >270 and < 300
Uosm < 300

Water deprivation test



Preparation

- Allow fluid overnight before the test, but avoid caffeine.
- Get body weight of patient.
- Contact the laboratory before the test.

Dehydration phase

- Take blood and collect urine for osmolality and electrolyte determination and urine volume measurement at 08:00 h.
- No fluid intake for 4–8 h.
- Get body weight every 2 h.
- Take blood and collect urine for osmolality and urine volume measurement regularly, preferably every 2 h. Interpret results as soon as available to decide whether to stop the test.
- End the test if weight loss >5% from start or thirst sensation becomes intolerable.

Renal DDAVP response

This test can be carried out on separate occasion and needs not follow the dehydration phase of WDT.

- Give 1–10 µg DDAVP solution intranasally; or inject subcutaneously, intramuscularly, or intravenously DDAVP 0.4 µg (<2 years old) to 1 µg (>2 years old). Oral DDAVP 50–200 µg can also be used. Monitor fluid consumption to avoid potential hyponatremia in a patient with PP.
- Measure urine volume and get urine and serum osmolality every 4–6 h.

Interpretation of water deprivation and DDAVP response

Urine osmolality, mOsm/kg

After fluid deprivations	After DDAVP	Diagnosis
<300	>750	CDI
<300	<300	NDI
>750	>750	PP
300–750	<750	Partial CDI, partial NDI, or PP

Example – Water Deprivation Test

Time (hours)		Urine Osmol	Serum Osmol	Serum Sodium	
08.00		197	303	146	
09.00		206			
10.00		204	307	150	
10:48	**DDAVP GIVEN**				
11:00		199			
12.00		205	317	150	

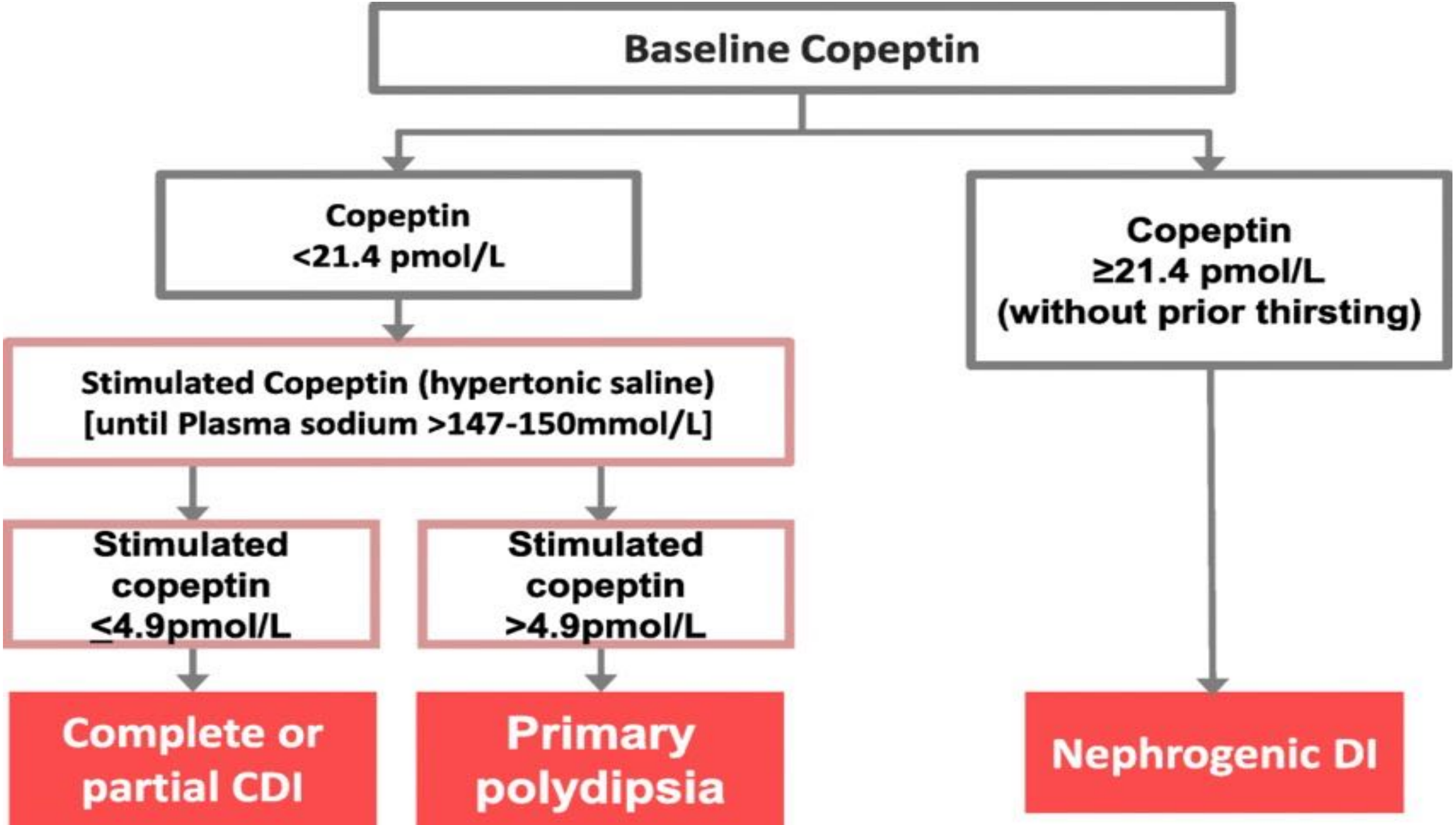
? Diagnosis

Copeptin

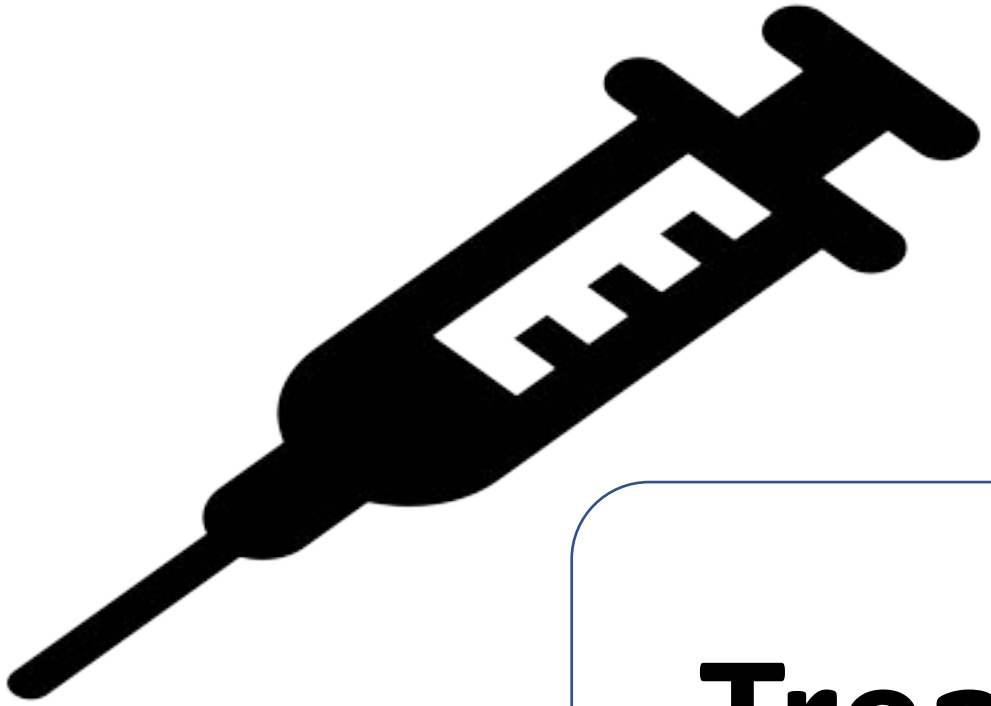
- Copeptin is the C-terminal peptide of pro-vasopressin that is co-secreted with AVP . Unlike plasma AVP measurement, which is technically challenging, copeptin remain stable for days after sampling of blood and can be measured relatively quickly .

- copeptin assays are not yet available worldwide .

- Once the test becomes more widely available in the future, it will be frequently used to diagnose and distinguish the various forms of polyuria-polydipsia syndromes.


Baseline Copeptin
Copeptin
<21.4 pmol/L
Copeptin
≥21.4 pmol/L
(without prior thirsting)
Stimulated Copeptin (hypertonic saline)
[until Plasma sodium >147-150mmol/L]
Stimulated
copeptin
≤4.9pmol/L
Stimulated
copeptin
>4.9pmol/L
Complete or
partial CDI
Primary
polydipsia
Nephrogenic DI

Time	BP	Weight	Urine volume	Urine osmolality	Serum sodium	Serum osmolality	**Copeptin**	
Baseline								



Treatment

Central DI

Fluids
AVP Analogs

Nephrogenic DI

Diet

- free water intake is necessary .
- Sodium restriction to (1 mEq/kg/day)
  (reduce the osmolar load and the need for associated water excretion.)
- A low protein diet is not advised since it may interfere with grow

Drugs

- ***Hydrochlorothiazide*** (2 to 3 mg/kg/day).
- (*increase sodium excretion* resulting in contraction of extracellular sodium content that leads to an increase in proximal tubular reabsorption of sodium and water.)
  -(Thiazides probably also *increase expression of the AQP2* protein.)
- Chronic thiazide therapy is associated with dyslipidemia
  , hyperglycemia and hyperuricemia.

Nephrogenic DI

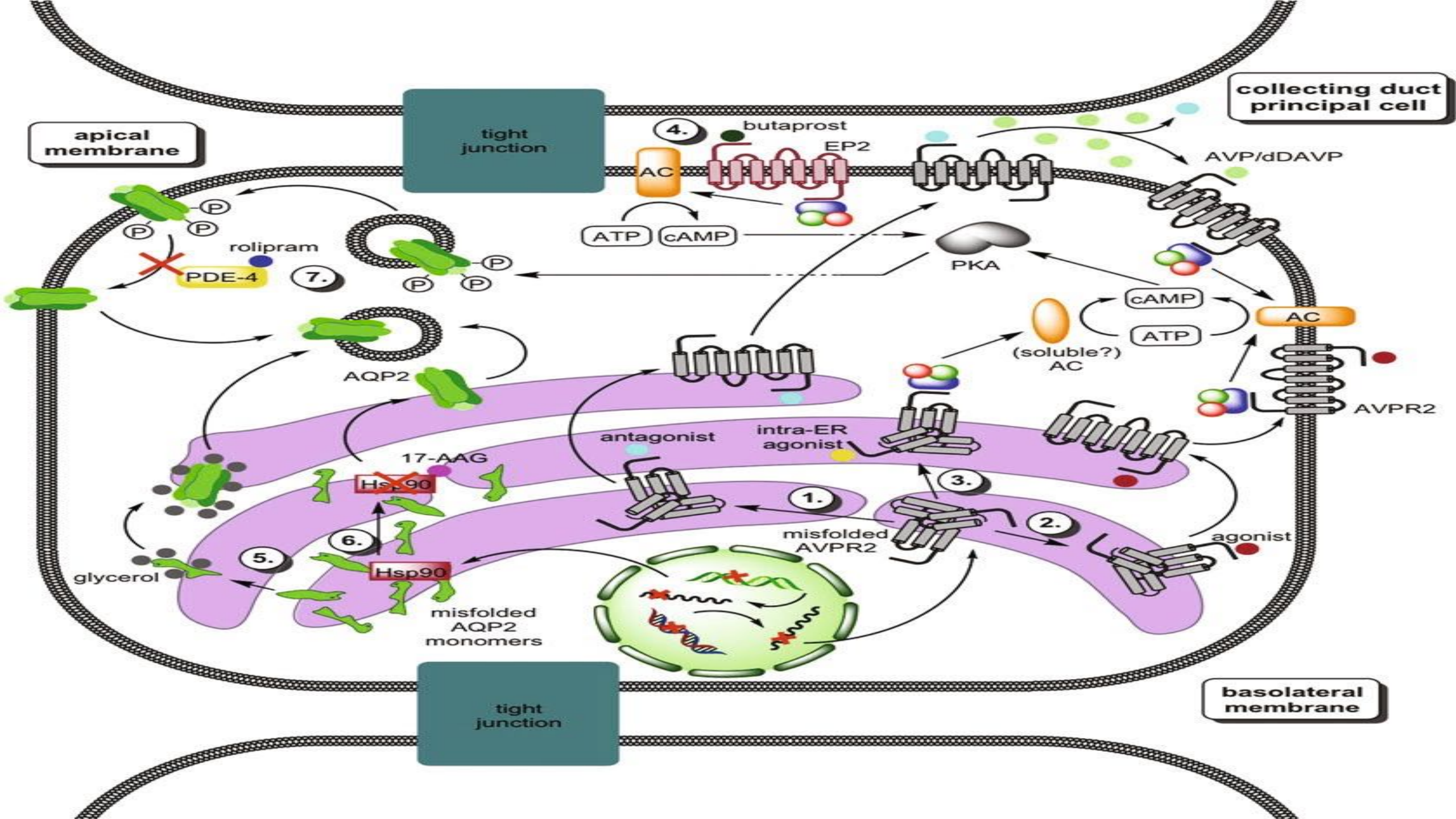
- ***Indomethacin*** (2 mg/kg/d) better than amiloride, but its prolonged use is not recommended since it may reduce GFR and cause gastrointestinal side effects.
- The mechanisms of action are unclear, but probably include reduction of GFR and stimulation of proximal Na (and thus water) reabsorption.

- ***Amiloride*** 20 mg/m2/day .
- Combination of the two agents also reduces the risk of hypokalemia.

- Future therapies for NDI shall focus on enabling ***trafficking of functional AVPR2/AQP2 protein trapped in endoplasmic reticulum to the site of their action***, through chemical or pharmacological therapies.

- Acquired causes

Correction of the cause of possible


collecting duct
principal cell
apical
membrane
tight
junction
4.
butaprost
EP2
AC
AVP/dDAVP
ATP
cAMP
PKA
rolipram
PDE-4
7.
P
AQP2
cAMP
ATP
AC
(soluble?)
AC
AVPR2
antagonist
intra-ER
agonist
17-AAG
Hsp90
1.
2.
3.
misfolded
AVPR2
agonist
6.
5.
glycerol
Hsp90
misfolded
AQP2
monomers
tight
junction
basolateral
membrane


Thank You