Paul F. Shanley, M.D. (January 2011)

Renal failure

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1. Normal renal functions and consequences of renal failure

Renal failure is the inability of the kidney to perform its functions in the maintenance of systemic homeostasis. The normal renal functions in the maintenance of systemic homeostasis and the consequences of renal failure are the following:

Normal Renal Functions	**Consequences of Renal Failure**
Fluid and electrolyte balance (net excretion of K^+, Na^+, water and PO_4^-)	Hyperkalemia Fluid retention with edema and hypertension Hyperphosphatemia and consequent hypocalcemia
pH homeostasis (net acid excretion)	Metabolic acidosis
Excretion of nitrogenous wastes	Azotemia (High BUN and serum creatinine) Uremia (Systemic poisoning; "urine in the blood")
Endocrine functions • Erythropoietin • Vitamin D activation • Renin production	 Anemia Hypocalcemia

The common denominator underlying all causes of renal failure is a severe decrease in the glomerular filtration rate (GFR). Although there is a large reserve of renal function, once there is loss of more than 75% of GFR a characteristic constellation of systemic findings develops. Salt and water retention results in signs of fluid overload such as hypertension and edema. Hyperkalemia from retention of potassium may result in life-threatening cardiac arrhythmias. Failure to produce erythropoietin causes decreased bone marrow production of RBC with consequent anemia.

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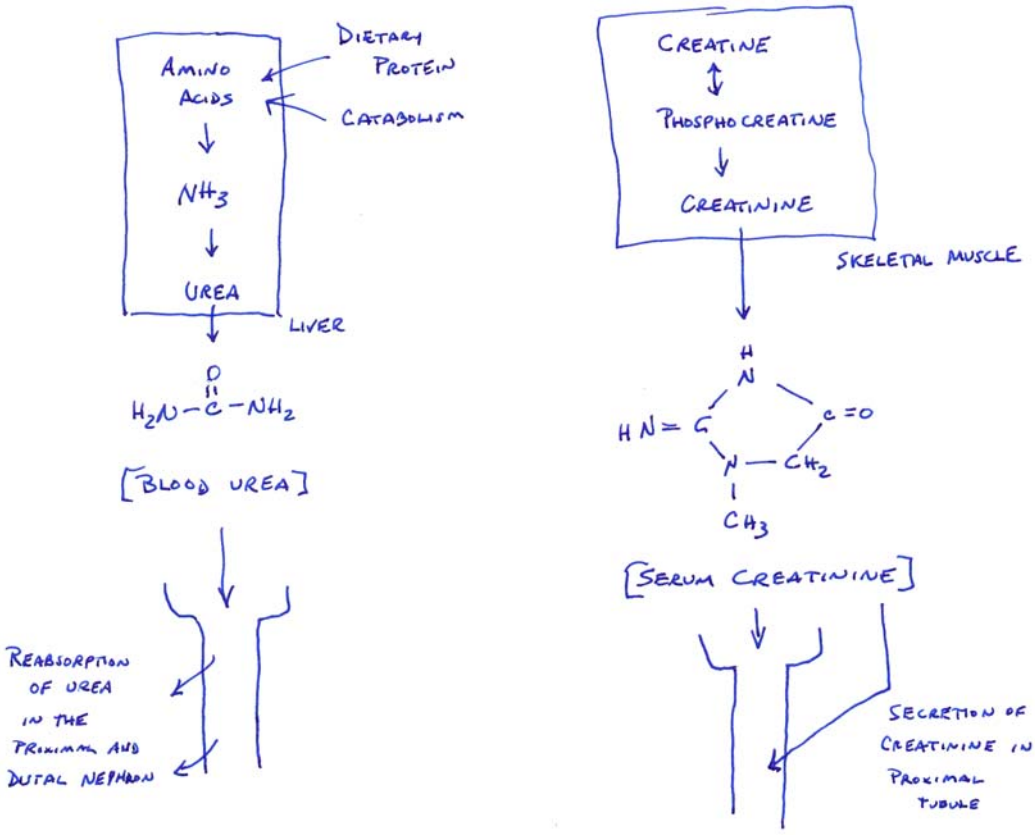
a.) Monitoring of renal function with serum creatinine, BUN and urine output

In clinical practice, the function of the kidney is routinely monitored by measurement of the serum creatinine and the blood urea nitrogen (BUN). Creatinine and urea are both primarily excreted by the kidney in a GFR-dependent fashion and they accumulate in the blood along with other nitrogenous waste products (**azotemia**) when the GFR falls. Creatinine is a metabolite of creatine and its production is dependent on muscle mass and thus, the serum creatinine at any level of GFR differs for different people depending on body constitution. At steady state, the GFR can be reasonably estimated by the creatinine clearance (though creatinine is not an ideal marker in this sense because it is secreted into the nephron and this secretion increases at very low GFR making creatinine clearance overestimate GFR in patients with severe renal failure).

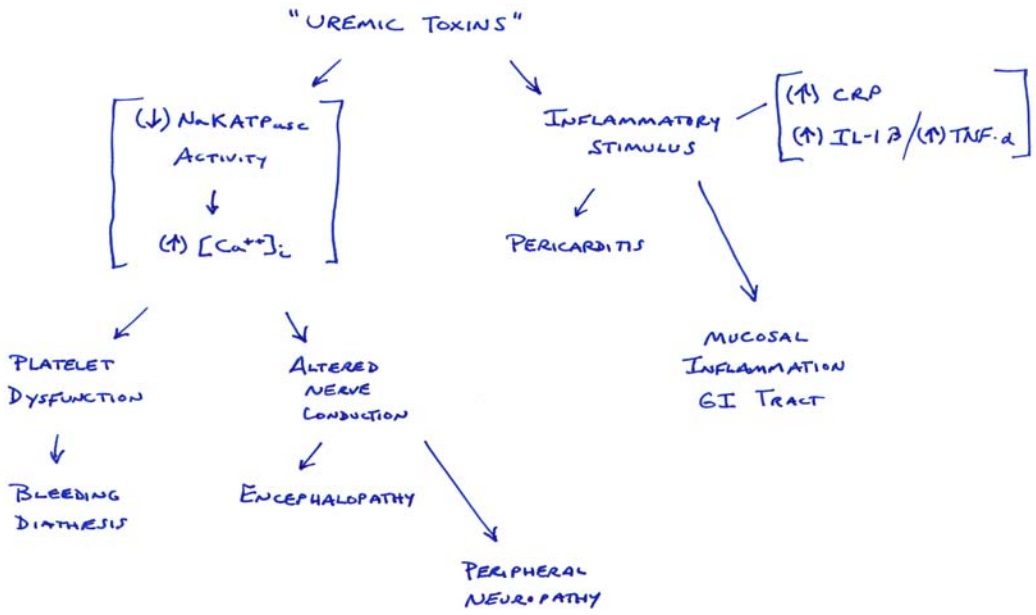
BUN also rises with a decrease in GFR. Urea is formed during protein metabolism and its production is related to dietary protein and catabolic rate. Urea is significantly reabsorbed in the nephron and is unsuitable for estimating GFR. The reabsorption of urea is variable, increasing along with sodium reabsorption as urine flow rate decreases (e.g., in ECF volume contraction).



A fall in urine output is often a feature of renal failure. **Oliguria** is a urine output of less than 400 cc/day in an adult and **anuria** is complete or near total lack of urine output. However, since urine output depends not only on the GFR but also on the tubular handing of solute and water, it is possible to have a low GFR and normal or even high urine output if tubular reabsorption is defective ("non-oliguric" renal failure).

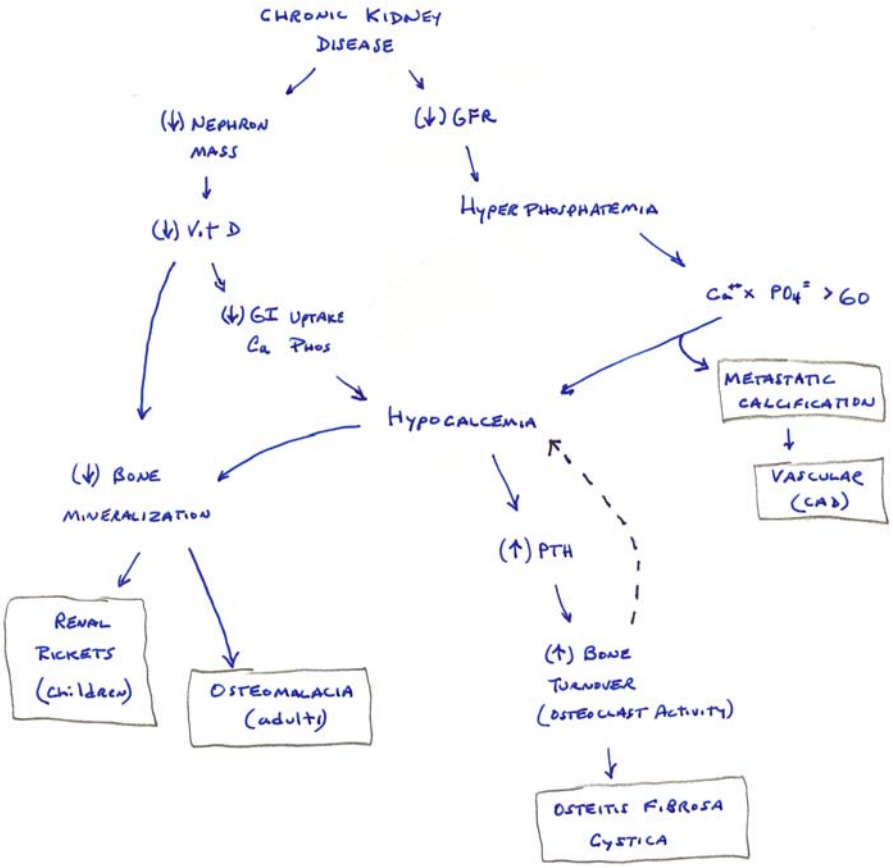
b.) Uremia

Severe renal failure (GFR < 10-15 cc/min) is associated with a syndrome of systemic poisoning termed "**uremia."** This results from accumulation of toxic substances due to failure of excretion of nitrogenous waste products. The word literally means "urine in the blood." The exact toxin(s) have not been identified, though there is general consensus that it is not urea per se even though the severity of the clinical findings correlates well with the BUN. The toxins are breakdown products of protein and a low protein diet is protective against symptoms in the patient with very low GFR. The constellation of findings that constitute uremia is given in Robbins 8th edition (*Table 20-1, pg 908*). Two types of symptoms dominate the syndrome, inflammatory damage in various organs and findings that can be linked to abnormal cation transport across cell membranes as summarized below.



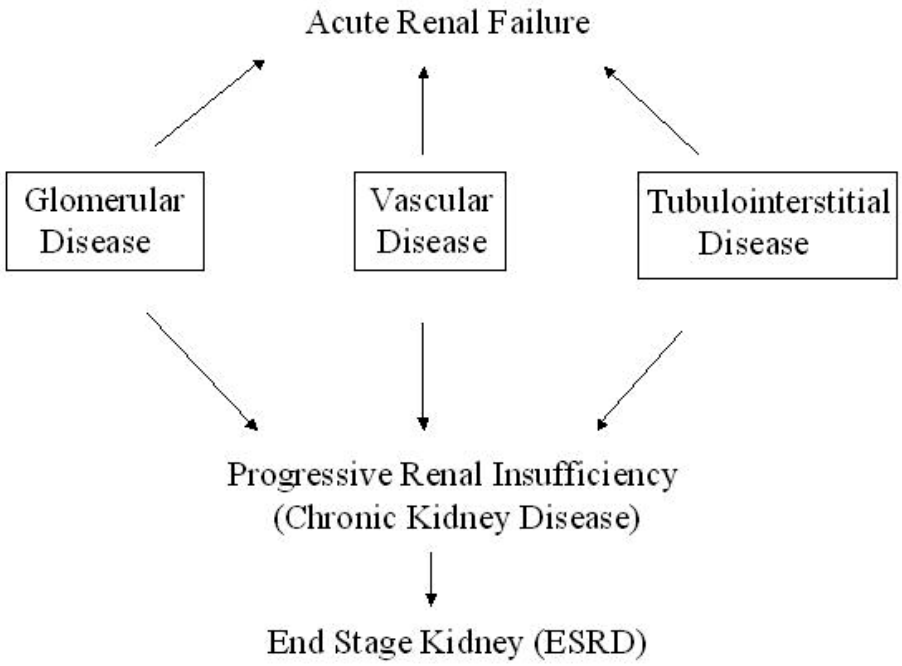
c.) Hypocalcemia and renal osteodystrophy

Phosphate retention results in precipitation of calcium-phosphate in soft tissues. The effects of hyperphosphatemia along with failure of vitamin D activation cause hypocalcemia. In the long run, the abnormalities in calcium, phosphate, vitamin D and the induced secondary hyperparathyroidism cause various bone abnormalities encompassed in the term "renal osteodystrophy."



2. Targets of injury: clinicopathologic correlations

Renal failure may occur acutely (days to weeks) or progressively over a prolonged time frame (months to years). Damage to any of the anatomical compartments of the kidney (glomeruli, tubules, interstitium or blood vessels) can cause either acute or chronic damage depending on the specific etiology and severity of the insult (see figure below). The anatomical compartment sustaining the primary injury is easily identified histologically in the early stages of injury and the specific target is often reflected in the type of the clinical presentation (e.g., hematuria or proteinuria syndromes in glomerulonephritis).



3. Acute renal failure

Acute renal failure (ARF) results from insults that cause damage or dysfunction to most of the nephrons all at once. Obviously when glomerular filtration collapses suddenly the patient is no longer in steady state and the rise in creatinine and BUN will lag behind and not reflect the actual severity of the renal failure. A daily rise in serum creatinine of 1-2 mg/dl is expected with severe renal shutdown.

The injuries causing ARF are often potentially reversible to some degree and thus prompt recognition of the cause is important. It is standard to divide the causes of acute renal failure into those that are a failure of kidney perfusion ("**prerenal**"), those that are due to damage to the kidney parenchyma itself ("**intrinsic renal**") and those that are due to urinary outflow tract obstruction ("**post-renal**"). It is usual in a patient with renal failure to obtain a renal ultrasound early to rule out urinary tract obstruction and to help with the decision about whether the renal failure is acute or chronic. In chronic renal failure the kidneys will likely be small and show increased echogenicity (though some types of chronic renal damage are less likely to result in small kidneys, notably diabetic nephropathy and amyloidosis) and it should be kept in mind that acute injury may be superimposed on chronic damage in some patients).

The most common cause of acute renal failure is hypoperfusion of the kidney as might occur in shock. Hypoperfusion initially causes a fall in glomerular hydrostatic pressure. Since glomerular filtration is dependent on hydrostatic and oncotic pressure differences across the filtration barrier, lowering of glomerular hydrostatic pressure by hypoperfusion causes a decrease in GFR. This easily reversible type of renal failure is known as "**prerenal azotemia."** With prolonged or severe hypoperfusion there is ischemic injury to the tubules ("**acute tubular necrosis**" or "**ATN**"), which maintains the decrease in GFR for a more prolonged period by various mechanisms. Drugs or toxins can also directly injure renal tubules causing ATN.

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The clinical distinction between prerenal azotemia and ATN is based on the fact that with intact tubules (in prerenal azotemia) the kidney will respond normally to the hypoperfusion by maximally retaining salt and water and thus producing a concentrated urine with very low sodium content. In ATN, the tubular injury precludes normal handling of sodium and the fractional excretion of sodium (FE_{Na}) rises.

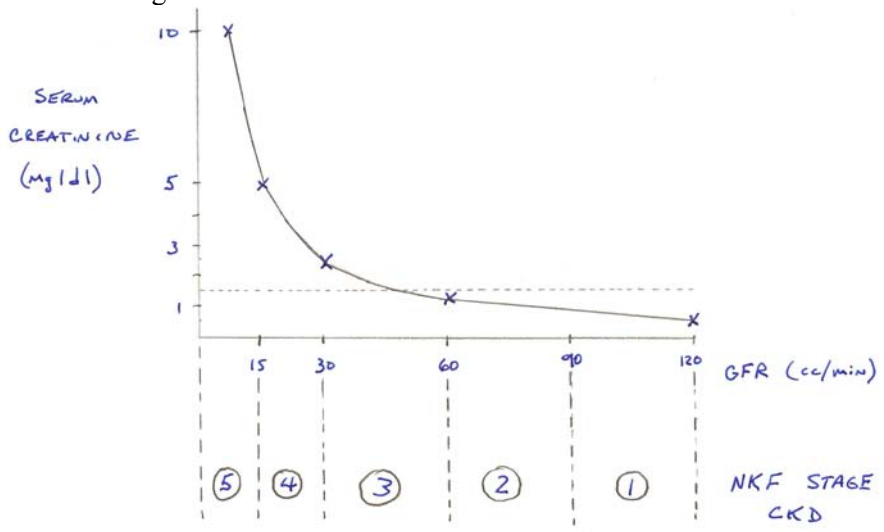
In addition to tubular damage, renal failure may result from injury to other compartments in the kidney (glomeruli, interstitium or blood vessels). The clinical distinction is important because acute injury is often reversible and management of the different types of acute renal failure differ. The site of injury is usually suggested by the clinical setting, urinalysis and laboratory studies (as summarized in the following table) but a renal biopsy is sometimes necessary to determine the cause of the renal failure after hypoperfusion and obstruction are ruled out.

Differential diagnosis of acute renal failure

Category	**Renal Pathology**	**Urine Findings**	**Clinical Features**
Pre-renal Azotemia		$FE_{Na} < 1$ $U_{Na} < 10$ mEq/L $U_{OSM} > 500$ mOsm/kg	Dehydration Hypotension
Intrinsic Renal Damage	Acute Tubular Necrosis (ATN)	$FE_{Na} > 2$ $U_{Na} > 30$ mEq/L $U_{Osm} < 350$ mOsm/kg Renal tubular epithelial cells Muddy brown casts	Hypotension/shock Nephrotoxin
	Glomerulonephritis (esp Crescentic GN)	Proteinuria > ++ Hematuria RBC casts Dysmorphic RBC $\Downarrow FE_{Na} / \Uparrow U_{Osm}$	ANCA Anti-GBM antibodies Hypocomplementemia
	Interstitial Nephritis	$\Uparrow FE_{Na} / \Downarrow U_{Osm}$ Pyuria Eosinophiluria White blood cell casts	Hypersensitivity triad - Fever - Eosinophilia - Rash
	Thrombotic Microangiopathy	Proteinuria Hematuria	Hemolytic Uremic Syndrome (HUS)
	Atheroembolic		Hypocomplementemia Eosinophilia
Post-renal (Obstructive)		$\Downarrow FE_{Na} / \Uparrow U_{Osm}$ (early) $\Uparrow FE_{Na} / \Downarrow U_{Osm}$ (late)	Rule out hydronephrosis early with ultrasound !!

4. Chronic kidney disease

Chronic kidney disease (CKD) refers to deterioration of renal function that occurs over a long time period with low grade but persistent or recurrent injury. Chronic injury ultimately causes renal failure by progressive loss of nephrons and irreversible scarring. The National Kidney Foundation (NKF) has identified 5 stages of severity of CKD depending on estimated GFR. Currently the clinical laboratory will report the estimated GFR as derived from formulas adjusting serum creatinine for a number of patient characteristics. Two examples of such formulas are given below.



$$GFR = \frac{(140 - Age) \times \text{Ideal Body wt (Kg)}}{S_{Cr} \times 72}$$

Cockcroft-Gault

(x 0.85 for women)

$$GFR = 170 \times [S_{Cr}]^{-0.999} \times [Age]^{-0.176} \times [BUN]^{-0.17} \times [Albumin]^{0.318}$$

(x 1.180) if Black

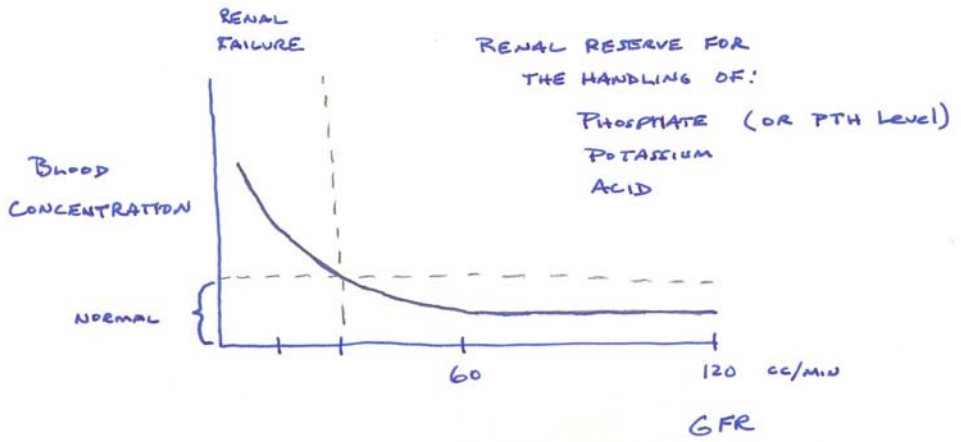
(x 0.762) if Female

MDRD

As seen in the curve above, the relationship of serum creatinine to GFR is not linear and serum creatinine is not sensitive to small decreases in GFR during chronic loss of nephrons. At a steady state the production of the creatinine is constant and the production equals the excretion. Since creatinine is only minimally altered during transit through the tubule, the excretion rate approximately equals the GFR times the plasma concentration. Thus, each time the GFR decreases to one-half its starting level, the plasma concentration doubles. As mentioned above, this estimate breaks down a little at the very lowest GFR levels where tubular secretion of creatinine plays a larger role.

The large renal reserve explains the fact that chronic renal disease can often progress silently through most of its course. The curve below represents the rising serum level of substances that individual nephrons can adjust their handling of in response to decreases in total GFR (such as phosphate, potassium or acid; the curve also represents the rise in parathyroid hormone in response to hypocalcemia of renal failure). In these instances, the plasma levels remain in the normal range until more than 75% of filtration is lost (the point at which individual

nephrons cannot further compensate to maintain normal function). Thus, patients below this level of GFR may begin to exhibit hyperphosphatemia, hyperkalemia and metabolic acidosis.



5. Hyperfiltration and progression of chronic kidney disease (CKD)

In CKD, individual nephrons are completely lost through scaring, but the nephrons that remain at any stage in the progression of chronic renal disease continue to function ("intact nephron hypothesis"). In fact, individual remnant nephrons increase their GFR ("hyperfiltration") and size ("residual nephron hypertrophy") to compensate for the functional deficit resulting from the lost nephrons. Ultimately, the initially adaptive hyperfiltration with its attendant glomerular hypertension proves detrimental to those last functioning nephrons. The mechanism of hyperfiltration is important because inhibiting it and preventing glomerular hypertension prolongs the life of the residual nephrons and delays the need for renal replacement therapy. The initiating mechanism is not completely known but hyperfiltration involves afferent arteriolar dilatation and a relative vasoconstriction of the efferent arteriole involving angiotensin II. The appropriate management is to block this effect with either angiotensin converting enzyme inhibitors (ACEi) or angiotensin II receptor blockers (ARBs).

6. Management of Chronic Renal Failure

a) End Stage Renal Disease (ESRD) statistics and costs [NKF Primer on Kidney Diseases, 4th ed, 2005]

- Approximately 325,000 patients on dialysis and 128,000 with transplants in USA in 2003, ~100,000 of them are new patients for that year.
- The cost for each patient on dialysis is ~ $63K/yr (Medicare pays for ~$53K/patient/yr) and for a transplant is ~$100,000 in the first year, less thereafter. Total Medicare spending is of over $18 billion (2003).

b) Major causes of ESRD (hard to get good numbers):

i) Diabetic nephropathy (probably about 45%)
ii) Hypertensive nephrosclerosis (often listed as the 2nd most common but this is a default diagnosis when cause is unknown; everyone is hypertensive at the time of diagnosis at ESRD)
iii) Chronic glomerular disease
iv) Pyelonephritis and obstructive uropathy
v) Polycystic kidney disease

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c) Therapy for ESRD

i.) Dialysis

- Based on principle of diffusion. Patient's blood equilibrated with dialysis solution across a semi-permeable membrane results in removal of metabolic waste products and normalization of plasma solute concentrations
- Originally developed as a way to get wounded soldiers to survive the acute renal failure of traumatic shock, it is now a long-term therapy for patients with irreversible chronic renal failure.

  Hemodialysis = circulation of patient's blood externally into apparatus where it is equilibrated with dialysis solution

  Peritoneal dialysis = infusion of dialysis solution into peritoneal cavity for equilibration across the patient's peritoneal membrane

- Mortality on dialysis ~ 24% per year (death mostly from cardiovascular disease and infection)

ii) Recombinant Erythropoietin is a major advance to prevent anemia of renal disease

iii) Renal transplantation

- Better quality of life and survival than dialysis
- Organ shortage limits availability (waiting list ~ 3 years nationwide, differs by state (CA is longer))
- Immunologic rejection of allograft mandates lifelong immunosuppression (regimens continually improving)
- Infectious and malignant complications of chronic immunosuppression