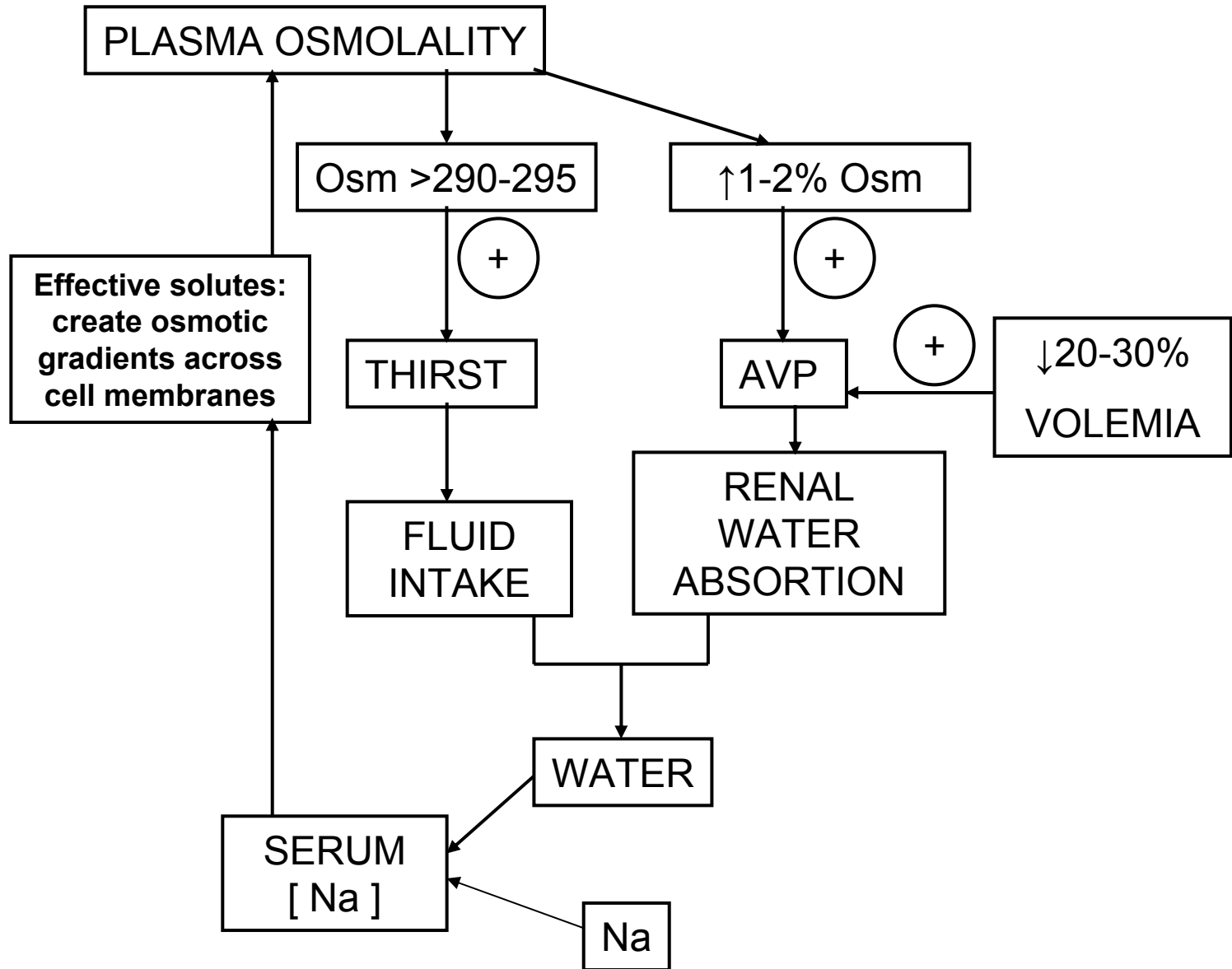


**EVALUATION
AND
MANAGEMENT
OF
HYPO-OSMOLALITY**

HYPONATREMIA is the most common electrolyte disorder in the clinical setting.

- Associated with a variety of underlying diseases and conditions.
- Acute hyponatremia related to substantial morbidity and mortality.
- Rapid onset or correction can produce severe neurologic deficits.
- Hospital incidence if defined:
 - $[\text{Na}] < 135 \text{ mEq/l}$: 15-22%
 - $[\text{Na}] < 130 \text{ mEq/l}$: 1-4%
- Incidence increases with age, specially in women
 - ↓ total body water content
 - Enhanced osmoreceptor sensitivity
 - ↑atrial natriuretic hormone
 - ↓activity of the renin-angiotensin-aldosterone system
- Iatrogenic hospital acquired hyponatremia:
 - Intravenous hypotonic fluids



TRUE HYPO OSMOLALITY VS. PSEUDOHYPONATREMIA

- Calculated P Osm = $2 \times [\text{Na p}] + \text{Glucose (mg/dl)} / 18 + \text{BUN (mg/dl)} / 2,8$
- Direct measurement: osmometer
- Total osmolality \neq effective osmolality (solutes that are freely permeable across cell membranes)
- Plasma osmolality normal or elevated with hyponatremia: elevation in serum lipids or proteins
 - [Na] serum artifactually decreased because of the increased relative proportion occupied by the lipid or protein \rightarrow rarely with the use the ion-specific electrodes.
- Hyperglycemia is the more frequent cause of hyponatremia in hospitalized patients: creates an osmotic gradient that causes water to shift from the ICF to the ECF
 - Misdiagnosis can be avoided by direct measurement of the osmolality or by correcting the serum [Na] by 1,6 mmol for each 100 mg/dL glucose above 100 mg/dL

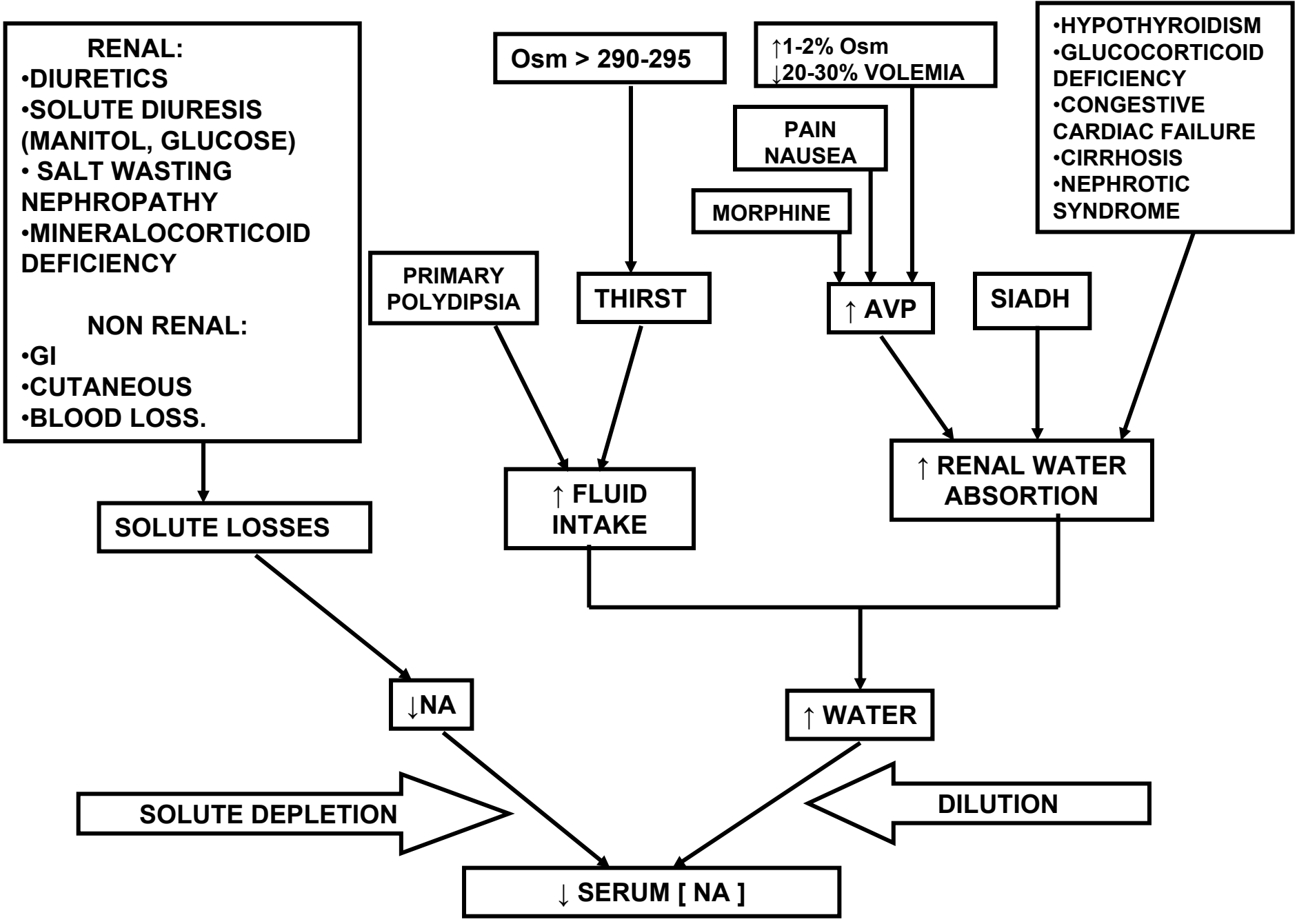
Box 1. Pathogenesis of hypo-osmolar disorders

Depletion (primary decreases in total body solute with secondary water retention)^a

1. Renal solute loss
 - Diuretic use
 - Solute diuresis (glucose, mannitol)
 - Salt wasting nephropathy
 - Mineralocorticoid deficiency
2. Nonrenal solute loss
 - Gastrointestinal (diarrhea, vomiting, pancreatitis, bowel obstruction)
 - Cutaneous (sweating, burns)
 - Blood loss

Dilution (primary increases in total body water with or without secondary solute depletion)^b

1. Impaired renal free water excretion
 - A. Increased proximal reabsorption
 - Hypothyroidism
 - B. Impaired distal dilution
 - Syndrome of inappropriate antidiuretic hormone secretion (SIADH)
 - Glucocorticoid deficiency
 - C. Combined increased proximal reabsorption and impaired distal dilution
 - Congestive heart failure
 - Cirrhosis
 - Nephrotic syndrome
 - D. Decreased urinary solute excretion
 - Beer potomania
2. Excess water intake
 - Primary polydipsia
 - Dilute infant formula



HYPOSMOLAR HYPONATREMIA

ECF VOLUME	DECREASED	NORMAL	INCREASED <small>INDICATES WHOLE BODY Na EXCESS</small>
CLINICALLY	Orthostatic changes in BP, HR	Low sensitivity of clinical examination	Oedema, ascites ↓effective arterial volume or pressure
LABORATORY	↑urea, Hct, Hb ↓ U Na <30 → non renal cause ↑ U Na > 30 → renal loss Metab alk and ↑K → adrenal insufficiency Metab ac and ↓K → diuretic	P Osm < 275 mOsm/Kg H ₂ O Inappropriate urinary concentration: U Osm > 100 mOsm/Kg H ₂ O for any P Osm < 275 mOsm/Kg H ₂ O	↓ U Na → 2 ^{ry} hyperaldosteronism ↑ U Na > 30 → advanced renal failure
CAUSES	<ul style="list-style-type: none"> •Diuretics (Thiazide >>Loop) •↓K → clue to diuretic use •↑ K → clue to primary mineralocorticoid deficiency •Salt wasting nephropathy: polycystic kidney, chronic pyelonephritis, obstructive uropathy, Bartter 	<ul style="list-style-type: none"> •SIADH: neurologic, tumours, drug induced, idiopathic •GLUCOCORTICOID DEFICIENCY: <ul style="list-style-type: none"> –Primary, Addison: depletion and dilutional –Pure glucocorticoid deficiency: dilutional •HYPOTHYROIDISM: severe, elderly or co-morbid conditions 	<ul style="list-style-type: none"> •CHF •Cirrhosis •Nephrotic syndrome

DIAGNOSIS CRITERIA FOR SIADH

ESSENTIAL

- P Osm < 275 mOsm/Kg H₂O
- Inappropriate urinary concentration: U Osm > 100 mOsm/Kg H₂O for any P Osm < 275 mOsm/Kg H₂O
- Clinical euvolemia (absence of signs of hypovolemia or hypervolemia)
- ↑ U Na while a normal salt and water intake, and excluded: Addison's disease or diuretic use. It is possible to become low U Na in hypovolemic patient or solute depleted.
- Absence of other potential causes of euvolemic hyposmolality: hypothyroidism, hypocortisolism, diuretic use → diagnosis of exclusion

SUPPLEMENTAL

- Abnormal water load test → inability to excrete at least 80% of 20 ml/Kg water load in 4 hrs or failure to dilute U Osm < 100 mOsm /KgH₂O
- Plasma AVP level inappropriately elevated relative to plasma osm
- No significant correction of serum Na with volume expansion but improvement after fluid restriction

DISORDERS ASSOCIATED WITH SIADH

- ECTOPIC SECRETION OF AVP:
 - most often caused by small-cell lung cancer (15%), other pulmonary and mediastinal tumours, gastrointestinal, prostate, uterine, leukaemia.
- CNS DISORDERS:
 - Mass lesions (tumour, abscess, subdural hematoma),
 - Inflammatory (encephalitis, meningitis, SLE, acute intermittent porphyria, multiple sclerosis),
 - Degenerative-demyelinative (Guillain Barre, spinal cord lesions),
 - Subarachnoid haemorrhage, head trauma, acute psychosis, delirium tremens, pituitary stalk section (5-10 days after surgery), transphenoidal adenomectomy, hydrocephalus
- DRUG INDUCED:
 - STIMULATES AVP RELEASE: nicotine, phenothiazines, tricyclics
 - RENAL EFFECTS/POTENTIATION AVP EFFECTS: dAVP, oxytocin, PG synthesis inhibitors
 - Angiotensin converting enzyme inhibitors, carbamazepine, oxcarbamazepine, chlorpropamide, clofibrate, clozapine, cyclophosphamide, Methamphetamine, omeprazole, serotonin reuptake inhibitors, vincristine, opiates
- PULMONARY DISEASES:
 - Infectious: TB, pneumonia, aspergillosis, empyema. MV. COPD
- AIDS
- Strenuous exercise
- Senile atrophy
- Idiopathic

SYMPTOMS

- Generally do not occur until Na >125
- Severity correlates with degree of hyponatremia and rate of develops
- Initial symptoms: headache, nausea, fatigue, anorexia, lethargy, confusion
- Severe cases: focal neurologic deficits, delirium, seizures, coma, cerebral herniation

TREATMENT

1. Severity of the hyponatremia
2. Duration of the hyponatremia
3. Symptomatology of the patient
4. True hypo-osmolality
5. ECF volume status
6. Depletional or dilutional mechanism
7. Criteria for SIADH and exclusion of hypothyroidism, hypocorticism

Acute Symptomatic Hyponatremia

- Brain volume regulation usually takes 48-72 hrs: initial rapid loss of Na, K, Cl, followed by slower extrusion of osmolytes.
- Defined: < 48 hrs in duration.
- Almost always symptomatic if $\text{Na} < 120 \text{ mmol/L}$.
- Greatest risk for neurologic complications.
- Should be rapidly correct at a rate of 1-2 mmol/L/Hr or 3-5 mmol/L/Hr in comatose or seizing patients.
- The increase of Na should not exceed 12 mmol/L in the first 24 hrs.
- Na level monitored at frequent intervals: at least every 4 hrs during the acute phase:
 - *First, from a practical and safety perspective, it is critical to monitor the PNa closely during and after therapy to be sure the goals of therapy are indeed being achieved.*

Chronic Symptomatic hyponatremia

- In the clinical practice: Hyponatremia of indeterminate duration, with some degree of brain volume regulation but not enough to prevent symptoms-brain oedema
- Na correction should be prompt but controlled and limited:
 - More severe neurologic symptoms: 1-2 mmol/l/Hr, not exceed 12 mmol/L in the first 24 hrs, not exceed 18 mmol/L in the first 48 hrs
 - Minimally symptomatic: 0,5 mmol/L/Hr
- Hypertonic NaCl solution (3%) by continuous infusion:
 - Initial infusion rate = Body weigh (Kg) x desired rate of increase in Na (mmol/L/Hr)

Chronic asymptomatic hyponatremia

- Minimal neurological symptoms
- Risk of pontine (PEM) and extrapontine myelinolysis with rapid correction:
 - Brain dehydration and blood-brain barrier disruption
 - Tremor, incontinence, hyperreflexia, pathologic reflexes, quadriparesis, quadriplegia, dysarthria, dysphagia, cranial nerve palsies, seizures, locked-in syndrome
 - Symptoms begin 1-6 days after the elevation of Na > 120 mmol/L
 - Predisponents: alcoholism, malnutrition, cirrhosis, hypokalemia, burns
- CT or MRI: could not show abnormalities until 3 – 4 weeks
- Differential diagnosis: mild asymptomatic hyponatremia caused by reset of the osmostat, associated with downward resetting of the threshold for AVP and Thirst: **NO THERAPY IS REQUIRED**
 - WATER LOAD OF 10-15 ML/Kg over 30 min → excretion more than 80% of water load in 4 hrs, whereas excretion is impaired in patients with SIADH

Fluid and solute management in SIADH:

- Fluid restriction: 500 ml a day below the average daily urine volume
 - Indicated: SIADH, edematous states, primary polydipsia, advanced renal failure
- Hypertonic saline:
 - Indicated in acute symptomatic and SIADH if Na needs to be elevated (osm of the fluid administered must be higher than the urine osm)
- Hypertonic saline combined with loop diuretics: in chronic persistent hyponatremia
- NaCl tablets: 4-8 g per day

Pharmacologic therapy for SIADH:

- **Lithium** antagonize AVP action in the kidney
 - side effects
- **Demeclocycline** causes nephrogenic diabetes insipidus → ↓ Urine concentration even in ↑ AVP plasma levels
 - 600-1200 mg/day → dose modification after 3-4 days of treatment
 - Nephrotoxicity
- **Urea**: decreasing fractional sodium excretion
 - 30 g/day
 - Poor palatability, azotemia
 - Problems: availability
- **Vasopressin receptor antagonists**: V2 receptor in kidneys, “aquaretics” → free water diuresis without natriuresis or kaliuresis
 - when approved for use, indications in preexisting edema and inability to tolerate a solute load.

