

DRUG THERAPY IN KIDNEY DISEASE

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Objectives

At the end of this session, you should be able to:

- List the main functions of the kidney
- Explain the basis of the various disorders associated with renal failure
- Discuss the pharmacological treatment of :
 - Hyperkalemia
 - Hyperphosphatemia
 - Secondary hyperparathyroidism
 - Metabolic acidosis
- Discuss the current treatment of the anemia associated with chronic kidney disease.
 - Epoetin alfa and Darbepoetin alfa
 - Iron supplementation
- Discuss the role of the kidney in drug disposition.
 - General Principles & Examples
 - Renal Dosage Adjustments (RDA)

In view of the wide range of vital functions performed by the kidney, it is not surprising that kidney failure results in life-threatening complications, affecting virtually every organ system in the body.

Renal failure may be acute or chronic. The onset of acute renal failure is relatively rapid, but the injury to the renal tissue may be partially or completely reversible. By contrast, chronic renal failure develops as a result of a progressive, irreversible tissue damage resulting in irreversible **nephron loss**. The remaining nephrons undergo adaptive changes both structurally and functionally to compensate for the nephron loss and continue to maintain homeostasis. However, as more nephrons are lost the ability of the kidneys to maintain balance is gradually compromised. The state of gradually and slowly declining renal function is referred as chronic kidney disease (CKD).

Acute Renal Failure (ARF)

ARF is defined as a precipitous decline in renal function over a relatively short time, ranging from several hours to several weeks. It is marked by rapid increases in serum creatinine (Scr) and urea nitrogen (BUN). Low urine output or **oliguria** (urine output <20 mL/hr) often occurs in ARF, but non-oliguric ARF is not infrequent.

When ARF develops during hospitalization, it is associated with a high mortality rate (25% - 35%). Cardiac complications, bleeding, and infections are the leading causes of death associated with ARF.

Conditions which precipitate ARF are classified as pre-renal, renal (intrinsic), or post-renal (Tables 1A, 1B, and 1C).

Table 1A
Pre-renal Causes of ARF
<ol style="list-style-type: none">1. Volume Depletion<ul style="list-style-type: none">• Renal losses (diuretics, glucose-induced osmotic diuresis, etc.)• GI losses (vomiting, diarrhea, bleeding, drainage, etc)• Evaporative losses (burns, sweat, fever, etc.)• Third space formation2. Hypotension<ul style="list-style-type: none">• Septicemia• Trauma / hemorrhage• Myocardial infarction (MI)• Congestive heart failure (CHF)3. Reduced “Effective Circulating Volume”<ul style="list-style-type: none">• Nephrotic syndrome• Hepatic cirrhosis4. Selective Renal Ischemia<ul style="list-style-type: none">• Bilateral renal artery stenosis (exacerbated by ACE-inhibitors)• Drugs (NSAIDs¹, calcium channel blockers)

¹ Hypotensive patients have elevated circulating levels of angiotensin II (AII) and norepinephrine which stimulate the production of prostacyclin and PGE₂ by the glomerular mesangial cells. The vasodilator effect of the PGs tends to counterbalance the strong vasoconstrictive effect of AII and norepinephrine on the renal vessels. By inhibiting the production of PGs, the NSAIDs may precipitate acute renal failure in volume-depleted patients.

Table 1B	
II. Intrinsic Renal Causes of ARF	
<p>1. Acute Tubular Necrosis (ATN) / Tubulointerstitial Damage</p> <ul style="list-style-type: none"> • Renal post-ischemic injury following: <ul style="list-style-type: none"> ▸ Sever protracted prerenal causes. ▸ Trauma / surgical procedures, burns, sepsis, etc. ▸ Thrombosis/embolism of renal vessels ▸ Transfusion reactions (hemolysis) • Rhabdomyolysis (muscle trauma, malignant hyperthermia, drugs) • Toxins/Poisons <ul style="list-style-type: none"> ▸ Heavy metals (e.g., Hg) ▸ Organic solvents (CCl₄, CH₄), pesticides, glycols, .. ▸ Poisonous mushrooms, snake bites, uric acid, etc. ▸ Radiographic contrast agents • Nephrotoxic Drugs <ul style="list-style-type: none"> ▸ Aminoglycosides, amphotericin, etc... ▸ Methoxyflurane, EDTA, expired tetracyclines ▸ Acyclovir, ganciclovir, cisplatin, omeprazole, etc <p>-----</p> <p>2. Glomerular and Vascular Disease</p> <ul style="list-style-type: none"> • Acute glomerulonephritis (e.g., post-infectious) • Polyarteritis nodosa • Lupus erythematosus • Hemolytic-uremic syndrome (HUS) • Goodpasture's syndrome (anti-GBM antibody disease) • Malignant hypertension 	

Table 1C	
Post-renal Causes of ARF	
<p>A post-renal condition refers to an obstruction at some point along the urinary tract which would partially or completely block urine flow.</p>	
<ul style="list-style-type: none"> ▪ Upper urinary tract obstruction <ul style="list-style-type: none"> ○ Ureter obstruction <ul style="list-style-type: none"> •Renal calculi •Pelvic or retroperitoneal malignancy (e.g., uterine tumor) •Congenital malformations. ▪ Lower urinary tract obstruction <ul style="list-style-type: none"> ○ Hypertrophy of the prostate (benign or malignant) 	

A prerenal condition is characterized by a marked reduction in renal blood flow (RBF) (renal hypoperfusion) which may be brought about by true ECF volume depletion (e. g., severe diarrhea), hypotension (e. g., congestive heart failure), or by a significant reduction in the effective circulating volume as in hepatic cirrhosis (see Table 1A).

Prerenal ARF is usually characterized by low urine output (oliguria), a normal or nearly normal urinalysis, an elevated ratio of blood urea nitrogen to serum creatinine (BUN/Scr ratio > 20) (except in patients with advanced liver disease), a relatively concentrated urine ($U_{osm} > 500$ mOsm/L), and a low fractional Na excretion (<1%) with relatively low urine sodium concentration ($U_{Na} < 25$ mEq/L.)²

In most cases of prerenal disease, re-hydration or plasma expansion leads to a relatively rapid improvement in renal function (increased urine flow and reduced serum creatinine). In contrast to prerenal disease, acute tubular necrosis (ATN) is characterized by a normal BUN/Scr ratio (10-15), and a dilute, but sodium rich urine ($U_{osm} \leq 350$ mOsm/L; fractional Na excretion >2%,; $U_{Na} > 40$ mEq/L). Urine output may be reduced or normal.

The main intra-renal, tubular and/or vascular, mechanisms of ARF are summarized in Table 1B. Acute tubular necrosis (ATN) may be post-ischemic or toxic. In either case, ATN is characterized by necrosis of the epithelial cells especially those of the proximal tubule and the thick ascending loop of Henle. Also, the tubule lumen is often filled with cellular debris, or heme-pigment precipitate as in the case of hemolysis or rhabdomyolysis.

Intensive pharmacologic **intervention** in the early stages of post-ischemic acute tubular necrosis (ATN) may help minimize tubular damage if administered within 24 hours of the initial ischemic insult. A combination of osmotic and loop diuretics (e.g., mannitol + furosemide) is believed to help wash out debris from the tubule lumen. The **loop diuretic** may help preserve cellular integrity in the loop of Henle by inhibiting active ion transport and reducing the cells energy (O_2) requirements. Hypertonic **mannitol** helps prevent post-ischemic cell swelling. Also, mannitol may act as a scavenger of reactive oxygen species (or oxygen radicals). Upon reperfusion, the production of oxygen radicals rises dramatically and it is thought to be largely responsible for the post-ischemic injury.

² \downarrow ECFV \Rightarrow \downarrow GFR \Rightarrow \uparrow % Na reabsorption in the proximal tubule \Rightarrow \downarrow Na excretion.

\downarrow RBF \Rightarrow \uparrow renin \Rightarrow \uparrow aldosterone \Rightarrow \uparrow Na reabsorption in the distal nephron \Rightarrow \downarrow Na excretion

\downarrow ECFV & \downarrow TBW \Rightarrow \uparrow ADH \Rightarrow \uparrow water reabsorption in collecting ducts \Rightarrow \uparrow U_{osm} & \downarrow urine flow.

Pharmacotherapeutic Management of Acute Renal Failure

Prevention:

Preventive measures should be instituted before undertaking procedures or drug therapies which can cause ARF (e.g., surgery, contrast media, and nephrotoxic drugs). Prevention is particularly important in high risk patients (Table 2).

1. The most important preventive measure is to ensure that the patient is well hydrated. This is usually accomplished by the administration of saline (0.45% or 0.90% NaCl solution). Elevated urine flow may help dilute toxins and promote their elimination. Osmotic and loop diuretics are also used in certain cases. However, the value of diuretics in this area is not proven. Sodium loading prior to and during amphotericin³ therapy is believed to mitigate its nephrotoxic effect⁴.
2. Administration of N-acetylcysteine (NAC) prior to the administration of radiocontrast material (600 mg by mouth every 12 hours the day before and the day of the test).

Treatment:

Once acute renal failure is established, treatment consists of:

1. **Supportive measures** including adequate hydration, Improving renal perfusion and oxygenation, avoiding fluid overload, and avoiding the use of nephrotoxic drugs as much as possible.
2. **Active pharmacologic intervention**
Drug therapy is aimed primarily at converting oliguric to non-oliguric ARF because non-oliguric patients (urine flow > 20 mL/hr) are less likely to require hemodialysis and are easier to manage in terms of fluid and electrolyte balance, nutrition, and pharmacotherapy. The conversion may be accomplished with diuretics and dopamine (**Table 3**).

Risk Factors for Acute Renal Failure (ARF)	
Post-operative ARF (5 % of pts)	Pre-existing renal insufficiency, advanced age, male sex, heart disease, and hypertension.
Aminoglycoside-induced ARF (5 - 10 % of pts)	Advanced age, co-administration of other nephrotoxins, prolonged aminoglycoside therapy, renal hypoperfusion, hypokalemia
Contrast Media-induced ARF (<0.02% of pts)	Ionic contrast agents, pre-existing renal insufficiency, co-administration of other nephrotoxins, advanced age, diabetes mellitus, hepatic disease.

³ Amphotericin B is an antifungal drug used treat difficult systemic infections, particularly those due to Aspergillus

The proposed mechanism involves the so-called tubulo-glomerular feedback (TGF): increased Na filtered load leads to a reflex reduction of GFR, reducing the amount of the drug that is filtered and delivered to the distal nephron ⁴

Agent	Adult Dosage	Comments
Dopamine	1 - 5 mcg/kg/min	Avoid extravasation; monitor BP and urine flow
Furosemide	100 mg iv bolus; if no response give 200 mg iv. If urine flow increases start continuous infusion at 0.1 - 1.0 mg/kg/hr	iv push rate should be <4 mg/min. Monitor serum Na, K, and urine flow. Bumetanide may be used instead of furosemide.
Mannitol	12.5 - 25 g over 5 min, may repeat in 1-2 hrs. If pt responds adequately (urine flow \geq 50 mL/hr) start continuous infusion (500 mL of 20% mannitol over 5 hrs)	Monitor urine flow and serum electrolytes and osmolality (keep osmolality <310 mOsm/L). Avoid pulmonary edema.
Thiazide	Chlorothiazide (500 mg iv bid) or oral metolazone (10 mg bid) may be given with mannitol and furosemide	Same monitoring as with furosemide.

Emergent Pharmacologic management of Hyperkalemia:

Hyperkalemia ($K^+ \geq 5.5$ mEq/L) and infection are the most life-threatening complications associated with acute renal failure (ARF)⁵. Acute hyperkalemia is poorly tolerated, especially when ARF is associated with extensive tissue damage (crush injuries, tumor lysis, and rhabdomyolysis)⁶.

The clinical symptoms correlate with the serum K^+ level and range from harmless peaking of the T wave of the ECG to ventricular fibrillation and cardiac arrest. Consequently, this complication must be addressed on emergent basis.

The clinical and pharmacologic interventions outlined below are aimed at preventing or reversing the cardiac manifestations of hyperkalemia. The management of clinically significant hyperkalemia consists of three immediate objectives: the first is to stabilize the cardiac cell membrane to prevent arrhythmia; the second is to achieve a relatively rapid reduction of extracellular K^+ level by causing an internal shift of K^+ ions from the ECF to the ICF; the third objective is to promote the elimination of K^+ from the body. The administration of Ca gluconate has a membrane-stabilizing effect on cardiac cells and serves to counteract the depolarizing effect of elevated extracellular K^+ concentration.

⁵ These are covered by the following vowels: A (Acidosis), E (Electrolyte imbalance), I (Intoxication), O (fluid Overload), and U (Uremia)

⁶ Tissue injury and the breakdown of cells result in the release of large amounts of K^+ into the extracellular fluid (ECF) compartment.

Management of Hyperkalemia

Step 1: Evaluate and confirm hyperkalemia

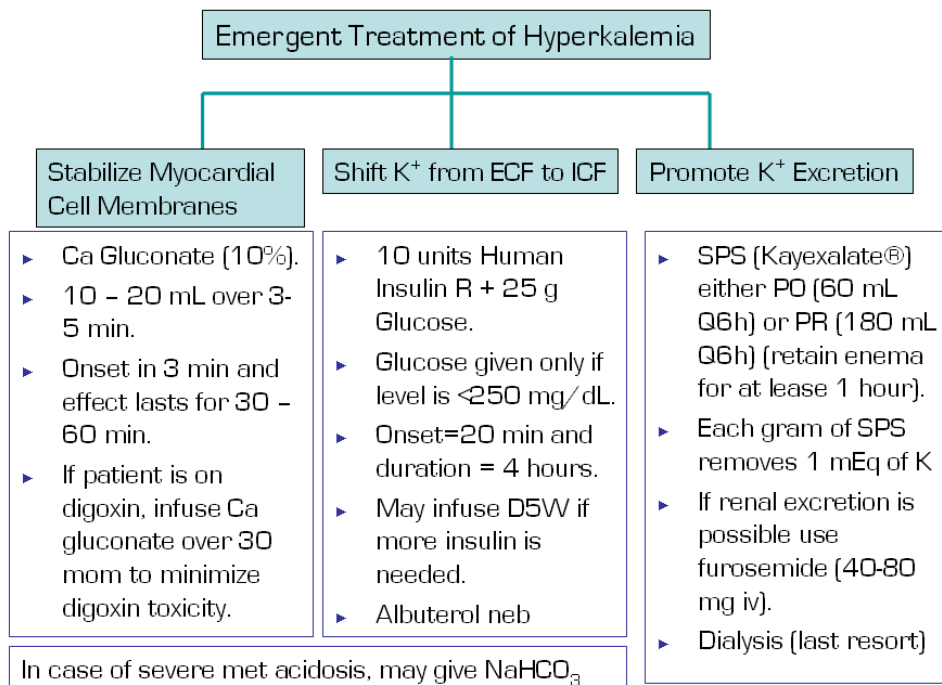
Step 2: Determine urgency of treatment. Criteria for emergent treatment include

- Rapid and recent rise in serum K^+
- ECG changes consistent with hyperkalemia. The presence of ECG changes suggests life-threatening hyperkalemia. However, hyperkalemia may be serious despite normal ECG
- Renal insufficiency
- Metabolic Acidosis

If criteria for emergent treatment criteria are not met or if serum $K^+ < 6.0$ mEq/L, go to non-emergent treatment (Step 4 below)

Step 3: Emergent management of hyperkalemia See schematic below and Table 4

Mnemonic: **C BIG K Drop**



Step 4: Non-emergent treatment

I. Promoting K^+ elimination

- Gastrointestinal excretion: See SPS (Kayexalate®) below
- Renal excretion: See furosemide below.
- Consider hemodialysis in severe, refractory cases

References:

- <http://www.fpnotebook.com/REN117.htm>
- Hollander-Rodriguez (2006) Am Fam Physician 73:283-90
- Kim H, Han, S. Therapeutic approach to hyperkalemia. Nephron 2002;92(suppl 1):33-40.
- Weiss-Guillet E-M, Takala J, Jakob SM. Diagnosis and management of electrolyte emergencies. Best Pract Res Clin Endocrinol Metab 2003;17(4):623-651.

Table 4				
Treatment of Hyperkalemia				
Treatment	Adult dose	Onset	Duration	Comments
Ca⁺⁺ gluconate (10 mL of 10%)	10 mL over 2-5 minutes. May repeat dose after 5 minutes if no response. Further Ca is ineffective unless patient is hypocalcemic.	immediate	30 min	Don't mix with HCO ₃ ⁻ . Avoid administering Ca ⁺⁺ with ceftriaxone ^a . Caution: Ca increases risk of digoxin toxicity. Use slower infusion (over 20-30 minutes). Consider Mg as an alternative to Ca in digoxin toxicity.
NaHCO₃ (1 mEq/mL)	50 mEq over 5 min. May repeat every 30 min if ECG changes persists.	30 - 60 min	0.5 - 3 hrs	Use only in acidosis. Large Na load. To minimize the risk of tetany and seizures, correct hypocalcemia if necessary before administering bicarbonate.
Insulin ± glucose	10 Units Regular Insulin + 50 mL D50W	30 - 60 min	3 - 4 hrs	Monitor glucose level. Give glucose only if blood level <250 mg/dL. May give D5/HNS infusion if further insulin is needed.
Albuterol (β-agonist)	0.5 mg iv over 15 min or 10-20 mg via neb over 15 min	<30 min	2 -6 hrs	Watch for tachycardia and tremor.
Na polystyrene sulfonate (SPS) (Kayexalate®) ^b	15 g (60 mL) PO or 30-45 g rectally every 6 hours.	2 - 3 hrs		Large Na load; Constipation
Furosemide (Lasix)	20-40 mg iv over 5 min	30 min	4 hrs	
Dialysis	---	hours	variable	
<p>^a Recent reports indicate that IV co-administration of ceftriaxone and Ca salts (even through separate lines) increases the risk of Ca precipitation in soft tissues.</p> <p>^bPrecautions: avoid sorbitol if bowel necrosis risk exists, and use caution in patients at risk for congestive heart failure; consider concurrent administration of furosemide to reduce Na load.</p>				
Abbreviations: D10W = 10% dextrose in water; D5/HNS = 5% dextrose in half normal saline				

Chronic Kidney Disease (CKD)

CKD is defined as a progressive, irreversible loss of nephrons and nephron function⁷. Many diseases can lead to CKD (**Table 5**). However, diabetes (40%)⁸, hypertension (30%), and glomerulonephritis (10%) account for approximately 80% of the cases.

Table 5	
Common Causes of Chronic Kidney Disease (CKD)	
1. Glomerular and Vascular Diseases (80% of all cases)	
<ul style="list-style-type: none"> ● Glomerulonephritis (10%) ● Diabetes (diabetic glomerulosclerosis / nephropathy) (40%) ● Hypertension (glomerulosclerosis) (30%) 	
2. Tubular and Interstitial Diseases (20%)	
<ul style="list-style-type: none"> ● Chronic interstitial nephritis (eg, phenacetin abuse nephropathy) ● Chronic pyelonephritis (usually due to vesico-ureteral reflux) ● Intratubular obstruction as in myeloma kidney, hypercalcemia, hyperuricemia (tumor lysis), poorly soluble drugs (acyclovir, methotrexate, sulfonamides, etc ● Polycystic kidney disease (PKD) (3.5%) ● Severe, irreversible ATN (e.g., due exposure to heavy metals) 	

The signs and symptoms depend on the extent and duration of renal dysfunction. The progression of the disease which generally takes place over a period of years may be divided in stages. The degree of renal deficiency and the severity of kidney disease are generally reflected in the decline of glomerular filtration rate (GFR). The National Kidney Foundation (NKF) Disease Outcome Quality Initiative (K/DOQI) classifies chronic kidney disease (CKD) into five stages (GFR is expressed in mL/min/1.73 m² of body surface area):

Stages of Chronic Kidney Disease		
Stage	Description	GFR
1	Kidney damage with normal or increased GFR	≥ 90
2	Kidney damage with a mild decreased in GFR	60-89
3	Moderate decreased in GFR	30-59
4	Severe decreased in GFR	15-29
5	Kidney failure; GFR<15 or need for dialysis	<15

⁷ The injured nephrons continue to function appropriately relative to their GFRs, which vary according to the extent of injury; the ratio of nephron function-to- GFR is similar in different nephrons. The *intact nephron hypothesis* postulates that *the kidneys fail in an organized fashion*. As some nephrons are destroyed, other nephrons continue to function at a capacity greater than normal.

⁸ Approximately one third of the patients with insulin-dependent diabetes will develop *diabetic nephropathy*, the general term for renal disease associated with diabetes.

When the GFR declines below 60 mL/min (<50% of normal), there is a significant decrease in **renal functional reserve**. However, the remaining nephrons are able, through complex physiologic adaptations⁹, to maintain the relative constancy of both volume and composition of body fluids (homeostasis). Therefore, in most cases no symptoms or abnormal laboratory values are observed. As the GFR drops below 30 mL/min, the functional reserve is essentially exhausted and fluid and electrolyte balance becomes precarious, particularly in the face of additional challenges (infection, dehydration, and nephrotoxins). Significant signs and symptoms may appear. There is clearly **renal insufficiency** and the patient may present with mild hypertension and slight anemia in addition to elevated serum creatinine and blood urea nitrogen (BUN). Gradually, the kidneys become unable to maintain normal fluid and electrolyte balance as a result of their failure to respond adequately even to the usual changes in the intakes of water and various electrolytes (Na⁺, K⁺, etc.). All or some of the symptoms of renal failure may become evident. Most patients can lose over 75% of GFR before developing overt clinical signs of renal failure (hypertension, CHF, edema, hyperkalemia, hypocalcemia, hyperphosphatemia, etc.)

End-Stage Renal Disease (ESRD; Uremia): This is the most advanced stage of CKD in which virtually all renal function is lost (GFR < 15 mL/min). Water and electrolytes are no longer in balance (input ≠ output), body fluids composition is markedly abnormal, and cellular function is grossly compromised (see below). At this point, **renal replacement therapy** (dialysis or kidney transplant) becomes necessary.

Table 6	
Abnormalities associated with CKD	
<u>Fluid and Electrolyte Imbalance.</u> <ul style="list-style-type: none"> • Water retention. • Hyperkalemia. • Hypocalcemia. • Hyperphosphatemia. • Metabolic acidosis. 	<u>Neurologic disorders</u> <ul style="list-style-type: none"> • CNS: lethargy, confusion, sleep disturbances, and irritability • Peripheral neuropathy (paresthesia) • ANS: orthostatic hypotension, gastroparesis.
<u>Endocrine Disorders</u> <ul style="list-style-type: none"> • Secondary hyperparathyroidism • Low calcitriol (active vitamin D₃) • Renal osteodystrophy • Insulin resistance 	<u>GI Disturbances</u> <ul style="list-style-type: none"> • Nausea, vomiting, and hiccups • Gastric hyperacidity & ulceration • Altered GI function due to gut edema
<u>Hematologic disorders</u> <ul style="list-style-type: none"> • Anemia • WBC dysfunction • Platelet dysfunction 	<u>Cardiovascular disorders</u> <ul style="list-style-type: none"> • Hypertension • Atherosclerosis • CHF and pulmonary edema • Pericarditis / Tamponade

⁹ The adaptations of the intact nephrons include increases in size (hypertrophy), single-nephron GFR, (hyperfiltration), plasma flow, solute excretion rates, as well as metabolic changes. For instance, there may be a four fold increase in the production of ammonia and the excretion of ammonium.

Disorders Associated with Chronic Kidney Disease (CKD)

Virtually all organ-systems and all body functions are affected by renal failure, resulting in multiple disorders and complex symptoms (**Table 6**). At the basis of these disorders is the body's partial or complete inability to:

1. Excrete excess water and electrolytes
2. Excrete organic metabolic waste products including fixed acid (H^+), urate, urea, and other unidentified "uremic toxins".
3. Produce sufficient amounts of the renal hormones calcitriol and erythropoietin.

Sodium:

As the number of functioning nephrons declines, the kidneys become unable to maintain Na balance in the face of the usual fluctuations in salt intake. If salt intake exceeds the excretory capacity of the remaining nephrons, extracellular fluid volume (ECFV) expansion, edema, and hypertension will result. Therefore, Na^+ intake restriction is often necessary¹⁰. It should be noted that with advancing renal failure and the inability of the kidney to dilute the urine and excrete excess water, the serum Na^+ concentration may be lower than normal (hyponatremia) despite a significant degree of Na^+ retention¹¹.

Potassium:

Normally, the kidneys excrete the equivalent of 90-95% of the K^+ intake. The colon excretes the remaining 5 - 10%, and its contribution to K^+ excretion increases in renal failure. Patients with renal failure retain K^+ and develop hyperkalemia (serum $K^+ >5$ mEq/L). Although a mild degree of chronic hyperkalemia is well tolerated by patients with chronic kidney disease, a further rise of serum K^+ can lead to life-threatening cardiac dysrhythmias and it is often an indication for dialysis. Long term management of hyperkalemia in a stable patient with CKD is summarized below:

Management of Chronic Hyperkalemia in CKD
<ul style="list-style-type: none"> ○ Eliminate any medication that may be causing or contributing to hyperkalemia. ○ Restrict dietary K^+ intake to 40-60 mEq/day ○ Administer oral SPS (Kayexalate) chronically

Calcium and Phosphate Metabolism:

Figures 1 & 2 summarize the normal daily turnover of calcium and phosphate in a healthy subject, and Fig 3 shows the formation and physiological actions of calcitriol. Chronic renal failure (CRF) can have a profound effect on bone metabolism, and is often associated with a complex bone disease known as **renal osteodystrophy** (Fig 4). The

¹⁰ In endstage renal disease (ESRD) patients, the dietary Na^+ intake may be restricted to 35 – 70 mEq per day.

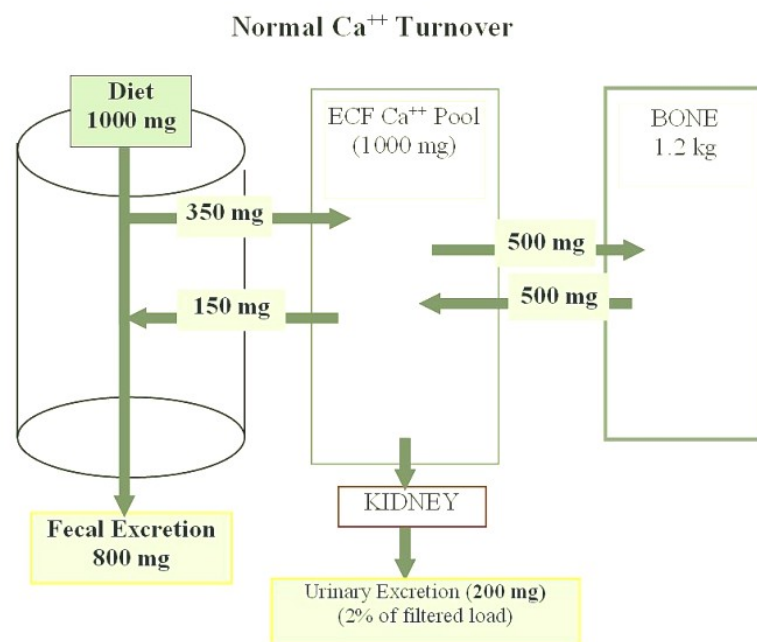
¹¹ This emphasizes the fact that changes in serum Na^+ level reflect changes in total body water and provide no information regarding Na^+ balance.

alterations in bone metabolism in CRF stem primarily from reduced calcitriol production, hypocalcemia, hyperphosphatemia, and secondary hyperparathyroidism. The combination of hypocalcemia, hyperphosphatemia, and low circulating calcitriol promotes the synthesis and release of parathyroid hormone (PTH), leading to secondary hyperparathyroidism and hyperplasia of the parathyroid glands. This stimulates bone turnover and the development of *osteitis fibrosa cystica*. The low levels of calcitriol interfere with normal bone remodelling, resulting in *osteomalacia*, which can be treated successfully with exogenous calcitriol. Furthermore, the ingestion of aluminum-containing antacids (once used as binders of dietary phosphate) may lead to aluminum intoxication, which leads to a type of *osteomalacia* that does not respond to calcitriol.

Normal Calcium Turnover

Fig 1. The average daily turnover of calcium.

Most of the body Ca (1.2 kg or 30,000 mmoles) is located in the mineral matrix of bone. A small but very important fraction of bone Ca (~ 4 grams or 100 mmoles) is readily available for exchange with the extracellular pool, which amounts only to one gram (25 mmoles). In addition, about 500 mg is exchanged daily in the course of normal bone remodeling, a process that is regulated by multiple factors including parathyroid hormone (PTH), calcitriol, calcitonin, etc.



Diet provides about 1000 mg of calcium per day of which only 350 mg are absorbed by the intestine. However, the extent of Ca absorption is regulated by calcitriol and PTH, and varies significantly, depending on the overall calcium balance. About 150 mg is secreted back into the intestine, so that the net absorption is only 200 mg. To maintain perfect external Ca balance, the same amount (200 mg) is excreted in the urine; this is the equivalent of about 2% of the filtered load of Ca. The extent of Ca reabsorption by the kidney is influenced by changes in Na balance and it is regulated by the same hormones that regulate intestinal Ca absorption (PTH, calcitriol, and calcitonin).

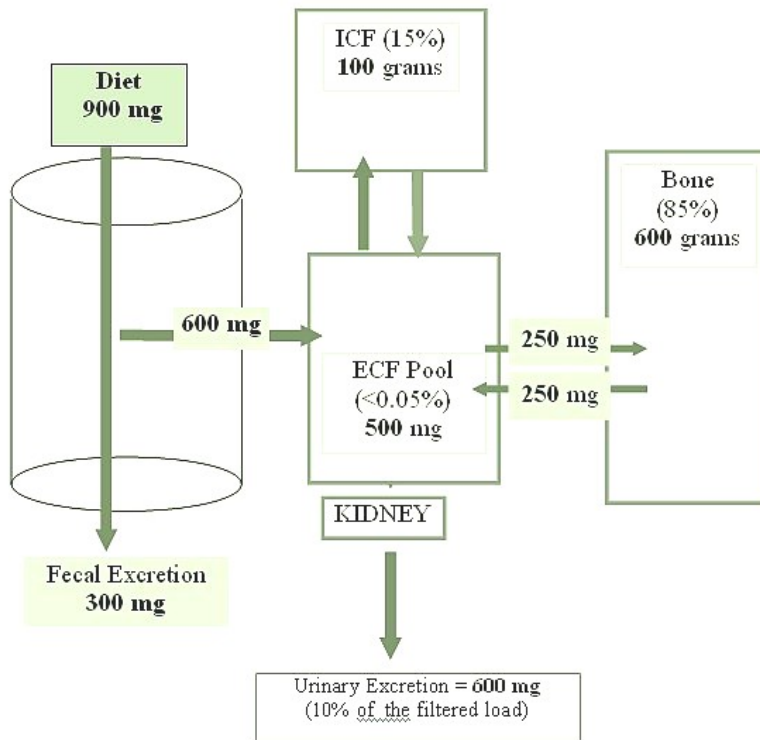
The normal total plasma calcium concentration is approximately 2.5 mmol/L (10 mg/dL). Nearly 50% of total plasma Ca is bound to plasma proteins and about 5% is present in complex form mainly with bicarbonate and citrate. The remaining 45% (1.125 mmol/L or 2.25 mEq/L) is present in ionized, free form which represents the physiologically active calcium.

Normal Phosphate Turnover

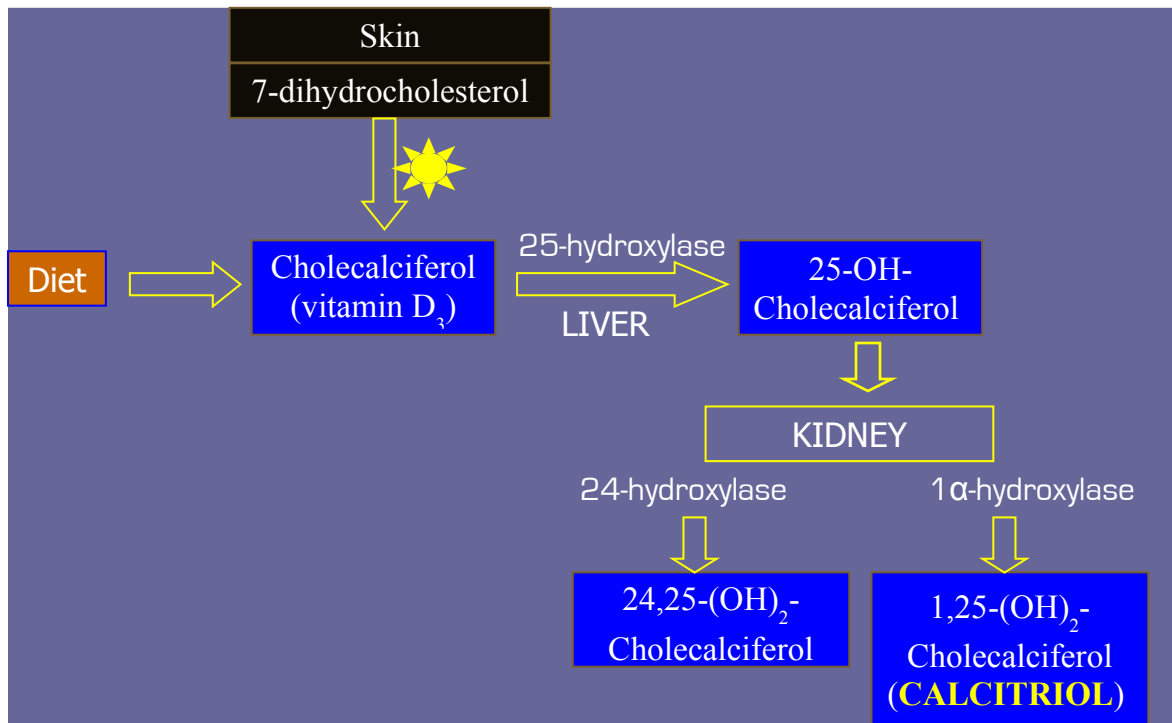
Fig 2: The average daily turnover of phosphate in an adult.

About 85% of the body phosphate (equivalent to 100 g of elemental phosphorus) is located in bone, 14.9% in ICF, 0.1% in the ECF pool. An average of 250 mg is exchanged per day between bone and the ECF pool in the course of normal bone remodeling. The average diet provides about 900 mg of phosphorus per day and most of which is absorbed by the intestine.

The percent absorption is relatively constant, so that there is a linear relationship between the amount ingested and the amount absorbed. Therefore, urinary phosphate



excretion provides the main mechanism for regulating phosphate balance. Normally $\geq 85\%$ of the filtered phosphate is reabsorbed in the proximal tubule by an active co-transport mechanism, whose maximum capacity is normally slightly lower than the filtered load, so that an amount of phosphate (~ 600 mg or 19 mmoles/day) is always excreted in the urine, mostly in the form of H_2PO_4^- . This is very important for urinary acid excretion; phosphate provides the main vehicle for titratable acid excretion which normally accounts for 1/3 of total urinary acid excretion. Note that clinical labs measure and report only the so-called *acid-soluble* phosphate which represents only one third of the total plasma phosphate. It is usually expressed as mg of phosphorus per dL (31 mg of phosphorus = 1.0 mmol of phosphorus = 1.0 mmol of phosphate); the normal range for serum phosphorus is 2.5 - 4.5 mg/dL or 0.8 - 1.45 mmol/L. The K/DOQI guidelines require that serum phosphorus level be maintained between 3.5 and 5.5 mg/dL (1.13 - 1.78 mmol/L)

Fig 3: The formation of calcitriol

Calcitriol is a hormone derived from vitamin D, which is considered a biologically inactive prohormone. Cholecalciferol (vitamin D₃) is produced in the skin from 7-dehydro-cholesterol under the effect of ultraviolet sun rays. It may also be added as a supplement to dairy products. Cholecalciferol undergoes 2 hydroxylation reactions, first in the liver (position 25), and then in the kidney (position 1), catalyzed by 25-hydroxylase and 1 α -hydroxylase respectively. These enzymes are under hormonal control, particularly the parathyroid hormone (PTH).

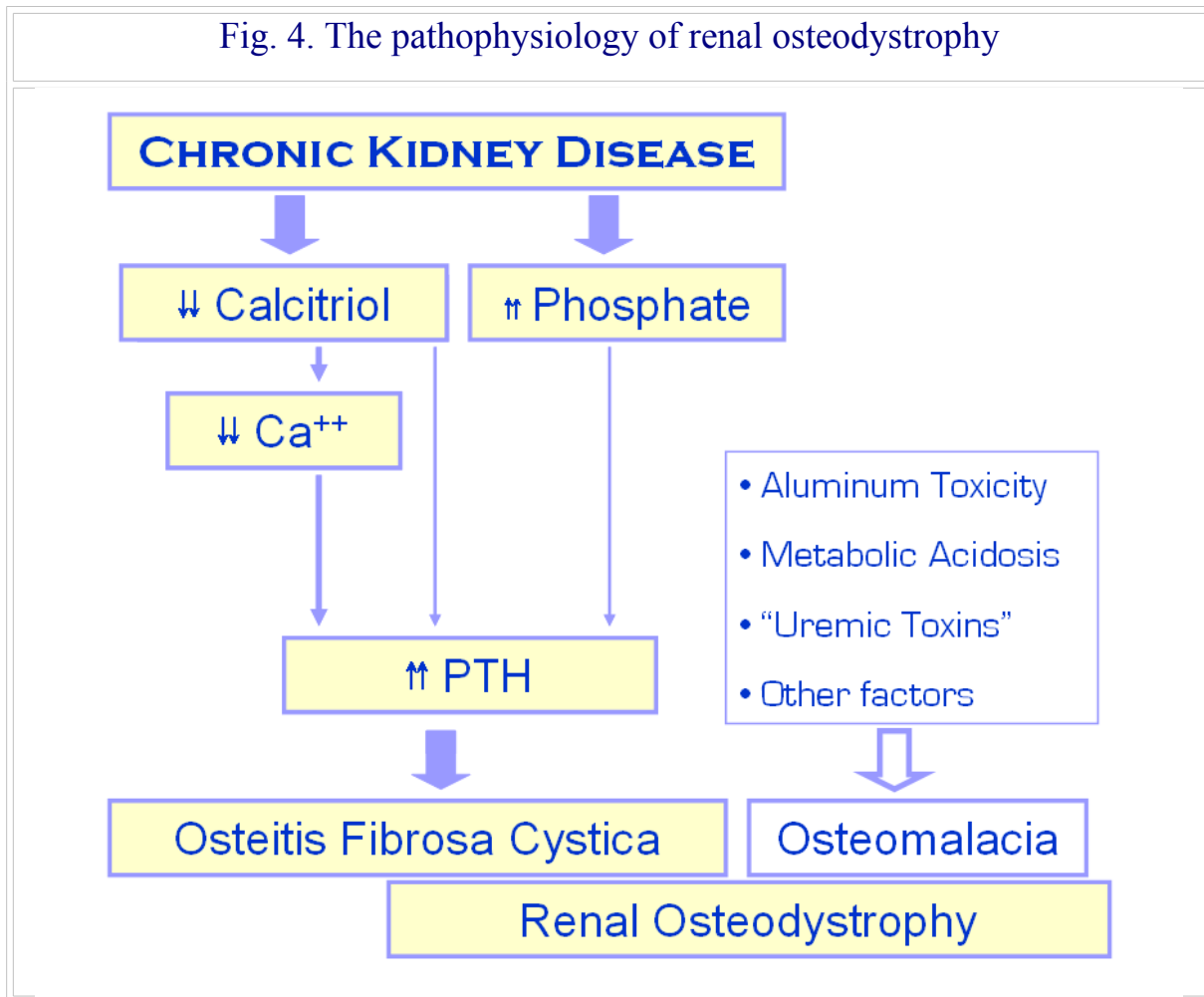
Calcitriol receptors are found in most cells, and studies indicate that this hormone exerts a strong influence on the differentiation and growth of cells in different types of tissues. Future research will likely demonstrate a much wider role for calcitriol than is currently established.

The principal target tissues of calcitriol are the small intestine, bone, the kidney, and parathyroid glands. The best known actions of calcitriol center on the regulation of calcium and phosphate balance and bone metabolism. It plays a major role in the regulation of blood calcium concentration by controlling the intestinal absorption of dietary calcium, the renal tubule Ca reabsorption, and, in conjunction with PTH, the mobilization of calcium from bone. Calcitriol and other active metabolites of vitamin D act directly on bone cells to stimulate skeletal growth, and on the parathyroid glands to suppress PTH synthesis and secretion.

In summary, calcitriol:

- Stimulates intestinal Ca absorption by the induction of specific proteins (e. g., Ca-binding protein) and the stimulation of Ca movement through the luminal membrane of the intestine.
- Promotes the renal conservation (reabsorption) of both Ca and phosphate. In this respect, its immediate precursor (25-hydroxy-cholecalciferol) appears to be more potent.
- Stimulates bone resorption leading to the release of both Ca and phosphate from bone.
- Inhibits the synthesis of PTH

Fig. 4. The pathophysiology of renal osteodystrophy



Pharmacotherapeutic Interventions

Hypocalcemia

The deficiencies of calcitriol and calcium are corrected mostly by oral administration.

Calcitriol is now available in the form of oral capsules (0.25 and 0.50 mcg), oral solution (1 mcg/mL), and injectable (1 mcg/mL). It may be dosed once a day or every other day depending on serum calcium and the Ca x P product, which should always be kept <70 to prevent extraosseous (ectopic) Ca phosphate precipitation.

A variety of oral **calcium supplements** are available. These include Ca carbonate and Ca acetate which are used mostly as phosphate binders (see management of hyperphosphatemia below). However, they do provide significant amounts of calcium. Calcium citrate (CitraCal) is another product used solely as a Ca supplement; it has the advantage of having a much higher bioavailability than either Ca carbonate or Ca acetate with added benefit of citrate whose metabolism results in the generation of the much needed buffer bases (bicarbonate).

Hyperphosphatemia

Despite dietary restriction, phosphate tends to accumulate in body fluids of renal failure patients leading to *hyperphosphatemia* (serum phosphorus level >5.5 mg/dL). High phosphate levels can lead to soft tissue calcification as the Ca x P product exceeds 70 (mg/dL)². Vascular calcification is a life-threatening condition particularly when involving the aorta and or the coronary arteries. Also high phosphate level is thought to stimulate PTH secretion leading to secondary hyperparathyroidism, parathyroid hyperplasia, and renal bone disease.

Management of hyperphosphatemia includes reduction in dietary intake of phosphate, inhibition of intestinal phosphate absorption with phosphate binders, and removal of phosphate with dialysis. Restriction of dietary phosphorus intake is limited by the need for a minimum amount of dietary protein intake to prevent malnutrition (approximately 1.25 g/kg/day). In addition, the usual regular dialysis treatment does not eliminate a sufficient amount of phosphate to maintain phosphate balance. Therefore, the main approach to manage hyperphosphatemia relies on minimizing intestinal phosphate absorption through the use of phosphate binders.

In the 1970s, aluminum (Al) containing antacids¹² were used effectively as phosphate binders. However, it was discovered that small amounts of Al were absorbed and may have contributed to the abnormal bone formation (osteomalacia) in addition to other dialysis-related adverse effects including, encephalopathy, and anemia. In current clinical practice, Al containing phosphate binders are strictly avoided.

In the 1990s, Al based binders were replaced by Ca carbonate and Ca acetate, somewhat safer compounds, despite their low phosphate-binding capacity and their tendency to cause hypercalcemia¹³:

- **Ca Carbonate** (e.g., Tums, Rolaids, etc):

- Usual dose: 650-1950 mg 3 times daily (~ 6 g/day) with meals.

- The need for high doses of Ca carbonate to achieve target phosphate levels has led to low compliance in some patients and hypercalcemia in others with increased risk of coronary artery calcification, a life-threatening complication.

¹² Examples include: Amphojel, Basaljel, Maalox, Mylanta, Nephrox, Phosphajel, and Rulox

¹³ Ca carbonate consists of 40% elemental Ca. Therefore, each 650 mg tablet contains 260 mg of Ca. By contrast, only 25% Ca acetate is elemental Ca, so that a 667 mg capsule contains 169 mg of Ca.

• **Ca Acetate** (PhosLo; 667mg capsules):

Usual dose: 2 capsules by mouth just before the meal 3 times daily. Ca acetate has a better solubility and a higher phosphate-binding capacity than Ca carbonate. It achieves the same level of phosphate binding with approximately half the Ca intake. For this reason Ca acetate is associated with far fewer hypercalcemic events than Ca carbonate.

Presently there are two additional FDA approved phosphate binders that contain neither Al nor Ca.

• **Sevelamer hydrochloride (Renagel®)** (400 and 800 mg Tablets)(FDA approved 1998):

Usual dose: 400-1600 mg 3 times daily (with meals)(maximum=4 g/day).

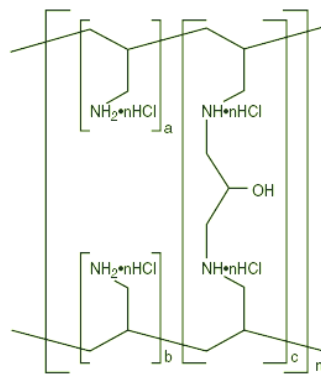
Sevelamer tablets expand in water; they should be swallowed intact and should not be crushed, chewed, or broken into pieces¹⁴.

Sevelamer is a cationic (positively charged) polymer containing a large number of primary amine groups. About 40% of these amine groups are protonated and are able to bind phosphate forming a non-absorbable polymer-phosphate complex. Sevelamer is water soluble but it is not absorbed by the intestine. It effectively binds phosphate with a capacity similar to that of Ca acetate. In terms of phosphate reduction, one 800-mg tablet of sevelamer is equivalent to a 667-mg capsule of Ca acetate.

However, sevelamer has additional benefits:

- It is associated with a significantly lower incidence of hypercalcemia and a significantly lower incidence of coronary artery and aortic calcification which sometimes occur in dialysis patients.
- It significantly lowers the level of LDL-cholesterol by 25 – 30% thereby decreasing the risk of atherosclerosis and coronary heart disease. The reduction in LDL-cholesterol is due to the binding of bile acids in the intestine.
- It inhibits PTH secretion and helps reverse the hypertrophy of the parathyroid glands.

Chemical Structure of Sevelamer Hydrochloride



a, b = number of primary amine groups
 c = number of crosslinking groups
 n = fraction of protonated amines
 m = large number to indicate extended polymer network

a + b = 9
 c = 1
 n = 0.4

¹⁴ The safety and efficacy of sevelamer (Renagel) in patients with dysphagia, swallowing disorders, severe GI motility disorders including severe constipation, or major GI tract surgery have not been established. Consequently, caution should be exercised when sevelamer is used in patients with these GI disorders.

- Lanthanum Carbonate (**Fosrenol**[®]): (chew tablets: 250, 500, 750, & 1000 mg)
Usual dose: 500-1000 mg 3 times daily taken with meals (maximum=4.5 g/day)¹⁵.
Lanthanum carbonate is a Ca-free, Al-free compound that possesses phosphate-binding activity similar to aluminum, with minimal absorption. The phosphate binding activity of lanthanum carbonate has a pH optimum of 3 to 5. Lanthanum absorption and tissue retention is extremely low. Ingested lanthanum is eliminated in the feces (via bile); therefore, it does not accumulate in the tissues of renal patients. Patients with ESRD treated with lanthanum carbonate up to 2.5–3.8 g/day for up to 2 years have been reported to achieve effective reduction of serum phosphorous level. However, long-term clinical studies documented increased serum lanthanum levels. Therefore, the long-term safety of lanthanum carbonate remains to be established.

Secondary Hyperparathyroidism (HPT)

Secondary HPT is a frequent complication of CKD initiated by the drop in circulating calcitriol and subsequent derangements in calcium and phosphate metabolism. Elevated PTH stimulates osteoclastic activity leading to cortical bone resorption and bone marrow fibrosis. Therefore limiting PTH elevation is an important clinical objective. Treating hyperphosphatemia using phosphate binders and maintaining serum Ca within the normal range and the administration of vitamin D are all helpful strategies in the management of secondary HPT, but they are insufficient to achieve the results required by current clinical standards.

The National Kidney Foundation **Kidney Disease Outcomes Quality Initiative (KDOQI™)** has published guidelines for the treatment of bone disease in CKD. These guidelines set specific goals for the certain clinical parameters, namely iPTH, serum calcium (Ca), serum phosphorus (P), and the Ca x P product.

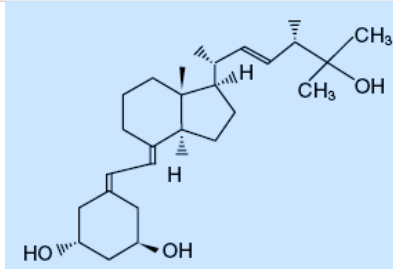
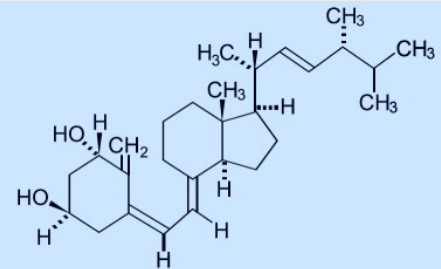
KDOQI™ Targets		
Am J Kidney Dis 42:S1-S202, 2003 (supplement 3)		
iPTH	pg/mL	CKD Stage 3: 35 - 70 CKD Stage 4: 75 - 110 CKD Stage 5: 150 - 300
P	mg/dL	CKD Stage 3: 2.70 – 4.60 CKD Stage 4: 2.70 – 4.60 CKD Stage 5: 3.50 – 5.50
Ca	mg/dL	8.4 – 9.5
Ca x P	(mg/dL) ²	<55
The lower case i in iPTH stands for <i>intact</i> after the laboratory method: intact immunoradiometric assay (IRMA)		

¹⁵ **Safe Rx writing:** Lanthanum carbonate can look like lithium carbonate when poorly handwritten, and the names can sound similar as well. The risk of error may be increased because the dose ranges for the two drugs are similar and may overlap. Furthermore, both products may be administered in divided doses taken with meals as well. Therefore it is good practice to write both brand and generic names as well as what the medication is prescribed for ("for hyperphosphatemia")

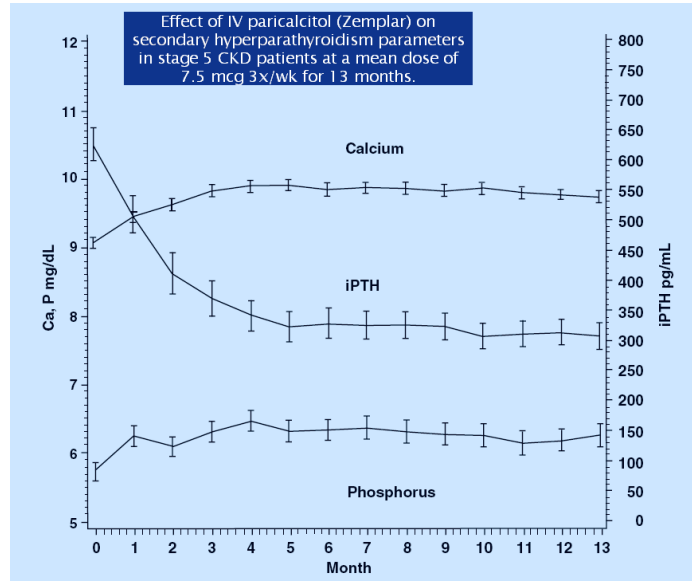
In addition to the traditional therapies mentioned above (phosphate binders and vitamin D and Ca supplement) there are presently two relatively new classes of drugs for the treatment of secondary HPT – vitamin D analogs (or calcitriol analogs) and calcimimetics.

1. Vitamin D analogs

These are molecules structurally similar to calcitriol. They possess the ability to suppress PTH synthesis and release and low tendency to raise serum calcium or phosphorus. However, because they still retain some of the actions of vitamin D, they are contraindicated in patients at risk of developing hypercalcemia or with current evidence of vitamin D toxicity. Currently there are two agents in this class: paricalcitol (Zemlar) and doxercalciferol (Hectorol) depicted in the table below:

	Paricalcitol (Zemlar)	Doxercalciferol (Hectorol)
		
		1 α -(OH)-D ₂ or 1 α -hydroxycalciferol
Indications & usage	Oral: Prevention and treatment of secondary hyperparathyroidism associated with CKD stages 3 and 4 (pre-dialysis). Injectable: Treatment of secondary hyperparathyroidism in patients with CKD on dialysis (stage 5).	Treatment of secondary hyperparathyroidism in patients with CKD stages 3, 4, and 5.
Available as	Oral capsules (1, 2, & 4 mcg) Injectable: 2mcg/mL 1-mL fliptop vial Injectable: 5mcg/mL 1-mL fliptop vial Injectable: 5mcg/mL 2-mL fliptop vial	Oral capsules (0.5 and 2.5 mcg) Injectable solution: 2 ml ampules (2 mcg/mL)
Initial Oral Dosage	Oral: iPTH <500 pg/mL: 1 mcg daily iPTH >500 pg/mL: 2 mcg daily (it may also be given 3x/wk maintaining the same total weekly dose)	Pre-dialysis (stages 3 & 4): 1 mcg (PO) once daily. The dose may be increased at 2-week intervals by 0.5 mcg to achieve the target range of iPTH. The maximum oral dose is 3.5 mcg per day. Dialysis (stage 5): 10 mcg PO three times weekly at dialysis (approximately every other day). The initial dose should be adjusted to lower iPTH into the target range. The dose may be increased at 8-week intervals by 2.5 mcg if iPTH is not lowered by 50% and fails to reach the target range. The maximum PO dose is 20 mcg 3x/wk at dialysis (total=60 mcg/wk). Treatment is stopped if iPTH falls <100 pg/mL and restarted one week later at a dose that is at least 2.5 mcg lower than the previous dose.
Initial IV Dosage	Injectable: 0.04 – 0.1 mcg/kg as iv bolus 3x/wk given during dialysis. . Dose is adjusted based on iPTH level (target 150 – 300 pg/mL)	Dialysis (stage 5): 4 mcg iv bolus every other day or 3x/wk (given at end of dialysis). Dose is adjusted based on iPTH level (target 150 – 300 pg/mL). Maximum=18 mcg/wk

The graph below illustrates the long term therapeutic effects of these agents:



2. Calcimimetics

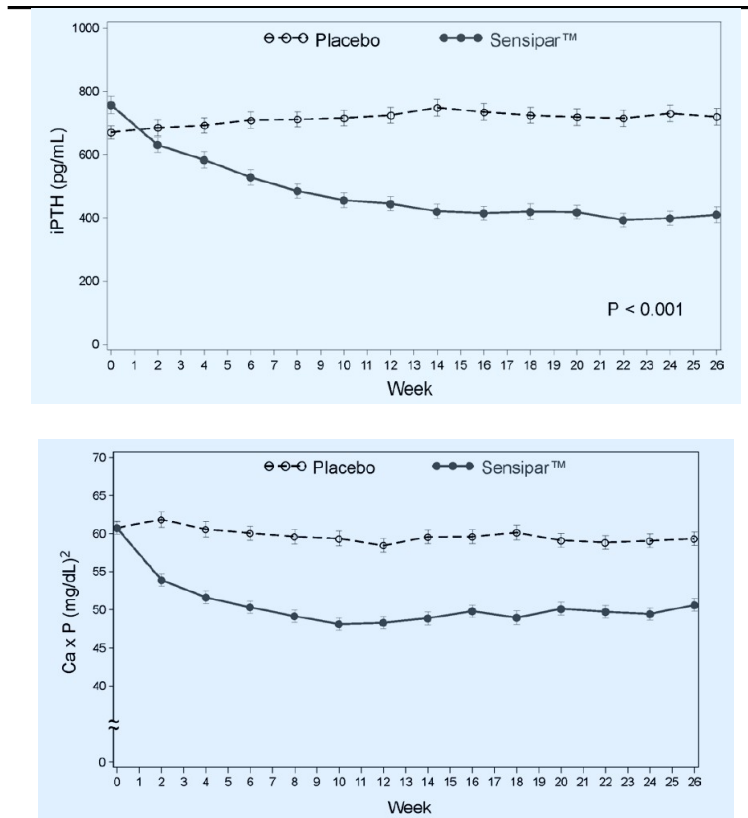
Calcimimetics suppress PTH secretion by enhancing the sensitivity of the Ca⁺⁺ receptors of parathyroid cells to extracellular ionized calcium acting similarly to allosteric modulators of enzyme activity.

Cinacalcet (Sensipar®) is the first calcimimetic agent approved by the FDA (March 2004) for treatment of secondary hyperparathyroidism in dialysis patients.

<p>Cinacalcet (Sensipar®)</p>	
<p>Indication and Usage</p>	<ol style="list-style-type: none"> 1. Treatment of secondary hyperparathyroidism in patients with CKD on dialysis. 2. Treatment of hypercalcemia in patients with parathyroid carcinoma
<p>Available as:</p>	<p>Oral tablets (30, 60, and 90 mg)</p>
<p>Initial dose for CKD</p>	<p>30 mg once daily. Dose is adjusted every 2-4 weeks based on iPTH level (target 150 – 300 pg/mL). Maximum=180 mcg/day</p>

The graphs below show the data from the phase 3 clinical trials. After 6 months of treatment the iPTH level was reduced by about 50% (from a mean of over 700 pg/mL) while at the same time the mean Ca x P value was reduced significantly from 61 to 52 (mg/dL)² These reductions in iPTH and Ca x P were maintained for up to 12 months of treatment. There was a small but significant decrease in serum Ca. Since cinacalcet lowers serum Ca patients should be carefully monitored for the

occurrence of hypocalcemia. Potential manifestations of hypocalcemia include paresthesias, myalgias, cramping, tetany, and convulsions. Treatment should not be started in patients with serum Ca <8.4 mg/dL, and patients at risk of developing hypocalcemia while on cinacalcet may be given Ca containing phosphate binders and vitamin D supplement to maintain their serum Ca between 8.4 and 9.5 mg/dL.



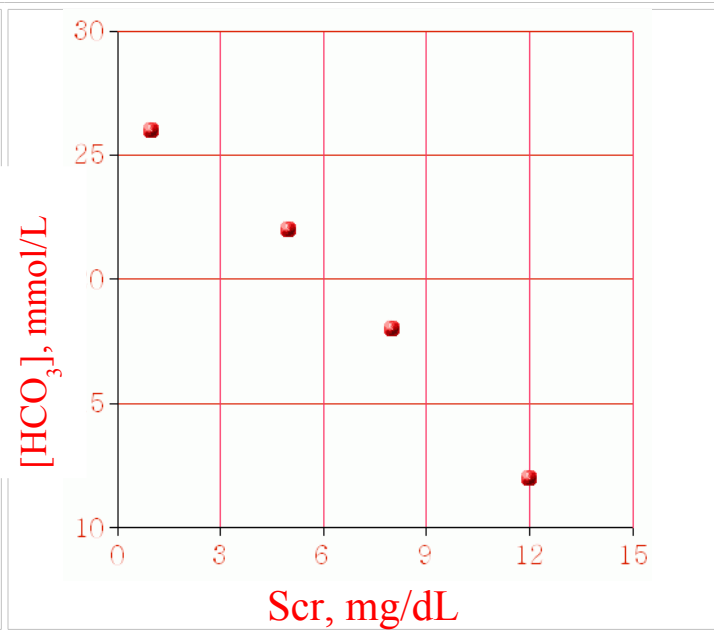
Chronic Metabolic Acidosis

In an average healthy individual, the non-volatile (fixed) acid production in the course of normal cell metabolism is approximately 1 mEq/kg/day. Normally, **2/3** of this metabolic acid load is excreted in the urine in the form ammonium (NH_4^+) and the remainder in the form of titratable acids such as H_2PO_4^- . In chronic renal disease the ability of each of the remaining, viable nephrons to excrete H^+ in the form of NH_4^+ may be increased by as much as four fold as a result of metabolic adaptations in the renal tubule cell induced by the chronic acidosis. This functional adaptation may be sufficient to maintain acid-base balance during the earlier stages of the disease, but as the number of functioning nephrons dwindles, H^+ accumulates, resulting in increasingly more severe metabolic acidosis, reflected in a markedly decreased arterial HCO_3^- level (see Fig 5 below). Excess H^+ are partly buffered by bone alkali (“skeletal buffering”), a process that promotes bone demineralization and contributes to the development of renal bone disease. Patients with chronic renal failure often receive alkali therapy in the form of sodium bicarbonate (NaHCO_3) (usual dose: 650 mg - 1950 mg 3 times daily). It should be

noted that the effect of this treatment (oral alkalization) is blunted by the co-administration of drugs that inhibit gastric acid secretion such as the proton-pump inhibitors (PPIs) like omeprazole (Prilosec) and pantoprazole (Protonix).

Fig 5

Progressive development of metabolic acidosis in chronic renal failure. As metabolic acid is neutralized, the buffering reserve of body fluids is gradually depleted as reflected in the decline of bicarbonate concentration in arterial blood. A state of chronic metabolic acidosis develops.



Anemia of Chronic Kidney Disease (CKD)

The normally kidney is responsible for the synthesis of *erythropoietin*, a peptide hormone which stimulates the proliferation and differentiation of red blood cells in bone marrow. Erythropoietin production increases above baseline whenever there is a decline in O₂ delivery to the kidneys due to reduced O₂ content in arterial blood as occurs following hemorrhage or ascent to high altitude. As kidney disease progresses erythropoietin production declines until it falls below a critical level. CKD patients become anemic mainly due to erythropoietin deficiency which results in a kind of anemia described as normochromic, normocytic anemia. Before the advent of human recombinant erythropoietin therapy, there was an inverse relationship between serum creatinine (an indirect measure of kidney damage) and blood hematocrit (an indirect measure of Hb level) as shown in figure 7:

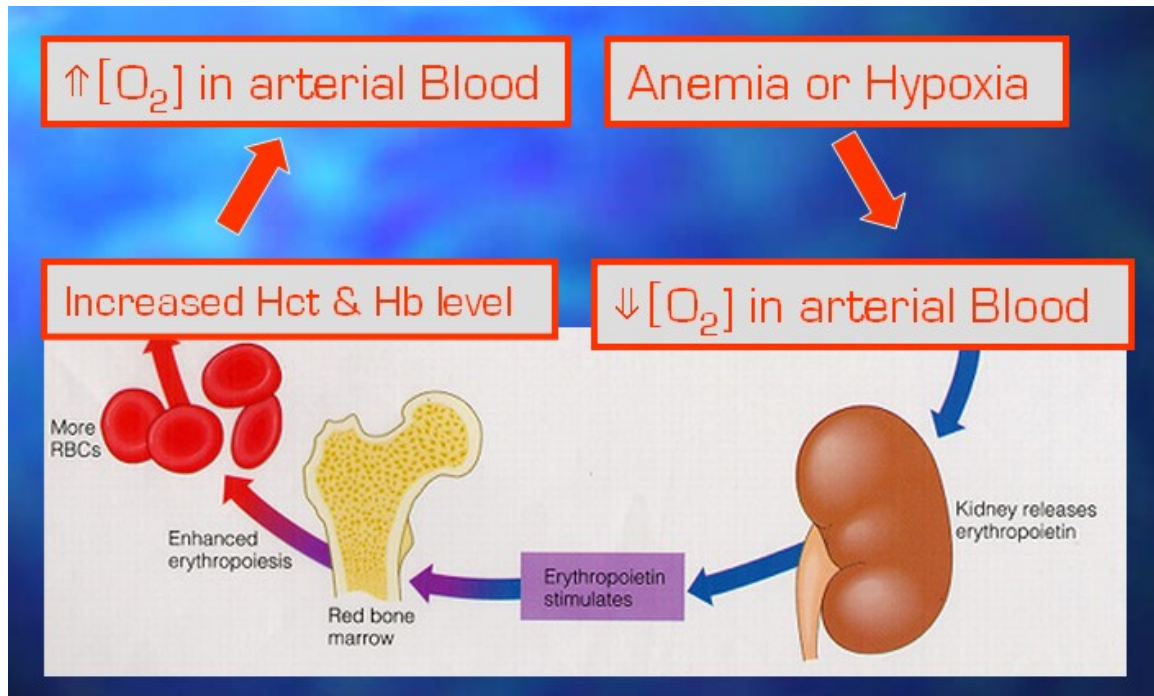
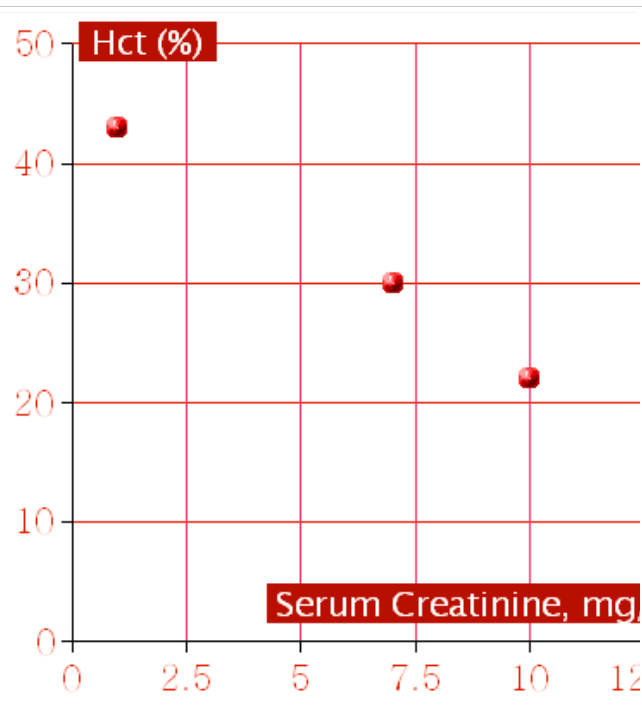


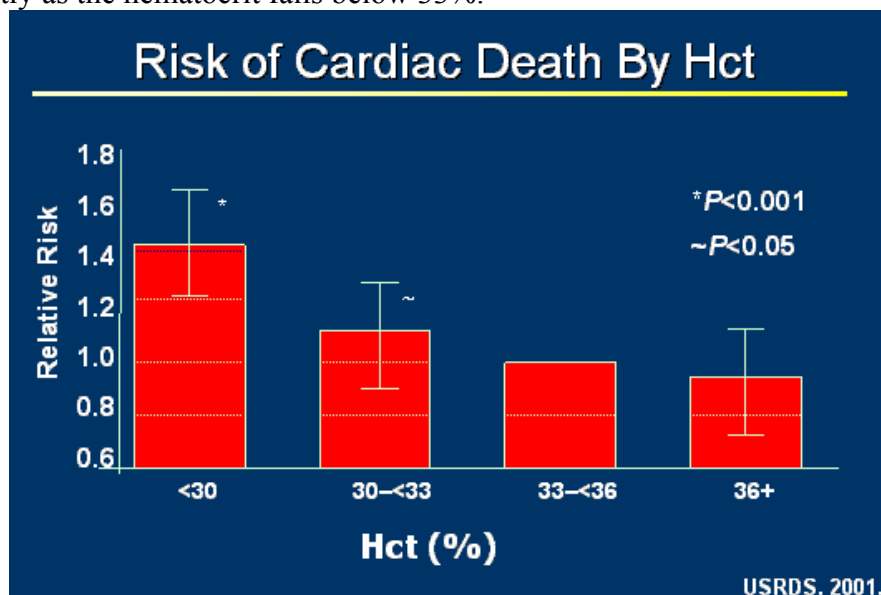
Fig. 7
 With advancing renal disease, renal erythropoietin production becomes insufficient to sustain an adequate rate of erythropoiesis, hence the progressive decline in hematocrit. This decline can be prevented by the administration of exogenous erythropoiesis-stimulating agent such epoetin alfa.



Anemia can have a dramatic impact on cardiovascular health and the quality of life of CKD patients:

Impact of Anemia in Patients with CKD	
Cardiovascular Effects	Quality of Life Effects
<ul style="list-style-type: none"> • Left ventricular hypertrophy (LVH) • Congestive Heart Failure (CHF) • Angina • Increased risk for stroke • Increased risk of morbidity & mortality 	<ul style="list-style-type: none"> • Reduced aerobic capacity • Reduced cognition • Low overall well being

As illustrated in the graph below, the risk of death due to a cardiac event increases significantly as the hematocrit falls below 33%.



For this reason, CKD patients with hematocrit < 33% or Hb<11 g/dL should receive treatment with an erythropoiesis-stimulating agent (ESA) such as epoetin alfa (EPOGEN[®], PROCRIT[®]) and darbepoetin alfa (ARANESP[®]).

The National Kidney Foundation K/DOQI work groups have issued detailed guidelines concerning the evaluation and treatment of anemia in CKD and have recently revised the target Hb levels for CKD patients and gave specific advice on the dosing of epoetin alfa and similar ESAs as well as the monitoring of the response to this treatment:

http://www.kidney.org/professionals/kdoqi/guidelines/doqi_uptoc.html#an

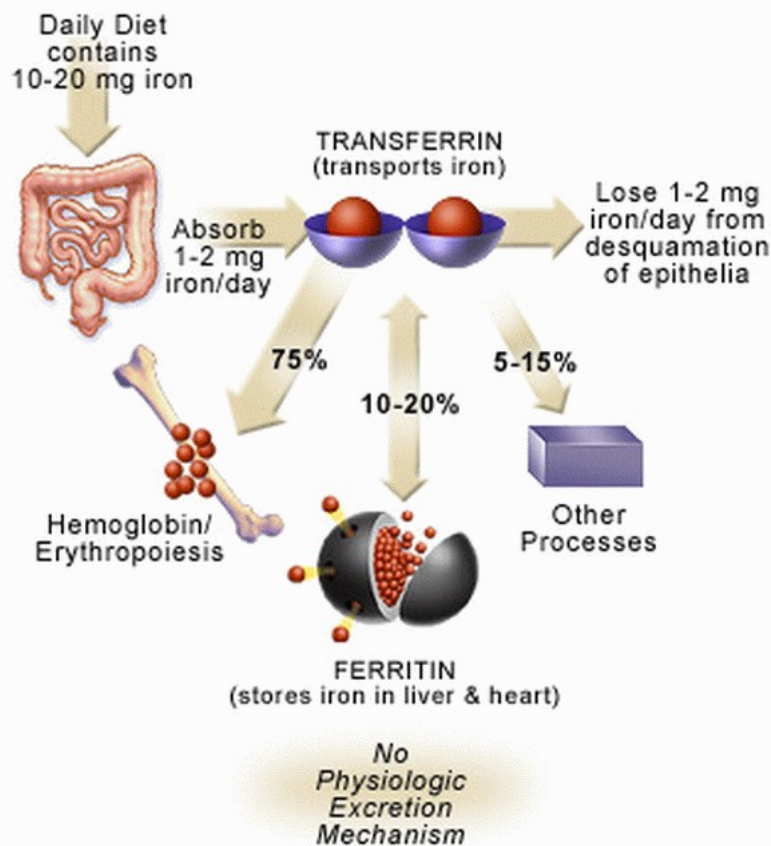
Target Hemoglobin Concentration

The recommended target Hb level is 11 – 12 g/dL corresponding to a hematocrit of 33% – 36%. It is recommended that epoetin alfa be given subcutaneously at an initial dose of 80-120 units per kg per week in divided doses (for example 2000 units three times per week or 3000 units twice per week). Alternatively, the intravenous route may be used in hemodialysis patients, in which case the dose should be raised by 50% (for example 3000

units 3x/week)¹⁶. The rate of rise of hemoglobin (Hb) level should be closely monitored to avoid rapid increases in hematocrit and the development of hypertension. The epoetin dose should be adjusted to achieve a gradual rise in Hb and reach the target Hb level in 2 to 3 months. The rise of Hb concentration should be between 0.2 and 0.5 g/dL per week.

Iron Stores:

During epoetin treatment, a special attention must be paid to the patient's iron stores¹⁷. Iron deficiency is the most common cause of "resistance to epoetin therapy". Normally, about 70% of iron is found in the circulating erythrocytes and approximately 20% of iron is stored as ferritin, mainly in the liver. Much smaller amounts of iron are associated with myoglobin, certain enzymes (e.g. cytochromes, catalase, peroxidase), and other proteins. Fig 9 shows the normal turnover of iron.



Transferrin saturation should be maintained $\geq 20\%$ to sustain the increased rate of erythropoiesis. This may require the administration of intravenous iron product or an oral iron product. In order to replenish the iron stores via the intravenous route, the total body

¹⁶ Despite its low bioavailability (25%), subcutaneous epoetin is preferable to the IV route because it provides a more prolonged ($t_{1/2} = 22$ hours) stimulation of erythroid precursors and a better hematocrit response.

¹⁷ Normal values: serum iron = 70 - 170 for males and 60 - 160 mcg/dL for females; total iron binding capacity (TIBC) = 240 - 440 mcg/dL; serum ferritin = 12 - 150 ng/mL; transferrin saturation = 20 - 50%. Transferrin or transferrin saturation = serum iron / TIBC.

iron deficit must first be estimated based on the patient's body weight and hemoglobin concentration (more about IV iron in the table below).

Parenteral Iron Supplementation

Available Products:

- ▶ INFeD[®] (iron dextran)(only product approved for both IV & IM).
- ▶ Dexferrum (iron dextran).
- ▶ Ferrlecit[®] (Na ferric gluconate complex).
- ▶ Venofer[®] (iron sucrose or iron saccharate complex).

Indications:

- ▶ Iron deficiency anemia, particularly in patients with end-stage renal disease undergoing hemodialysis and receiving epoetin therapy.
- ▶ Iron deficiency in patients for whom oral iron supplementation is ineffective.
- ▶ Iron replacement following significant blood loss.

Calculation of total iron deficit for adult patients:

Total iron deficit may be estimated using one of the following equations (note: Hb_t = target Hb level; Hb_o = observed or actual Hb level; Bwt = body weight; for obese pts, use lean body wt.)

$$\text{Total Dose (mg)} = 50 \{ 0.0442 \text{ Bwt} (\text{Hb}_t - \text{Hb}_o) + (0.26 \text{ Bwt}) \}$$

$$\text{Total Dose (mg)} \approx 2.4 \text{ Bwt} (15 - \text{Hb}_o) + 500$$

Most adult patients require a cumulative dose of elemental Fe of at least one gram.

Contraindications and Precautions:

- ▶ Parenteral iron supplementation is ineffective in aplastic or hypoplastic anemia and acute leukemia.
 - ▶ Parenteral iron supplementation is contraindicated in early pregnancy, in patients with liver disease or acute renal failure.
 - ▶ IV iron products must be used with caution to minimize acute adverse reactions. An anaphylaxis management kit should be at hand.
 - ▶ Conservative estimates of iron deficit should be used to avoid *iron overload*.
 - ▶ Measures of iron status (ferritin, total iron binding capacity, & transferrin saturation) and red blood cell indices must be checked periodically to reevaluate the patient's need for additional iron supplementation.
-

Oral iron is available as ferrous sulfate, gluconate, or fumarate. The usual adult dose ranges from 38 to 65 mg of elemental iron two or three times daily. Iron supplement should be taken on empty stomach and should be separated by at least 2 hours from antacids, phosphate binders and other drugs that tend to raise stomach pH.

Renal Drug Disposition

An important aspect of renal function is the elimination of foreign chemicals (*xenobiotics*), including pharmacological agents and their metabolites. The liver and the kidneys constitute an integrated drug disposal system. In many cases, the drug is first altered chemically by drug metabolizing enzymes primarily in the liver, and the resulting polar water soluble metabolite is then excreted in the urine. The majority of drugs are eliminated as inactive metabolites, but a large number of drugs are excreted in the urine unchanged (e.g., atenolol, gabapentin, digoxin, vancomycin) or as active metabolites (e.g., ACE inhibitors, azathioprine, metoprolol). Table 7 lists some examples.

Three basic renal processes determine the rate of drug excretion in the urine - glomerular filtration, active secretion by the tubule cells, and passive reabsorption. The contribution of filtration to drug elimination is a function of the glomerular filtration rate (**GFR**), the plasma concentration of the unbound (filterable) drug, and the extent of passive reabsorption of the drug following its filtration. Glomerular filtration does not contribute significantly to the elimination of drugs that are highly protein bound such as the non-steroidal antiinflammatory drugs (NSAIDs), some penicillins, and most diuretics. The same is also true for drugs that have a large molecular size (e.g., certain dextrans), particularly those bearing negative charges (e.g., heparin) because they are unable to freely cross the glomerular filtration barrier.

Active secretion results in the net transfer of the drug from the peritubular capillaries into the tubule lumen (see figure below). It is a much more efficient mechanism of drug elimination than glomerular filtration particularly for drugs that are highly protein bound. Approximately 80% of the renal plasma flow (**RPF**) is exposed to the secretory sites, whereas only about 20% of the RPF is filtered. There are two independent secretory systems, both of which are located in the proximal tubule. The **organic anion transport system** is responsible for secreting acidic substances such as aspirin, penicillin, and furosemide (Table 8A). The second (the organic cation transport system) specializes in the secretion of basic (cationic) compounds such as ephedrine, epinephrine, cimetidine, and morphine (Table 8B).

The renal clearance of a particular drug depends on how it is *handled* by the kidney. A drug that is freely filtered, but neither secreted nor reabsorbed (e.g., gallamine, vitamin B₁₂, inulin, iothalamate, etc.) is cleared at a rate that is equivalent to GFR. A freely filterable, nonpolar (lipophilic) drug¹⁸ will be mostly reabsorbed, and its clearance will be equal to the urine flow rate. The clearance of a drug that is completely removed (by active secretion) during a single pass through the kidney will equal the RPF; familiar examples include penicillin, p-aminohippurate (PAH), and iodopyracet (Diodrast).

¹⁸ Such a drug will equilibrate passively between plasma and urine.

Table 7A

Drugs excreted mostly unchanged by the kidney

Acyclovir, amantadine, aminoglycosides, amphetamine, ampicillin, atenolol, carbapenems, carbenicillin, chlorothiazide, cimetidine, clonidine, cyanocobalamin (vitamin B₁₂), digoxin, furosemide, gabapentin, methotrexate, neostigmine, oxytetracycline, penicillin G, propantheline, pyridostigmine, and vancomycin.

Table 7B

Drugs whose active metabolites are excreted mainly by the kidney

Adriamycin, acebutolol, azathioprine, captopril, ceftazidime, chlordiazepoxide, chloroquine, ciprofloxacin, cyclophosphamide, cytarabine, diazepam, digitoxin, disopyramide, enalapril, flecainide, meperidine metoprolol, methyl dopa, nitrofurantoin, nitroprusside, primidone, procainamide, propoxyphene, sulfamethoxazole, valproate, and vidarabine.

Table 8A

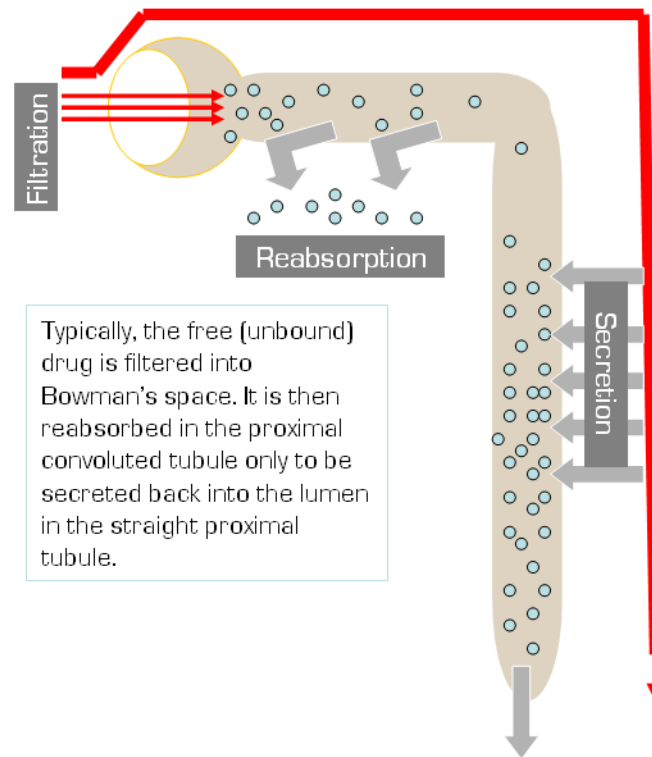
Drugs Secreted by the Organic Acid Transport System

- NSAIDs like salicylates and ketorolac.
- Many penicillins and cephalosporins
- Most loop diuretics and thiazide diuretics
- Acetazolamide, enalaprilat, methotrexate, etc

Table 8B

Drugs Secreted by the Organic Base Transport System

Amiloride, atropine, choline, dopamine, ephedrine, epinephrine, ethambutol, H₂-blockers, morphine, neostigmine, procainamide (& NAPA), pseudoephedrine, quinidine, quinine, trimethoprim, etc.



Drug Dosing in Patients with Renal Insufficiency

Renal insufficiency can markedly alter one or more of the pharmacokinetic parameters of a drug including oral bioavailability, volume of distribution, drug binding to plasma proteins, and most importantly the rates of metabolism and excretion, i.e., drug clearance.. *To minimize drug toxicity and maximize therapeutic benefits*, it is often necessary to adjust drug dosage in proportion to the degree of renal insufficiency.

A drug will most likely require dose adjustment in renal disease if:

1. A substantial fraction ($\geq 50\%$) of the drug dose is normally excreted by the kidney either unchanged or as active (or toxic) metabolites.
2. The drug has a narrow therapeutic window such that drug accumulation cannot be tolerated.
3. The kidney is a major site for the inactivation of the drug. This applies mainly to peptides like insulin, glucagon, PTH, and imipenem.
4. There is a significant drop in the binding of the drug to plasma proteins. For instance, a decrease in the protein binding from 99 to 95% results in a fourfold rise in the unbound, active drug concentration.

Dose adjustment may involve one or a combination of the following measures:

1. Extending the dosing interval.
2. Giving smaller maintenance doses.
3. Administration of a loading dose.
4. Monitoring serum drug levels.

Reduced renal drug excretion prolongs its half life ($t_{1/2}$) as well as the time required for the serum level to reach a steady state (4 times $t_{1/2}$). Therefore, whenever it is clinically desirable to rapidly achieve a therapeutic steady state level a loading dose should administered.

To maintain a therapeutic level and, at the same time, avoid drug accumulation and toxicity in a patient with reduced renal function, the clinician must consider reducing the size of the maintenance dose or the dosing frequency or both. In general, this reduction should be proportional to the degree of renal impairment (see below), but should also take into account adaptive or compensatory changes in the metabolism and excretion of the drug through non-renal routes.

The **maintenance dose reduction method** is used whenever a more constant (less oscillating) serum drug level is therapeutically preferable (e.g., β -lactam antibiotics), whereas the **interval extension method** is used for drugs for which a constant serum level is either unnecessary (e. g., vigabatrin) or undesirable (e.g., aminoglycoside antibiotics)¹⁹. This method is also used for drugs that normally have short elimination $t_{1/2}$. However, a combination of the two methods is often used. In addition, for a drug whose therapeutic serum level range is known and routinely measured, dosage adjustment is often guided by monitoring the serum drug level and the patient's response in terms of the therapeutic benefit and adverse drug reactions (toxicity).

Clinical Evaluation of Renal Function

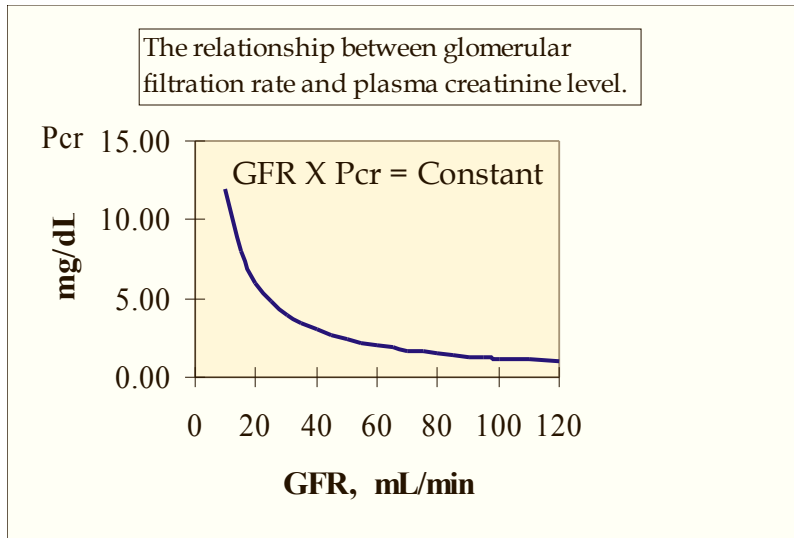
In the vast majority of clinical situations, the GFR is an accurate measure of overall renal function, particularly the ability of the kidney to excrete metabolic waste products, drugs, and drug metabolites. In a healthy, young adult male the GFR is about 125 mL/min (70-75 mL.min⁻¹.m⁻² BSA). This rate is maintained until about the age of 45 years, after which it declines by 10-15 mL/min per decade. The normal GFR of the adult female is approximately 85-90% of that of the male.

In clinical practice, an approximate value of the GFR may be obtained either by direct determination or indirect estimation of the endogenous creatinine clearance (CL_{cr}). Creatinine is derived from the metabolism of muscle creatine. The production rate of creatinine is dependent on muscle mass and the metabolic rate of the individual²⁰. Under steady state conditions creatinine production and excretion are equal. Since creatinine is excreted primarily through glomerular filtration, its plasma level (P_{cr}) is determined by the GFR according to the relationship:

$$\text{GFR} \times P_{cr} = \text{constant}$$

¹⁹ Aminoglycosides are nephrotoxic and should be avoided in renal patients.

²⁰ Normally creatinine production ranges from 80 to 280 $\mu\text{moles.kg}^{-1}.\text{day}^{-1}$



It is clear from this relationship that as the GFR declines the P_{cr} rises and vice versa.

To determine the CL_{cr} *directly*, urine is collected over a known time interval (usually 8, 12, or 24 hrs), its volume is measured, and the urine flow rate (V , mL/min) is calculated. Urine and plasma creatinine concentrations (U_{cr} and P_{cr}) are measured, and the clearance is then calculated as follows:

$$CL_{cr} = \frac{VU_{cr}}{P_{cr}}$$

Because this process is time consuming, clinicians are often content with an indirect estimate of CL_{cr} obtained using one of several empirical equations such as Cockcroft's:

$$CL_{cr} (mL / min) = \frac{BW (140 - A)}{72 P_{cr}}$$

Where: A = age (years); BW = body weight (kilograms); P_{cr} = plasma or serum creatinine level (mg/dL). For female patients the value obtained using the above equation is multiplied by 0.85 to take into account the lower muscle mass in the female body. Such estimates of CL_{cr} are valid only when the $P_{cr} < 5$ mg/dL

The "normal range" of P_{cr} is 0.6 - 1.2 mg/dL (approximately 50 – 110 micromoles/L), but the P_{cr} value should be interpreted in the context of the patient's conditions. Consider, for example, two patients having the same P_{cr} of 1.0 mg/dL; patient A is a 60 years old male weighing 85 kg, and patient B is an 85 years old female weighing 60 kg. Using the above equation, the estimated CL_{cr} values are 94 and 39 mL/min respectively. Thus, one must not rely solely on the fact that the P_{cr} is within "the normal range". Elderly, frail, malnourished, or cirrhotic patients may show "normal" P_{cr} levels despite markedly reduced GFR. Elderly patients with significantly reduced muscle mass (e.g., atrophy due to a neurological disorder) may have extremely low P_{cr} despite having poor renal function. Using the **Cockcroft equation** in these patients leads to a gross over-estimate of GFR. Better estimates of GFR in these patients can be obtained using the **Sanaka equations**, which make use of the patient's serum albumin level:

$$\text{CLcr} (\text{♂}) = \text{BW} (19 \text{ Alb} + 32) / 100 \text{ P}_{\text{cr}} \quad \text{CLcr} (\text{♀}) = \text{BW} (13 \text{ Alb} + 29) / 100 \text{ P}_{\text{cr}}$$

Where: BW = actual body weight in kg, and Alb = albumin level (g / dL).

Starting from a baseline of < 2.7 mg/dL, an increase in P_{cr} by ≥ 0.1 mg/dL per day for ≥ 3 days strongly suggests a developing acute renal failure (ARF). The latter afflicts 2-5% of patients during their hospital stay. This demonstrates the need for monitoring daily the P_{cr} values of critically ill patients.

For patients with chronic renal disease, a plot of $1/\text{P}_{\text{cr}}$ vs time is a useful tool to follow long-term changes in renal function.