In the name of
God

ELECTROLYTE AND ACID BASE DISORDER IN CKD

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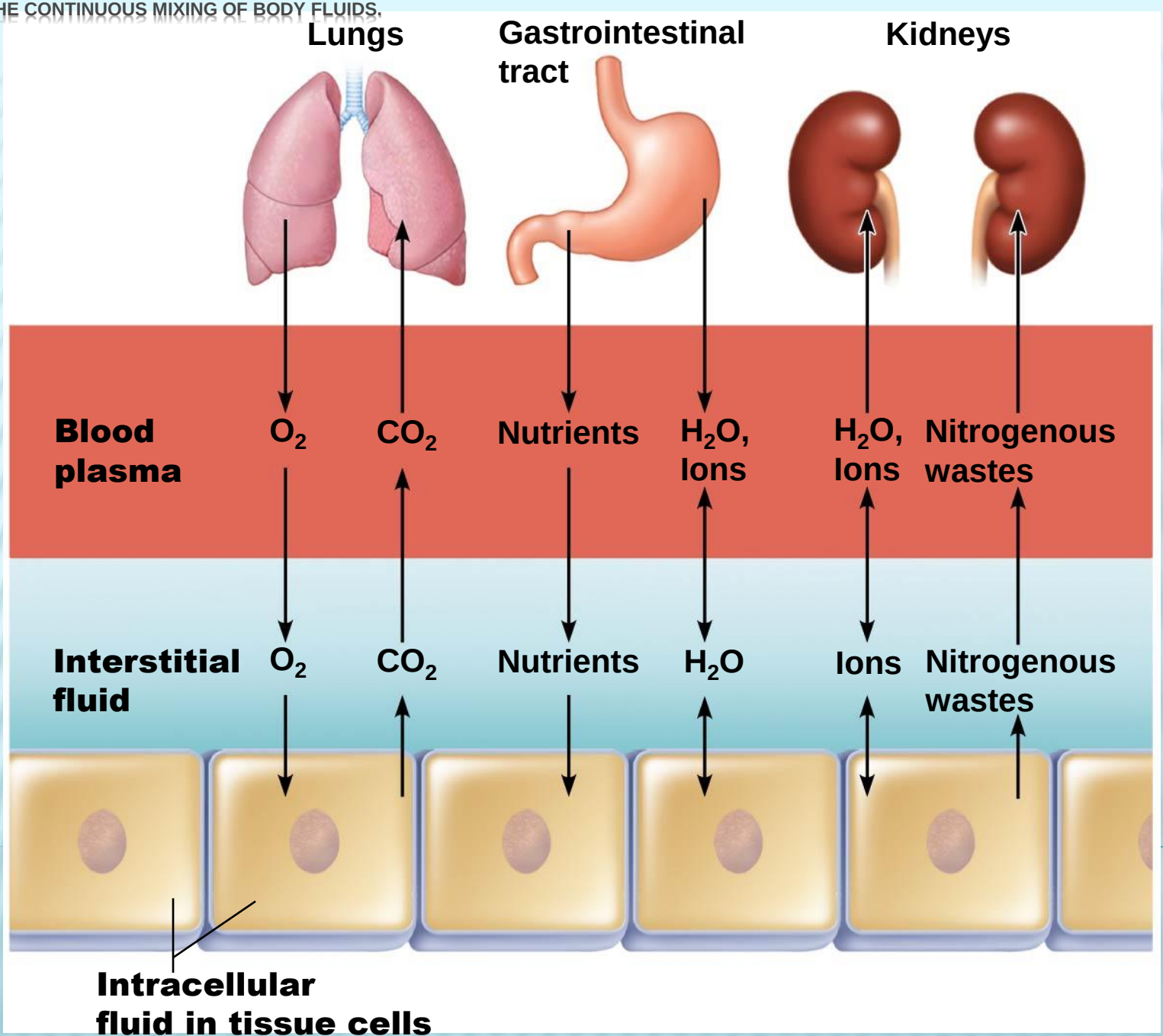
WHAT IS IN YOUR BLOOD? KIDNEYS HELP MANAGE FLUID, ELECTROLYTE, AND ACID-BASE BALANCE

- ***Blood composition depends on:***
  1. Diet
  2. Cellular metabolism
  3. Urine output

- ***How the kidneys manage blood composition:***
  1. Excretion of nitrogenous wastes
  2. Water/electrolyte balance of the blood
  3. Ensuring proper blood pH

FIGURE 15.9 THE CONTINUOUS MIXING OF BODY FLUIDS.



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WATER AND SALT

- ***Electrolytes***: are charged particles (ions) that allow reactions requiring electrical charge to take place
  - Cell membrane stability
  - Muscle contraction
  - Nerve impulse

- **Body electrolytes include**:
  - Sodium (Na^+)
  - Potassium (K^+)
  - Calcium (Ca^{++})
  - Magnesium (Mg^{++})

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THE THIRST MECHANISM

- **Osmoreceptors:** cells in the *hypothalamus*
  - Activated by small changes in blood composition
    - Results in a dry mouth
    - Reinforces the drive to drink water

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HORMONAL REGULATION OF WATER INTAKE/OUTPUT

- Hormones regulate reabsorption of water and electrolytes by the kidneys
  - ***Anti*diuretic hormone (ADH)**
    - Hypothalamus tells posterior pituitary to release ADH
    - prevents excessive water loss in the urine
    - increases water reabsorption
  - **Aldosterone** (produced by adrenal cortex)
    - increases sodium and water reabsorption;
    - decreases potassium reabsorption

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THE RENIN-ANGIOTENSIN MECHANISM

- **Regulates blood pressure**
  - The juxtaglomerular (JG) apparatus of the renal tubules sense drop in BP or ***solute concentration***
    - Causes release of the ***enzyme renin*** into blood
- **Renin** produces angiotensin II
  - Acts *directly* on the blood vessels to **vasoconstrict**
    - The goal is to reduce filtrate volume

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MAINTAINING ACID-BASE BALANCE IN BLOOD

- Ideal blood pH: between 7.35 and 7.45
- Kidneys : biggest impact in controlling pH
  - Other acid-base controlling systems
    - Blood buffers
    - Respiration

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CONTROL OF pH BY THE KIDNEYS

- **When blood pH rises (basic):**
  - Bicarbonate ions are excreted
  - Hydrogen ions are retained by kidney tubules
- **When blood pH falls (acidic):**
  - Bicarbonate ions are reabsorbed
  - Hydrogen ions are secreted

CKD

- **Acidosis in CKD**
- The prevalence of metabolic acidosis increases with progression of CKD. In a cross-sectional analysis of the baseline data from the Chronic Renal Insufficiency Cohort (CRIC) study involving 3,900 patients in CKD stages 2–4, the prevalence of metabolic acidosis (serum $HCO3^{-}$ <22 mEq/L) was 7% for CKD stage 2, 13% for CKD stage 3 and 33% for CKD 4 with an overall acidosis occurrence of 17.3% . Normal AG acidosis is predominant in early stages of CKD

CKD

- AG acidosis occurs in late stages (GFR <30 mL/min/1.73 m^2) due to retention of anions such as sulfate, phosphate, and urate. It should be noted that net endogenous acid production is relatively unchanged in CKD . Intrarenal ammonia and acid retention, consequences of acidosis, can cause complement activation and chronic tubule-interstitial inflammation and increased generation of endothelin-1, angiotensin II and aldosterone production

CKD

- potentially promoting CKD progression. Indeed, metabolic acidosis in CKD is associated with more rapid progression of CKD and increased mortality . acidosis in CKD is associated with the development of sarcopenia, bone demineralization, impaired function of growth hormone and insulin, and growth retardation in children.

CKD

- Correcting metabolic acidosis with alkali administration or dietary intake of alkali precursors slows CKD progression and improves nutritional status. KDIGO 2012 guidelines recommend correction of metabolic acidosis . Oral $NaHCO_3$ is a commonly used alkali and may be initiated at a dosage of 650 mg (7.7 mEq of bicarbonate) 2–3 times daily

CKD

- Dosage should be adjusted to keep serum HCO_3^- in the range of ***22–26 mEq/L***. The treatment is well tolerated and has not been shown to cause or worsen fluid retention and hypertension . The most common adverse effects are bloating and abdominal fullness. Sodium citrate is an alternative agent but should be avoided in patients on aluminum-based phosphate binders due to the risk of aluminum intoxication.

Symptoms of metabolic acidosis and alkalosis

CKD

Symptoms of metabolic acidosis	Symptoms of metabolic alkalosis
Central nervous system	*Central nervous system*
(1) Headache	(1) Confusion
(2) Sleepiness	(2) Light-headedness
(3) Confusion	(3) Stupor
(4) Loss of consciousness	(4) Coma
(5) Coma	*Peripheral nervous system*
Respiratory	(1) Hand tremor
(1) Shortness of breath	(2) Numbness and tingling in the
(2) Dry cough	face and extremities
Cardiovascular	*Cardiovascular*
(1) Tachycardia	(1) Arrhythmias (especially when
(2) Arrhythmia	associated with low K^+ or low Ca^{2+})
(3) Hypotension	(2) Decreased contractility
Musculoskeletal	*Musculoskeletal system*
(1) Weakness	(1) Muscle spasm
(2) Spasms/seizure	(2) Twitching
Gastrointestinal	*Gastrointestinal*
(1) Nausea and vomiting	(1) Nausea and vomiting
(2) Diarrhea	

CKD

- **Metabolic Alkalosis**
- Metabolic alkalosis can result from a net loss of acid or a net gain of bicarbonate (generation phase). The alkalosis is then perpetuated by hypokalemia, chloride depletion, hypovolemia or excessive mineralocorticoid stimulation. These conditions prevent the kidney from unloading the accumulated HCO_3^- (maintenance phase). Clinical manifestations are summarized in Table Table33 (right panel). The major causes, pathophysiology, diagnostic features, and therapy in the general population are summarized in table4

CKD

Causes	Pathophysiology	Diagnostic features	Treatment
Vomiting and gastric suction	Loss of gastric acid	↓urine Cl (<10 mEq/L)	Saline administration
Thiazide or loop diuretics	↑urine loss of Cl^-	Hypovolemia or euvolemia, ↑urine Cl	Discontinue offending agents
Hypokalemia	↑urine NH_4^+ excretion ↑ renal Rhbg expression	Refractory alkalosis until serum K^+ is restored	KCl
$NaHCO_3$ administration	Exceeding the capacity of renal HCO_3^- excretion	Euvolemia or hypervolemia	Discontinue $NaHCO_3$
Chloride diarrhea (chloridorrhea)	GI loss of HCO_3^- poor fluid	Hypovolemia	Treat diarrhea Saline administration
Primary hyperaldosteronism	↑renal H^+ excretion	Hypervolemia (urine Cl >20 mmol/L)	Correcting hyperaldosteronism

CKD

- Although less common than metabolic acidosis, metabolic alkalosis can occur in patients with CKD. CKD patients are commonly on diuretics as well as calcium carbonate or citrate which can cause hypokalemia and alkalosis. Diagnosis is based on elevations of serum HCO_3^- and pH (>7.45). Measurement of urine Cl^- may not be helpful as renal Cl^- regulation is likely impaired in CKD.

CKD

- **Potassium Regulation and Dyskalemia**
- Potassium (K^+) is the most abundant intracellular cation, with >98% of total body K^+ (3,500 mEq) being intracellular and <2% (70 mEq) extracellular. The steep intracellular and extracellular K^+ gradient is the major determinant of the plasma membrane potential. K^+ also participates in the regulation of cell volume, pH and multiple cellular functions. In excitable tissues, such as heart, nerves, and skeletal muscle, K^+ is critical for the dynamic action potentials and electrical excitability. In a steady state, kidneys excrete approximately 95% of dietary K^+, and the remainder is excreted through the gastrointestinal system.
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CKD

- **Renal Potassium Regulation**
- Potassium is freely filtered through glomeruli. The proximal tubules reabsorb approximately 65% of the filtered K^+, while the TALH reabsorbs approximately 25%. Distal nephron (the DCT and collecting duct) is the major site of renal K^+ regulation. Depending on physiological needs, distal nephron can excrete or absorb K^+.

CKD

- On a typical Western diet, K^+ intake is higher (~90–120 mEq/day) than the total extracellular K^+ (70 mEq). By and large, distal nephron excretes K^+ to achieve balance. Key factors that determine the distal nephron K^+ secretion are (1) serum K^+ concentration, (2) distal tubular Na^+ delivery, (3) tubular fluid flow, and (4) serum aldosterone level.

CKD

- **Hyperkalemia**
- Hyperkalemia is the most common electrolyte disorder in patients with CKD. Its prevalence increases as CKD progresses. In a retrospective study (*n* = 240,000), CKD patients were more prone to hyperkalemic events ($K^+ \geq 5.5$ mEq/L) than patients without CKD, with odds ratios of 2.2 for CKD stage 3, 5.9 for CKD stage 4, and 11 for CKD stage 5 . ***Decreased glomerular filtration and ability of tubular K^+ secretion, often in combination with a diet generous in K^+, are the major cause of hyperkalemia.***

CKD

- Other causes of hyperkalemia pertinent to CKD patients are (1) medications that further reduce the already limited capacity of distal nephron K^+ excretion such as renin angiotensin aldosterone system inhibitors, K^+-sparing diuretics and calcineurin inhibitors, (2) transcellular K^+ shift due to insulin deficiency, mineral metabolic acidosis, and tissue breakdown (hemolysis, rhabdomyolysis, tumor lysis syndrome), and (3) hyporeninemic hypoaldosteronism (type IV) RTA.

CKD

- Hyperkalemia is defined as serum K^+ concentration >5.3 mEq/L and is often arbitrarily classified as mild (5.4 to <6 mEq/L), moderate (6 to <7 mEq/L), and severe (≥7 mEq/L) . Symptoms and signs of hyperkalemia vary widely from nonspecific muscle weakness to paresthesia, muscle paralysis, cardiac arrhythmias, and cardiac arrest. Electrocardiogram may show arrhythmias, peaked T waves, prolonged PR interval, loss of P waves, widening of QRS complex and sine waves. It is important to note that ECG changes are not sensitive in detecting hyperkalemia. ***CKD patients can develop life-threatening hyperkalemia without appreciable EKG changes .***

CKD

- Treatment for hyperkalemia should be multipronged. Dietary modification with initiation of a low K^+ diet (<75 mEq/day) is an important part of intervention. Medication regimen must be reviewed to minimize the exposure of drugs that may induce hyperkalemia. Loop and thiazide diuretics can be used to promote kaliuresis. Patiromer is a newer K^+-lowering oral agent and can be tried when appropriate.

CKD

- Patiromer is a nonabsorbable, sorbitol containing Ca^{2+}-K^{+} exchange polymer that selectively binds K^{+} mainly in the colon. Its onset of action is 7 h. Placebo-controlled clinical trials have demonstrated its efficacy and safety. It is FDA approved for treatment of chronic hyperkalemia in non-dialysis CKD patients in a nonacute setting. Patiromer comes as a powder (in 3 strengths of 8.4, 16.2, and 25.2 g) with a recommended starting dose of 8.4 g daily.

CKD

- Its dosage may be titrated up in increments of 8.4 g weekly to a maximum daily dose of 25.2 g. Its intake should be spaced at least 3 h apart from other medications due to a potential risk of drug-drug interaction. The most common known side effects are constipation and mild hypomagnesemia.

CKD

- Management of acute and symptomatic hyperkalemia requires monitoring in an inpatient setting. In the presence of ECG changes, intravenous calcium should be administered to stabilize myocardium. Temporizing measures that shift K^+ into the cells such as albuterol (10 mg) inhalation and intravenous regular insulin (10 units) combined with dextrose are indicated. Sodium bicarbonate can be considered if there is coexistent metabolic acidosis.

CKD

- loop diuretics and/or thiazide to promote renal K^+ excretion, Kayexalate (sodium polystyrene sulfonate) to promote bowel excretion when appropriate, and hemodialysis if indicated. Hemodialysis is the most effective and definitive treatment for hyperkalemia.

CKD

- **Hypokalemia**
- Hypokalemia (serum [K^+] <3.5 mEq/L) is less common in CKD than hyperkalemia. It can, however, occur due to a multitude of reasons including non-K^+-sparing diuretic use, alkalosis, hypomagnesemia, vomiting, and diarrhea.
-

CKD

- Management of hypokalemia in CKD patients involves correcting the underlying causes and cautious K^+ replacement. Hypokalemia can precipitate digoxin toxicity. Withholding digoxin when appropriate may be necessary.

CKD

- Serum [Na^+] represents water balance and is the primary determinant of serum osmolality. Changes in serum osmolality drive fluid in and out of cells and affect cell volume and function**. Serum [Na^+] is tightly regulated by arginine vasopressin (AVP) and thirst in a narrow range of 135–145 mEq/L.** AVP is produced in the supraoptic and paraventricular nuclei of the hypothalamus and released from the posterior pituitary in response to increased serum osmolality (sensed by osmoreceptors in the hypothalamus) and reduced intravascular volume (sensed by baroreceptors in the carotids and aortic arch)

CKD

- In the kidneys, AVP binds to V2 receptors in the basolateral membrane of collecting ducts, activates adenylyl cyclase-mediated cAMP production and PKA signaling, leading to increased production and phosphorylation/apical membrane insertion of aquaporin 2 channels. This, in turn, leads to free water absorption in the presence of tubulomedullary osmotic gradient.

CKD

- In a retrospective study involving a cohort of veterans (*n* = 655,000) with non-dialysis-dependent CKD, Kovesdy et al. found a U-shaped association between serum [Na^+] and mortality with both hypernatremia (Na^+ >145 mEq/L) and hyponatremia (Na^+ <136 mEq/L) associated with increased mortality.

CKD

- **Hyponatremia**
- Hyponatremia, defined as the serum [Na^+] <135 mEq/L, is the most common electrolyte disorder in both the community-dwelling population and in hospitalized patients with occurrence rates of 7.7–15 and 44%, respectively . **Patients with CKD are at higher risk of hyponatremia than the general population due to diminished GFR and tubular regulation.** In the same study noted above, veterans with CKD (mean eGFR of 52 mL/min/1.73 m^2) were followed for a median period of 5.5 years, and 26% of the subjects developed at least 1 episode of hyponatremia [35

CKD

- Clinical signs and symptoms of hyponatremia are relatively nonspecific and dependent on the severity and rate of hyponatremia onset. Patients with mild-to-moderate hyponatremia may be asymptomatic or present with malaise, nausea, lethargy and fatigue. The more overt neurological symptoms often manifest when hyponatremia is severe (<120 mEq/L) and has developed rapidly. Patients can present with headache, slowing of mentation, confusion, ataxia, seizures, and coma

CKD

- . Measurement of serum osmolality (normal serum osmolality = 280–290 mosm/kg) is necessary to rule out pseudohyponatremia, isotonic hyponatremia in the setting of hyperlipidemia and paraproteinemias, and hyperosmolar (>290 mosm/kg) hyponatremia in the setting of hyperglycemia or mannitol administration. Low serum osmolality (<280 mosm/kg) along with hyponatremia indicates true hypotonic hyponatremia.

CKD

- After confirming the presence of hypotonic hyponatremia, the patient's volume status should be determined to guide treatment decisions. Volume replacement with isotonic fluids is the treatment of choice in patients with volume depletion. Restoration of volume will turn off the stimulus for vasopressin release, leading to renal water excretion and correction of hyponatremia. Causes, clinical features, and treatment for euvolemic hyponatremia are not discussed here (SIADH) Hypervolemic hyponatremia due to liver or heart failure should be treated with loop diuretics combined with free water restriction (≤1L/day).

CKD

- Management involves free water restriction, use of loop diuretics and, if necessary, dialysis.

CKD

- Regardless of the etiology, the rate of serum [Na^+] correction depends on 2 key factors: (1) whether the patient is symptomatic, and (2) the rate of hyponatremia onset (<48 h or ≥48 h). For symptomatic hyponatremia, 3% saline should be administered intravenously with the goal of raising serum [Na^+] by 4–5 mEq/L. If asymptomatic and the onset of hyponatremia is ≥48 h, serum [Na^+] should be corrected slowly (not exceeding 6–8 mEq/L in the 1st 24 h and 18 mEq/L within 48 h) to prevent neurological damage such as central-pontine demyelination syndrome.

CKD

- Inadvertent over correction should be reversed with hypotonic fluids. Serial serum [Na^+] measurements (every 2–6 h) may be necessary to evaluate treatment adequacy, especially during the initial 24 h.

CKD

- **Hypernatremia**
- Hypernatremia (serum [Na^+] >145 mEq/L) is relatively common with a reported incidence of 1–3.4% in hospitalized patients . In CKD, as cited above , there is a reported 2% (*n* = 13,289) prevalence of hypernatremia and 7% (*n* = 45,666) occurrence of at least 1 episode of hypernatremia in non-dialysis CKD veterans with 5.5 years follow-up.

CKD

- Hypernatremia signifies total body water deficiency relative to total body sodium. It can result from either (1) loss of water or hypotonic fluid (loss of water > loss of Na^+) or (2) gain of Na^+ (and K^+), such as incidental hypertonic fluid ingestion or infusion. Diabetes insipidus, chronic hypokalemia, hypercalcemia, hyperglycemia, and medications such as loop and osmotic diuretics, lithium, and vasopressin V_2 receptor blockers can cause hypernatremia due to renal hypotonic fluid loss.

CKD

- Nonrenal causes of hypernatremia include osmotic diarrhea, vomiting, excessive sweating, and burns. Sustained hypernatremia typically occurs when thirst mechanism is impaired (thirst stimulates AVP secretion leading to renal water preservation) and or there is lack of access to water. Hence, intubated patients, patients with altered mental status or under sedation, elderly nursing home residents, and infants are more susceptible to hypernatremia.

CKD

- Clinical symptoms and signs of hypernatremia are nonspecific and vary from asymptomatic to comatose depending on the severity and rate of onset of hypernatremia. Common manifestations include intense thirst (if thirst mechanism is intact), fatigue, and lethargy, muscle weakness, slowing of mentation, confusion, and coma.

CKD

- Hypernatremia is a hypertonic state. Thus, measurement of serum osmolality is, in general, unnecessary. Measurement of urine osmolality is useful in differentiating renal water loss such as diabetes insipidus (inappropriately dilute urine) from extrarenal water loss (concentrated urine). In patients on diuretics, urine osmolality may vary depending on the timing of diuretic intake. Patients with severe hyperglycemia can be in a hyperosmolar state, but their serum [Na^+] may be falsely normal or even reduced. Typically, serum [Na^+] is reduced by ~1.6 mEq/L for each 100 mg/dL elevation of glucose above normal range.

CKD

- Management of hypernatremia should focus on (1) correction of the underlying cause and (2) treatment of hypernatremia. If hypernatremia is chronic (≥48 h) or of unknown duration, serum [Na^+] correction should be gradual, not exceeding 8–10 mEq/L in the first 24 h to prevent cerebral edema . More rapid serum Na^+ correction (up to 1 mEq/L per hour) may be appropriate if onset of hypernatremia is acute (<48 h).
- Total body free water deficit in hypernatremia can be estimated with the following formula:

CKD

- Free total body water
  = body weight × (0.6 for men; 0.5 for women)
- Where total body water = body weight × (0.6 for men; 0.5 for women)
- The calculation provides an initial estimate of total body water deficit. The rate and amount of daily water replacement should be based not on the calculated water deficit, but on the repeated measurements of serum [Na^+] to prevent under- or overcorrection.

THANKS FOR YOUR ATTENTION