Team Medicine

Chronic Kidney Disease (CKD)

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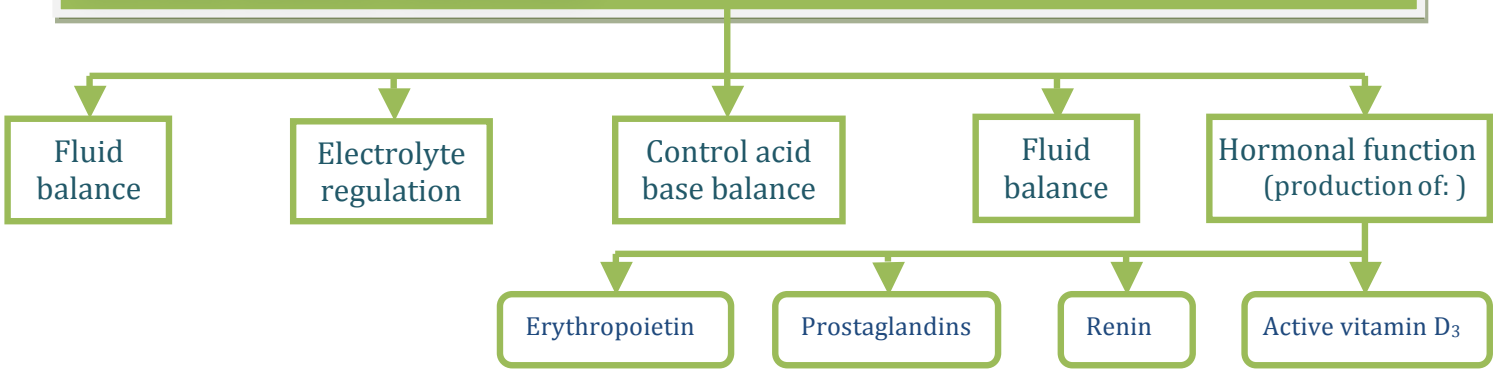
■ Important notes ■ Notes and doctor's notes ■ In slides, but not mentioned by the doctor

431 Teams
medical students

Normal Kidney Functions:



"Bones can break, muscles can atrophy, glands can loaf, even the brain can go to sleep without immediate danger to survival. But – should kidneys fail… neither bone, muscle, nor brain could carry-on." – Hamer Smith

Definitions:

- **Chronic Kidney Disease (CKD) (Chronic Renal Failure {CRF}):** chronic progressive **irreversible** **(to differentiate from acute kidney injury)** loss of renal function.
- **End Stage Renal Disease (ESRD):** advanced CKD (Stage-5) requiring **dialysis** or kidney **transplantation**.

Chronic Kidney Disease – Stages:

- **Since 2001, the term CRF was changed to CKD, and the staging system for the disease changed from "mild, moderate to severe" to staging from stage 1 to stage 5.**

Stage	Description	GFR (ml/min/1.73m²)
1	Kidney damage with normal or ↑ GFR Evidence by lab (e.g. ↑ uria, ↑creatinine, proteinuria, hematuria…) or by radiology (e.g. cysts, stones, atrophic kidney…) + ↑ or normal GFR	> 90
2	Mild ↓ GFR	60 – 89
3	Moderate ↓ GFR	30 - 59
4	Severe ↓ GFR	15 – 29
5	Kidney failure, ESRD	<15 or dialysis

Etiology of Chronic Kidney Disease (CKD):

- **Diabetes mellitus (DM)** **40%**
- **Hypertension** **30%**
- **Glomerulonephritis** **15%**

Remember: these 3 leading causes of CKD

- Hereditary cystic and cong. renal disease 4%
- Interstitial nephritis/pyelonephritis 4%
- Tumours 2%
- Miscellaneous

Pathophysiology:

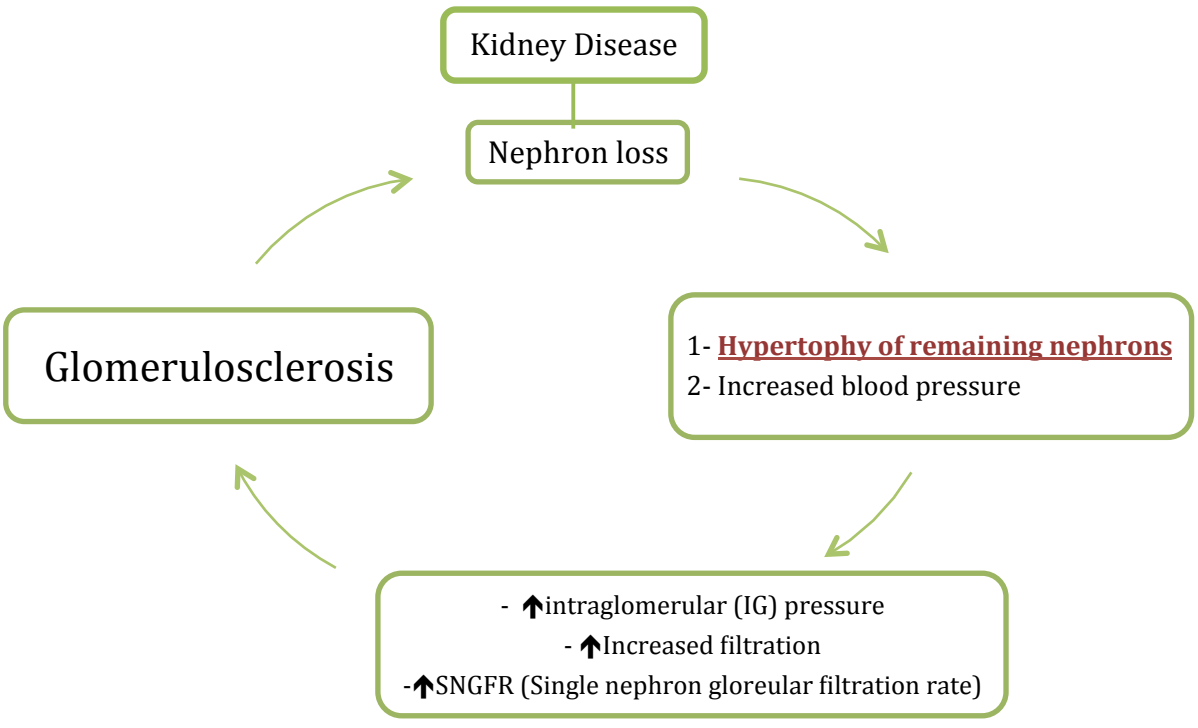
1. **Loss of nephron mass (by any cause: DM, HTN, glomerulonephritis, stones, cysts) → hypertrophy of the remaining nephrons:**
   - The hypertrophied nephron plasma flow and glomerular pressure increase (vasodilatation of the aff. Arterioles)
   - Proximal reabsorption of NaCl, Fluids and PO4
   - Collecting ducts secretion of K+ and H+

   Enhanced **in the remaining nephrons in order to compensate**
   - These **adaptations** initially restore hemeostasis [temporarily]
   - But glomerular **hyper**filtration → glomerular injury, glomerulosclerosis and further loss of renal function.

2. **↑ production of growth factors:**
   - Transforming growth factor-B
   - Platelets derived growth factors
   - Osteopontin, angiotensin-II
   - Endothelin

   → Interstitial fibrosis **in the kidneys**

➢ Vicious cycle of CKD that leads to ESRD:



Factors contributing to the Progression of CKD:

- Degree of hypertension
- Severity of proteinuria
- Hyperlipidemia
- Drugs (NSAID)
- High protein diet
- Persistent metabolic acidosis
- Extent of tubulointerstitial disease

Managing these risk factors will help the patient to live without dialysis for as long as possible.

Uremic syndrome

- **Uremia** results from **retention** of **end products** of **protein metabolism**.
- **Group of signs and symptoms that the patients present with when they develop kidney failure.**
- **Previously, it was thought that accumulation of only urea was the cause of Uremic Syndrome, but later it was found that it is caused by other toxins.**
- Administration of urea causes only mild symptoms.
- Other potential uremic toxins:
  - Guanidine
  - P2 microglobulin
  - Hipurate
  - Homocysteine
  - Parathyroid hormone (PTH)
  - Phenoles
  - Phosphate
  - Polyamines
  - Purines
  - Dimethyl arginine

Metabolic and electrolytes abnormalities in CKD:

A. Carbohydrate intolerance:

- Insulin is degraded by the liver and kidneys.
- The **decrease in insulin clearance** is offset by peripheral insulin resistance.
- Hyperparathyroidism inhibits insulin secretion.
- **Decrease in requirements for insulin** and OHD in diabetic patients as they develop renal failure. (**Diabetic patients who don't decrease their insulin doses eventually will develop hypoglycemia**)

B. Dyslipidemia:

- ↓ HDL cholesterol
- ↑ TG and lipoprotein(α)

C. Fluid and Electrolytes:

- ↓ GFR and defective tubular function → expansion of plasma and ECF volumes, edema, and hypertension.
- **Hypertension** is common unless Na+ intake is restricted to 100 meq/day.
- **Hyponatremia** can result from **failure to excrete free water** when intakes exceed 1.5 L/day [sodium is diluted]
- Patient with salt lossing nephropathy require stepwise increases in Nacl and fluid intake.

- K+ elimination in CKD is **initially** [in the beginning] maintained by:
  - enhanced K+ secretion in surviving nephrons
  - colonic K+ secretion (from aldosterone stimulated by hyperkalemia and metabolic acidosis)...
  - However, as GFR decreases, K+ elimination is curtailed **(reduced)** → hyperkalemia

D. Acid-Base abnormalities "metabolic acidosis":

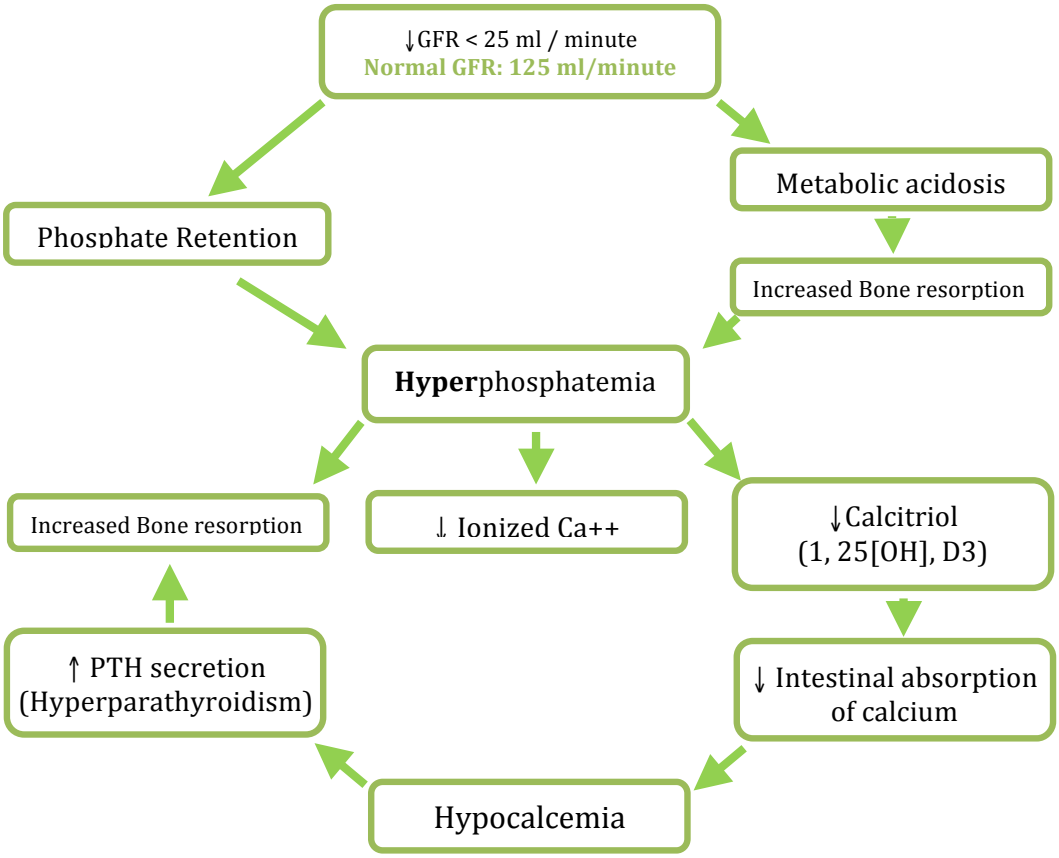
1. The body produces about **80 mmol of non-volatile acids** from metabolism everyday. **The only way to get rid of these acids is through the kidneys.** These acids accumulates as renal failure progresses.

   Volatile acid (الحموض الطيارة): Acid that can be excreted by lungs (E.g: carbonic acid). Non-volatile acids cannot be excreted by lungs.

2. **Production of ammonia NH_3** (in distal and CD cells) **decreases → limits distal tubular H+ trapping to create NH_4 (ammonium)** and hence, **decreases renal bicarbonate regeneration.**

3. Additionally, there may be **proximal HCO_3 wasting** or **reduced distal H+ secretion**.

E. Calcium and phosphate abnormalities: (IMP.)



[Rephrasing of text in Kumar 7th ed. p.628: Phosphate retention (due to direct or indirect causes) results in an increase in PTH synthesis and release. This is secondary hyperparathyroidism. Long-standing secondary hyperparathyroidism will cause hyperplasia of the glands → autonomous hyperparathyroidism (tertiary hyperparathyroidism) in which hypercalcemia is also present.]

Hyperphosphatemia:

- Independent risk factor in the increased morbidity and mortality of **stage-5 CKD from cardiovascular events**.
- Hyperphosphatemia, ↑ ca * po4 product (>55 mg/dl), and ↑ calcium load (dietary + dialysate) predict **coronary artery calcifications** (> 50% of stage 5 CKD patients) as evaluated by electron beam computed tomography.

Renal Osteodystrophy (ROD):

➢ **"Renal osteodystrophy is an old terminology, 'CKD bone mineral disease' is the new terminology."**

- Is a complex disorders of bones in uremic patient resulting from abnormalities of mineral ions (Ca, PO_4, Mg) ,PTH and Vit-D metabolism in the presence of factors related to the uremic state.
- Spectrum of bone abnormalities in ROD:
    1. Osteitis fibrosa cystica (high bone turnover) due to:
        - PTH
        - activity of both osteoclast and osteoblast
    2. Osteomalacia
    3. Adynamic bone disease (low bone tumour)
    4. Combination of the above

- Adynamic bone:
    - Risk factors:
        - Advanced age
        - CAPD
        - Diabetes mellitus
        - Calcitriol therapy
        - Parathyroidectomy
        - Flouride and iron intoxication
    - Mechanism:
        - Defect in osteoblast development or activity cause by factors related to the uremic state.

Cardiovascular abnormalities of ESRD (CKD-5): [IMP.]

1. Hypertension:

- Occurs in 90% of patients with ESRD.
- Causes:
    - **Salt and water retention (the primary cause).** 
    - Inappropriate secretion of RAA system.
    - ↑ Sympathetic tone.
    - ↑ Generation of vasoconstrictors (endothelin).
    - ↓ Generation of vasodilators (nitric oxide).

2. Cardiomyopathy:

- Left ventricular hypertrophy (LVH).
- Coronary artery disease (CAD).
- Congestive heart failure (CHF).
- Diastolic dysfunction.

3. Pericarditis and pericardial effusion

- **[Step up p.275: pericarditis in CKD is uremic pericarditis]**
- **These abnormalities increase 2-5 folds in ESRD**
- About one-half of all hemodialysis patients have significant ischemic heart disease
- Dyslipidemia, HTN, ↑homocystin, DM, and insulin resistance contribute to atherosclerosis
- Anemia aggravates LVH (Left ventricular hypertrophy)
- Hyperparathyroidism, amyloidosis, and iron overload cause also cardiac dysfunction.

Neuromuscular abnormalities:

- **CNS dysfunction:**
  - Decreased attention, agitation, confusion, insomnia, and impaired memory.
  - May develop also: depression, hallucinations, delusions, hiccups, cramps, **flapping tremor**, myoclonus, fasciculation, and seizures.

- **Peripheral neuropathy:**
  - Usually symmetric, lower limbs.
  - **Sensory precedes motor dysfunction**.
  - Restless leg syndrome and burning feet.
  - Postural hypotention (autonomic dysfunction).

Hematologic abnormalities:

- **Anemia:**
  - Develops as serum creatinine increases > 180 mcm/L and GFR declines to < 30 ml/minute.
  - **Normocystic, nomochromic anemia.**
  - Main cause: decrease production of EPO (erythropoietin).
- **Platelet Dysfunction: [Step-up p.276:Platelet functions are disturbed in uremia]**
  - Bruising, ecchymoses, bleeding from mm
  - Platelets dysfunction (count is normal): ↓**VWF** (Von Willebrand Factor), which facilitate the interaction between platelets and endothelium through its binding to platelet glycoprotein (IIb, IIIa) receptors.

Gastrointestinal abnormalities: [V. common]

- Anorexia, nausia, and vomiting.

- Uremic factor, stomatitis, esophagitis, gatritis, and peptic ulcer disease.
- ↑ Gastrin in CKD.

Dermatologic abnormalities:

- Uremic **pruritus** is related to:
  - Calcium and phosph deposition (Secondary ↑ PTH).
  - Hypercalcemia.
  - Peripheral neuropathy.
  - Dry skin.
  - Anemia.
  - Inadequate dialysis.

Evaluation of Patients with CKD:

- The history should document the presence of uremic symptoms and possible etiology from: Diabetes Mellitus, Hypertension, congestive Heart Failure, MM, NSAID.
- Family history can suggest PCKD or hereditary nephritis.
- Volume depletion and obstructive nephropathy should be identified and treated promptly.
- Ultrasound – small, shrunken kidneys.
- Normal kidney size with CKD: DM, amyloid, MM.

Management of Patients with CKD:

1. Fluid and electrolytes disorders:

- Salt intake restriction – **daily Na+ < 100 meq (2-4 grams)**
- Loop diuretics
- Hyponatremia – **fluid restriction 1 – 1.5 L/day**
- **Hyperkalemia:**
  (Patients with hyperkalemia should avoid exogenous sources of K+ and medications that increase K+)
  - Exogenous sources of K+ **[to be avoided]:**
    Dates, dried fruits, citrus fruits, banana, chocolate, salt substitute.
  - Medications that ↑ K+ **[to be avoided]**:
    ACEI, ARB, NSAID, K+- sparing diuretics, B-Blockers, and heparin.
  - Treatment of Hyperkalemia:
    - IV calcium gluconate 10 cc of 10% **to protect the heart.**
    - Followed by 25 ml of 50% dextrose solution with 5-10 units regular insulin.
    - B_2-adrenergic agonist nebulizer (salbutamol).
    - $NaHCO_3$ IV/oral.

    To redistribute K^+ inside cells

2. Hyperphosphatemia and secondary hyperparathyroidism:

- Reduce phosphate intake to < 10 mg/kg/day
- Phosphate binders:
  - Calcium carbonate

- Sevelamer (Renagel) **without calcium → (for patients with tendency to have hypercalcemia)**
- Lanthanum carbonate **with calcium → (for patients with hypocalcemia)**

- Vitamin D (Calcitriol) 0.125 mcq/day:
  - Must be withheld until s. phosphate concentration has been controlled to < 6 mg/dl because it may cause severe soft tissue calcifications.
  - Vitamin D compounds can cause hypercalcemia and hyperphosphatemia, which may increase coronary calcification, so: parcicalcitrol (Zemplar) is an analogue that inhibits PTH synthesis without elevation of calcium/phos.

- Indication for parathyroidectomy:
  - PTH > 800 pg/ml with symptoms of bone disease (myopathy, bone pain) persistent hyperphosphatemia soft tissue calcifications.

3. Hyperlipidemia:

The goal is to keep LDL cholesterol < 100 mg/dl by diet control and **statin group**.

4. Anemia

- Target Hb/Hct:
  - K DOQI [Kidney Disease Outcomes Quality Initiative] → Hb 11-12
    Hct 33-36%
  - Anemia: ↑ LVH
    ↓ quality of life
    reduces survival in patients on HD
  - Conversely: Hb > 13
    Hct > 42 associated with more coronary events and increased mortality as evidenced by CHOIR (USA) and CREATE (Europe) studies.

- Target iron levels:
  - Percent transferrin saturation (T-SAT) reflects iron available for erythopoiesis .
  - Serum ferritin (S. ferritin) reflects overall iron stores
  - In CKD: target T-Sat > 20 (20 – 50)
    target S. ferritin > 100 ng/ml to 500 ng/ml
  - Iron supp should be withheld, if: T-sat > 50
    S. ferritin > 800 ng/ml

Treatment Guidelines (Anemia):

➢ Oral iron

- In non-dialysis patients (CKD 1-4): 100-200 mg elemental iron should be given daily in 2-3 days, either one hour before meals or two hours post. (1 tab Ferrous fumerate, 200 mg contains 66 mg elemental iron)
- In dialysis patients (CKD 5): IV iron should be given as on-going iron losses tends to be higher

- **IV iron**
  - 1 gr of iron saccharate (ferrosac) divided into 10 doses of 100 mg given with each dialysis session.
- **Recombinant Erythropoeitin – epoeitin alfa (eprex) (Short acting)**
  - Patients on: starting dose 120 – 180 IU/kg/week, IV
  - Pre-dialysis patients and PD patients: 80-120 IU/kg/week subcutaneously weekly dose
  - Hb/Hct monitoring every 4 weeks
  - The most common side effects: headache, HTN, arthralgia, and diarrhea
  - Resistance to epoeitin:
    1. Inadequate Epo dose
    2. Anemia of chronic disease (infection, inflammation)
    3. Functional iron deficiency
    4. Secondary to hyperparathyroidism
    5. Carnitine deficiency
    6. Hemoglobinopathies
    7. Aluminum toxicity
    8. B12/folate deficiency
    9. Malnutrition

- **Darbepoetin Alfa (Aranesp) (Long acting)**
  - Recombinant Epo
  - Half-life: threefold longer IV and twofold longer S/C than that of epoetin
  - Recommended starting dose 0.45 mcg/kg S/C weekly or double the dose every 2 weeks.

Summary:

- Chronic kidney disease (Chronic renal failure) is **irreversible**.
- **Chronic kidney disease (CKD)** has **5 stages**. Stage 5 is end stage renal disease (ESRD).
- **Diabetes mellitus**, **hypertension** and **glomerulonephritis** are among the **top 3 causes of CKD**.
- **Pathophysiology** of CKD includes:
  1. **Loss of nephron mass**. → Because of that, the remaining nephrons try to compensate. → hypertrophy of remaining nephrons and later on →causes glomerulosclerosis → eventually cause loss of nephron mass (a vicious cycle)
  2. **Increased production of growth factors**
- Since the kidney is responsible for excreting products of protein metabolism (eg: urea and many other toxins), when kidneys fail, these products will accumulate → **uremic syndrome**.
- Kidneys play a role in metabolic and electrolytes balance. Once **kidneys fail**, the following occurs:
  1. **Insulin is not degraded properly** by failing kidneys → patients need less insulin

2. **Dyslipidemia**
3. **Hyponatremia** might occur (large amounts of water retained → sodium is diluted)
4. **Hyperkalemia** (when compensatory mechanisms fail + GFR significant reduction)
5. **Metabolic acidosis** occurs because: volatile acids aren't excreted, bicarbonates regeneration in the kidney is decreased, HCO_3 wasting is increased and H^+ secretion to urine is decreased.
6. **Calcium and phosphate abnormalities** occur in CKD: **Hyperphosphatemia** and **hypocalcemia** which lead to increased parathyroid hormone production (hyperparathyroidism)

- **Hyperphosphatemia** is an independent **risk factor** for morbidity and mortality from **cardiovascular events in ESRD**.
- **Renal osteodystrophy (ROD)** in CKD results from: disturbances in mineral ions levels (Ca^{++}, Mg^+, PO_4), disturbance in PTH and Vit-D levels.
- **Spectrum of ROD:** Osteitis fibrosa cystic, osteomalacia, adynamic bone disease and combination of any of those.
- **Abnormalities** in CKD:
  - **Cardiovascular** (in ESRD): HTN, cardiomyopathy, pericarditis and pericardial effusion
  - **Neuromuscular**: **CNS** abnormalities (confusion, decreased attention, flapping tremors, seizures... etc).
    Peripheral neuropathy (postural hypotension, restless leg syndrome, sensory neuropathy precedes motor).
  - **Hematologic:** Anemia (normocytic normochromic), platelet dysfunction (↓vWF)
  - **Gastrointestinal:** Nausia, vomiting, anorexia
  - **Dermatologic:** Pruritis
- **Management** of CKD patients:
  - **Treat fluid & electrolytes disorders:**
    - Restrict Na^+ intake
    - Loop diuretics
    - Restrict fluid intake
    - Restrict potassium intake
    - Avoid drugs that cause potassium elevation in blood
    - Treat hyperkalemia: Calcium gluconate, insulin, B2 agonist, NaHCO3 I.V.
  - **Treat hyperphosphatemia & hyperparathyroidism:**
    - Restrict phosphate intake
    - Phosphate binding agents: calcium bicarbonate, sevelamer, lanthanum carbonate
    - Treat Vit-D deficiency: (Make sure levels of phosphate are corrected first.)
  - **Treat hyperlipidemia**: **statins**
  - **Treat anemia**:
    - **Iron** supplement (IV or oral), make sure T.sat and S. ferritin are within normal.
    - **Erythropoietin**: epoietin alpha (short acting), darbepoietin alpha (long acting)