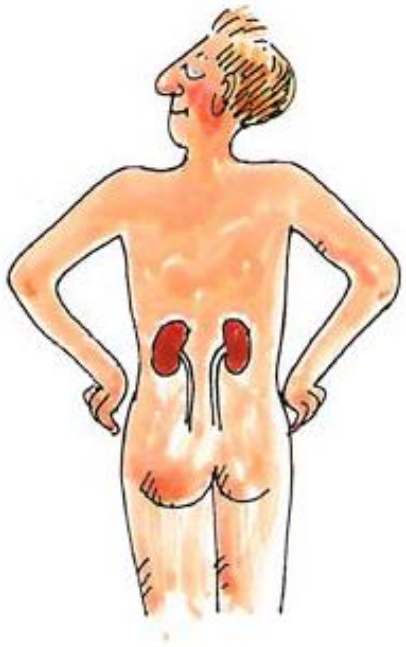
Pathophysiology of kidneys – part II

Acute renal failure (acute kidney injury)

Acute tubular necrosis

Chronic kidney disease

End stage renal disease



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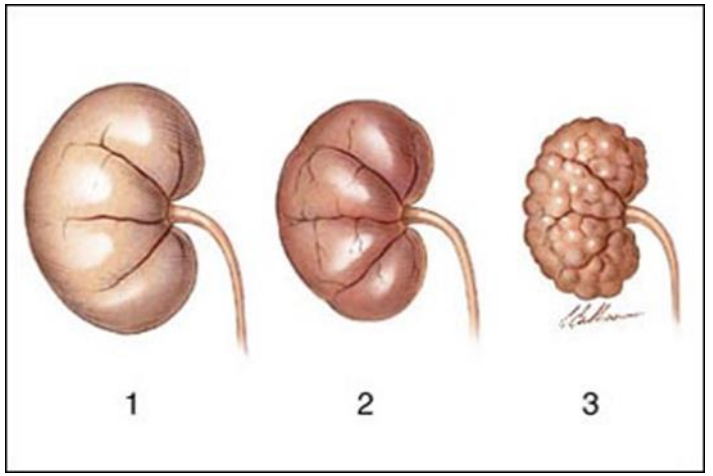
Terminology – renal failure (RF)

- situation when kidneys are not able to
  - a) excrete waste products of protein catabolism (nitrogen-containing compounds) metabolism
  - b) maintain volume and electrolyte homeostasis and AB balance
- under the basal conditions with normal protein (min 0.5g/kg/day) and energy intake
- **azotemia** = increased concentration of non-protein nitrogen-containing compounds
  - creatinine, blood urea nitrogen (BUN)
  - accompanies RF (diagnostic sign) and is a feature of uremic syndrome
- **uremia** („urine in blood“) = cluster of clinical abnormalities (uremic syndrome) due to RF
- causes of RF:
  - suddenly in subject without pre-existing renal pathology = **acute RF** (ARF, situation 1 in figure below)
    - **acute kidney injury** (AKI) is a synonym
  - as a consequence of a chronic renal disease with progressive loss of renal function = chronic RF (situation 3 in figure below)
    - **end-stage renal disease** (ESRD) is a synonym
- etiology
  - 1) pre-renal
  - 2) renal
  - 3) post-renal
- 70% patients with ARF/AKI develop **acute tubular necrosis**



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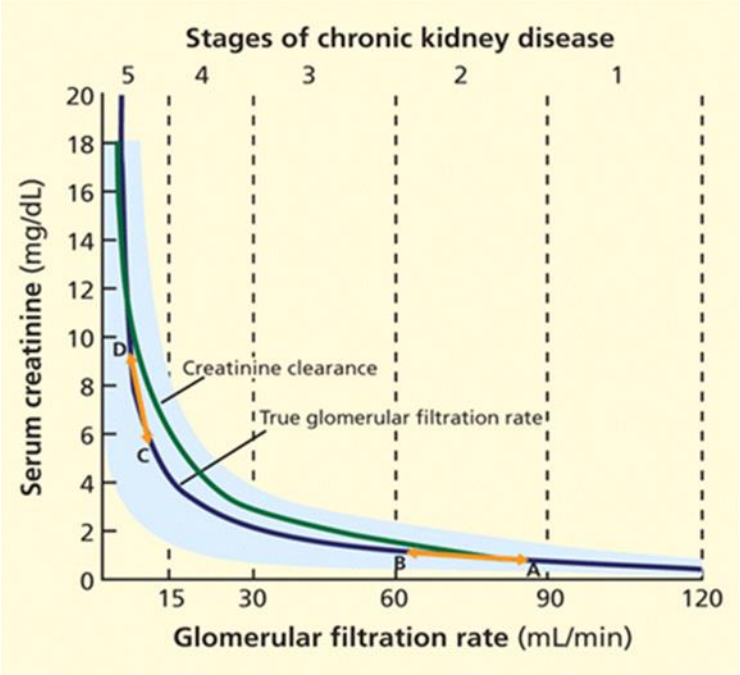
Terminology – renal insufficiency

- situation when kidneys are able to maintain homeostasis under the basal conditions, but not under the stress, e.g.:
  - — infection
  - — surgery
  - — excess intake of protein, fluid or electrolytes
- typically product of **chronic kidney disease** (CKD)
  - — CKD (stages 1 - 5) defined (disregard of etiology) solely based on GFR (see table)
  - — degree of albuminuria can be taken into account
    - renal insufficiency corresponds to stages 3 - 4
    - renal failure to stage 5

Stage	Description	GFR (ml/min/1.73m^2)
1	Kidney damage with normal or ↑GFR	≥ 90
2	Kidney damage with mild ↓GFR	60 - 89
3	Moderate ↓GFR	30 - 59
4	Severe ↓GFR	15 – 29
5	Kidney failure	< 15 (or dialysis)



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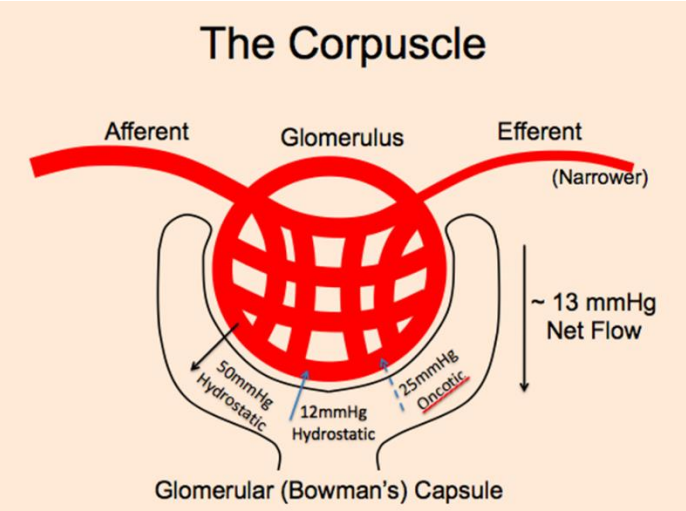
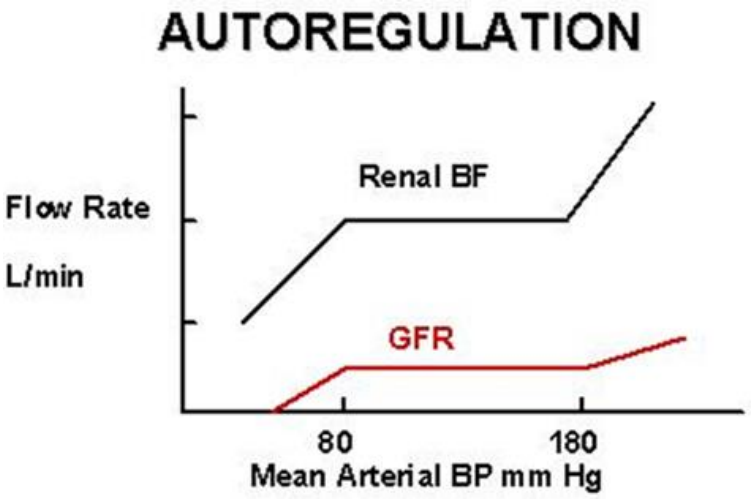
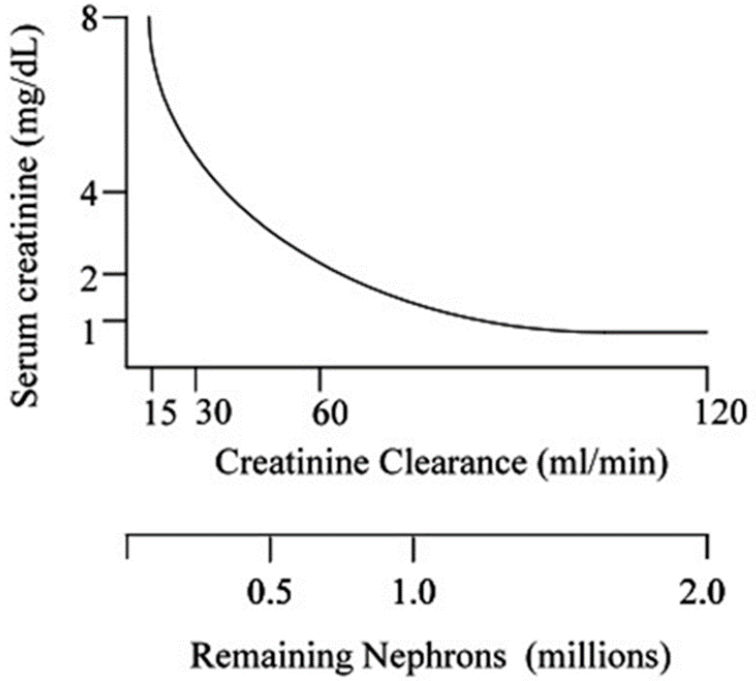
Regulation of and its relationship with serum creatinine



- no significant changes of GFR with loss of up to 50% of functional glomeruli
  - non-linear relationship of [Cr] and GFR
- with progressive renal disease (another ~50% of the remaining capacity) initial GFR decline is not accompanied by rise of [Cr]
  - with more pronounced GFR decline serum Cr levels rise more steeply
  - only then have Cr serum levels diagnostic value
- estimated GFR (eGFR)
  - calculation of GFR using serum Cr, age and body weight
    - Cockroft-Gault and other formulas → mathematical expression of hyperbolic relationship

GFR ~120ml/min/1.73m²





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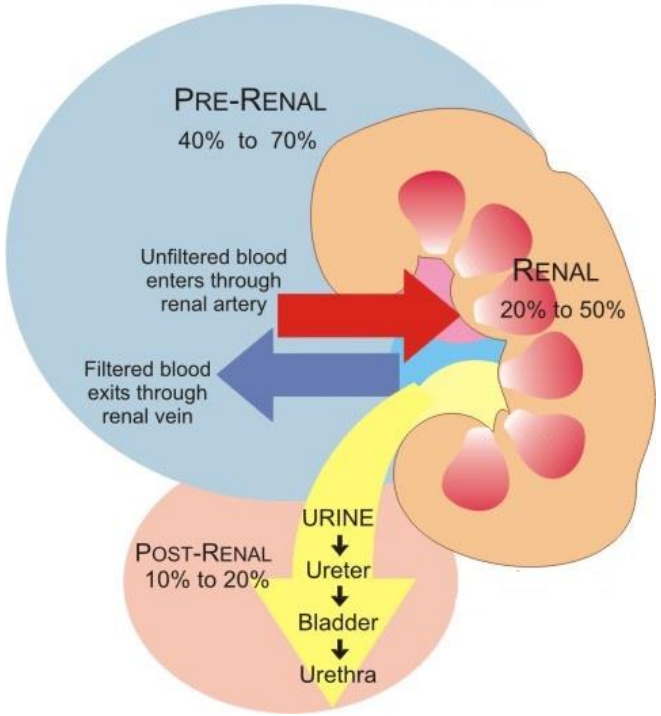

ACUTE RENAL FAILURE (ARF)
[NEWLY ACUTE KIDNEY INJURY] (AKI)

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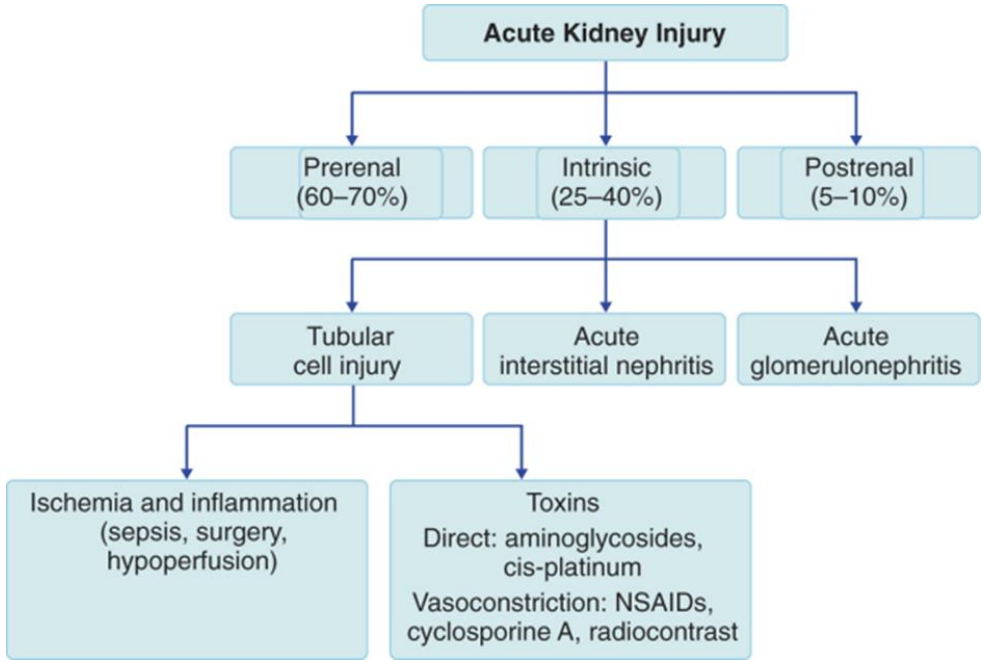
Who is in immediate risk of AKI

- most episodes of AKI occur in the hospital !!!
  - mortality rates ranging from 36% to as high as 86% (depends on the setting in which AKI is acquired, the age of the patient, and the acuity of the illness)
- **5–20% of critically ill patients** experience an episode of acute renal failure during the course of their illness, in many cases accompanied by **multi-organ dysfunction syndrome** (MODS)
- recognition of risk patients
  - patients after extensive surgery
  - heart operations (extracorporeal circulation)
  - septic shock
  - but also less critically ill patients with
    - **pre-existing kidney disease** (serum creatinine >180 µmol/l)
    - **multiple comorbidities** (heart and liver!)
      - renovascular disease has been found in 34% of elderly people with heart failure!
    - those treated with **NSAID, ACEI or ARBs**
- prevention of progression of pre-renal ARF into the renal form
  - **acute tubular necrosis**
- maintenance of sufficient renal perfusion
  - isovolemia, cardiac output, normal BP
  - attention to administering potential nephrotoxins



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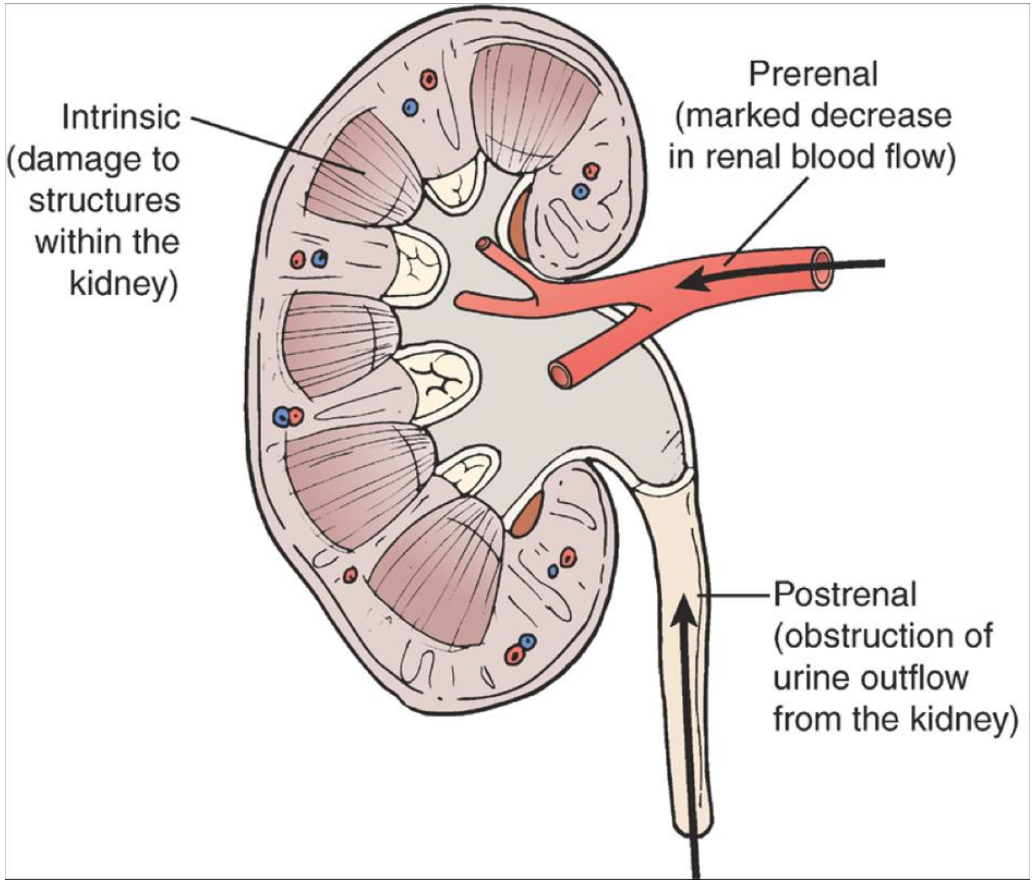
Etiology and pathogenesis of AKI

- acute and rapidly progressive (within hours to days) decrease of glomerular filtration and excretion in both kidneys
- classification stages AKI into three levels of severity on the basis of increases in serum creatinine level, decreased urine output or need for renal replacement therapies
  - oliguria < 500 ml/day
  - anuria < 100 ml/day

Stage	Serum creatinine	Urine output
1	1.5–1.9 times baseline OR ≥26.5μmol/L increase	<0.5ml/kg/hour for 6–12 hours
2	2.0–2.9 times baseline	<0.5ml/kg/hour for ≥12 hours
3	3.0 times baseline OR Increase in serum creatinine to ≥353.6μmol/L OR Initiation of renal replacement therapy	<0.3ml/kg/hour for ≥24 hours OR Anuria for ≥12 hours

- etiology
  - (A) pre-renal azotemia
  - (B) renal (intrinsic) azotemia
  - (C) post-renal azotemia
- pathogenesis
  - decreased blood flow through glomeruli
  - loos of filtration area
  - increased pressure in tubules or Bowman capsule
- Although the process may be reversible, **full recovery of kidney function is uncommon**
  - each episode of AKI is associated with considerable mortality and long-term adverse outcomes, including cardiovascular complications, chronic kidney disease and end-stage renal disease



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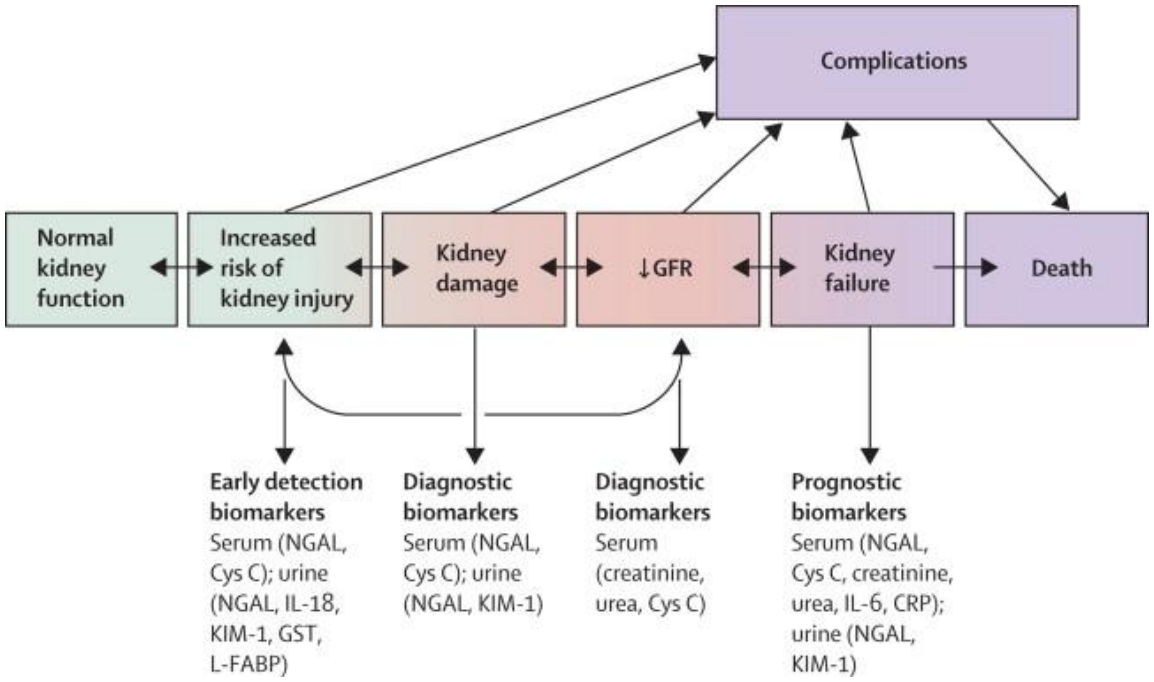
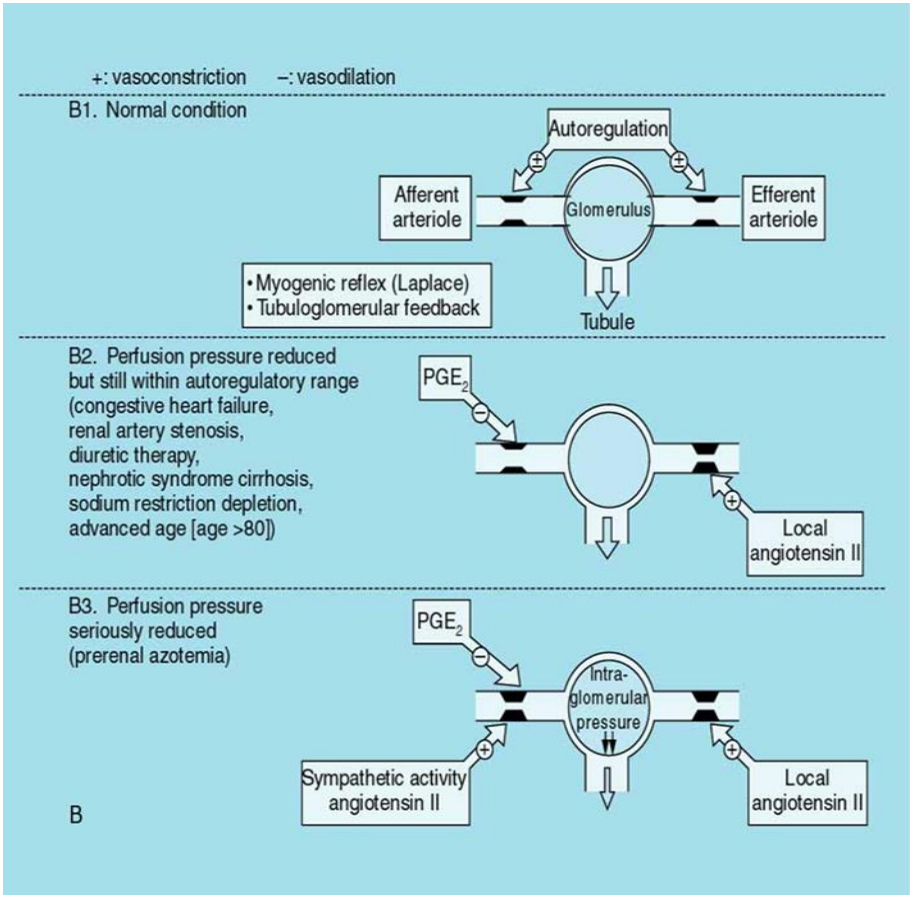
Specific etiology of AKI – (A) pre-renal

- most common type of AKI caused by **impaired renal blood** flow below the range of autoregulation
  - GFR declines because of the decrease in filtration pressure
    - massive activation of RAAS
    - systemic sympathetic activity
  - AKI may superimpose on chronic renal condition under the sudden stress
- failure to restore normal blood perfusion through kidneys may cause **acute tubular necrosis** (ATN)
  - therefore progress to a renal form of ARF
- **biomarkers** are being used to monitor the dynamics of AKI





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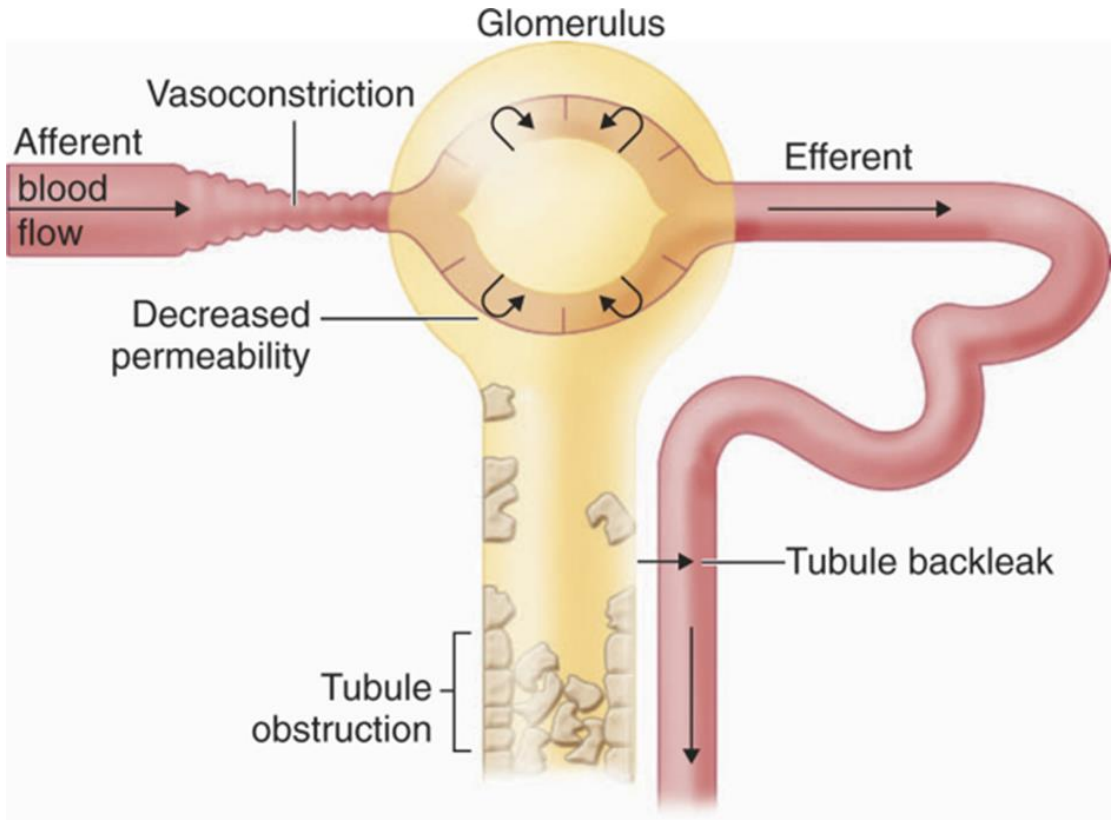
Specific etiology of pre-renal AKI

- acute heart failure & cardiogenic shock
  - acute myocardial infarction
  - arrhythmias with low cardiac output
  - pericardial tamponade
- intravascular volume depletion and hypotension
  - hemorrhage
  - gastrointestinal, renal, and dermal losses (burns)
- decreased effective intravascular volume
  - congestive heart failure
  - cirrhosis (ascites)
  - peritonitis
- systemic vasodilation/renal vasoconstriction
  - sepsis
  - hepatorenal syndrome
  - inappropriate anti-hypertensive therapy



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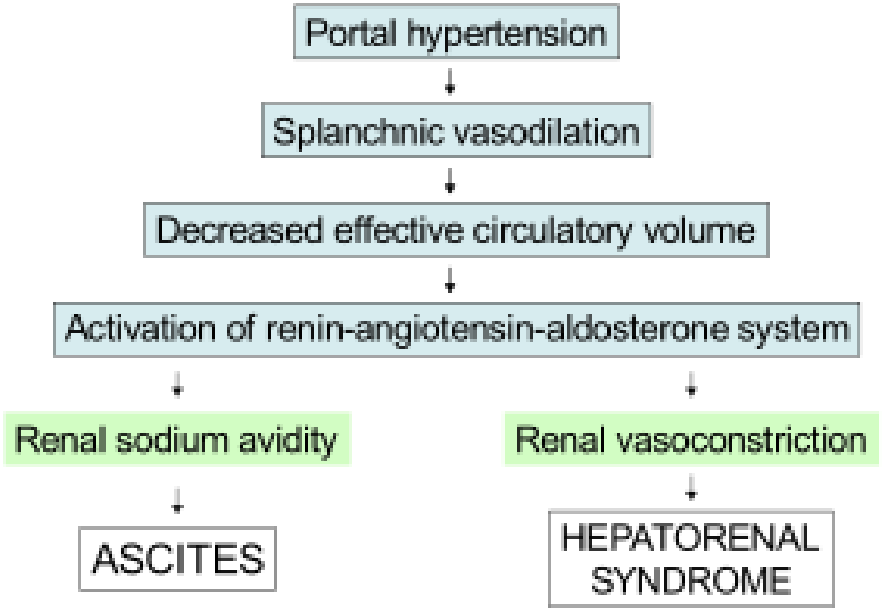
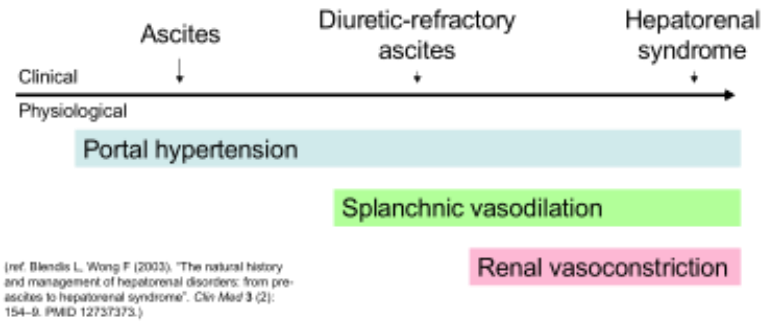
Typical pre-renal AKI: hepatorenal syndrome

- development of ARF in patients with advanced chronic liver disease who have portal hypertension and ascites
  - at least 40% of patients with cirrhosis will develop HRS during the natural history of their disease
- pathogenesis
  - hypovolemia
    - congestion in GIT due to portal hypertension
    - ascites
    - bleeding
  - decreased RBF in generally hyperkinetic circulation (typical liver failure)
    - drop of BP due to peripheral vasodilation lead to constriction of afferent arterioles (mediated by sympathetic innervation) and subsequent ischemia of renal cortex





(ref. Blendis L, Wong F (2003). "The natural history and management of hepatorenal disorders: from pre-ascites to hepatorenal syndrome". *Clin Med* 3 (2): 154–9. PMID 12737373.)

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Circulation abnormalities in liver cirrhosis

Liver cirrhosis

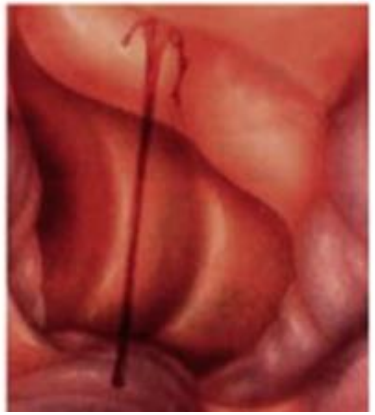
↓

Increase in intrahepatic resistance

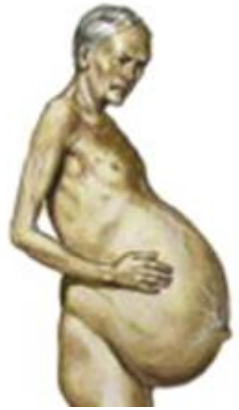
↓

Portal (sinosoidal) hypertension

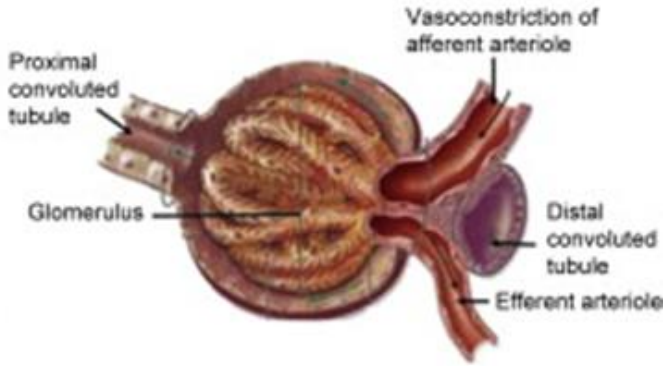
- development of collateral porto-systemic shunts
  - ↓
  - development of varices in the oesophagus
    - ↓
    - **Variceal Bleeding**



- Splanchnic/systemic vasodilation
  - ↓
  - Reduction in effective arterial blood volume
    - ↓
    - Activation of vasoconstrictive neurohumoral systems
      - ↓
      - Water and sodium retention
        - ↓
        - **Ascites**



      - ↓
      - Renal vasoconstriction
        - ↓
        - **Hepatorenal Syndrome**



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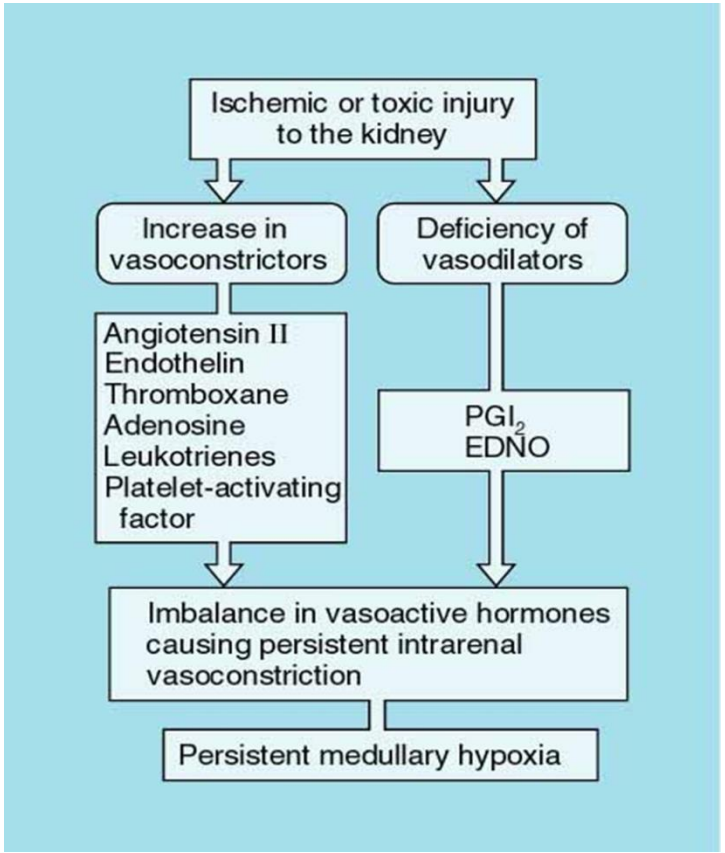
Specific etiology of AKI – (B) renal (intrinsic)

- large-vessel renal vascular disease
  - renal artery thrombosis or embolism
  - renal artery stenosis
  - thrombosis of renal veins
- small-vessel renal vascular disease
  - vasculitis
  - hemolytic-uremic syndrome
  - others
    - malignant hypertension, scleroderma, preeclampsia, sickle cell anemia, hypercalcemia, transplant rejection
- impaired renal blood flow
  - ↓ post-glomerular resistance (ACEs, ARBs)
  - ↑ pre-glomerular resistance (NSAIDs)
  - radiocontrast agents
- glomerular diseases
  - acute glomerulonephritis
- acute tubular necrosis
  - ischemia
  - toxins
  - obstruction (hemolysis, rhabdomyolysis, paraprotein)
- ac. interstitial diseases
  - toxo-alergic
  - infection
  - idiopathic



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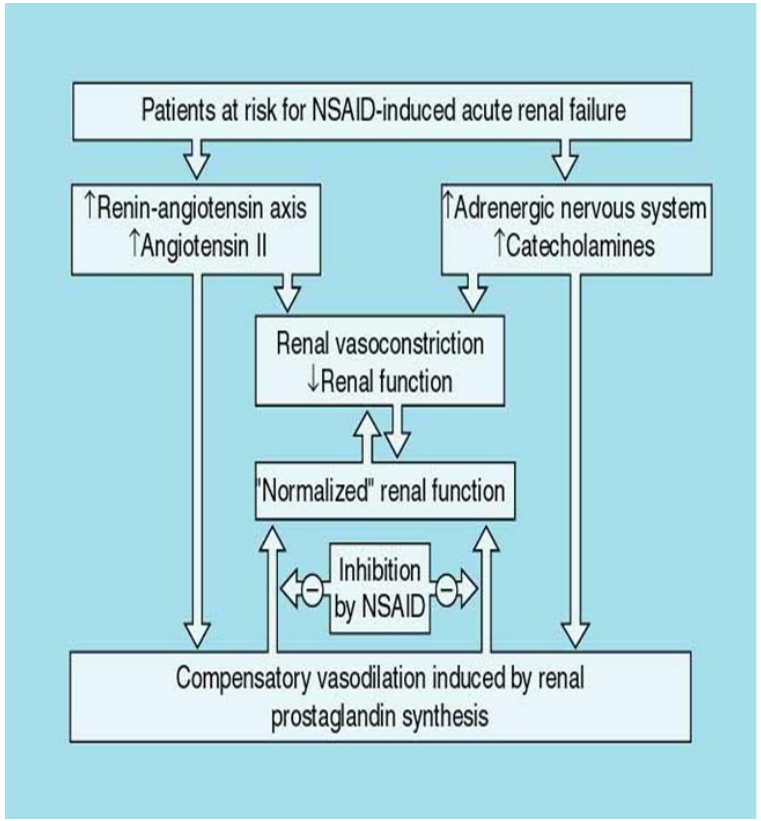
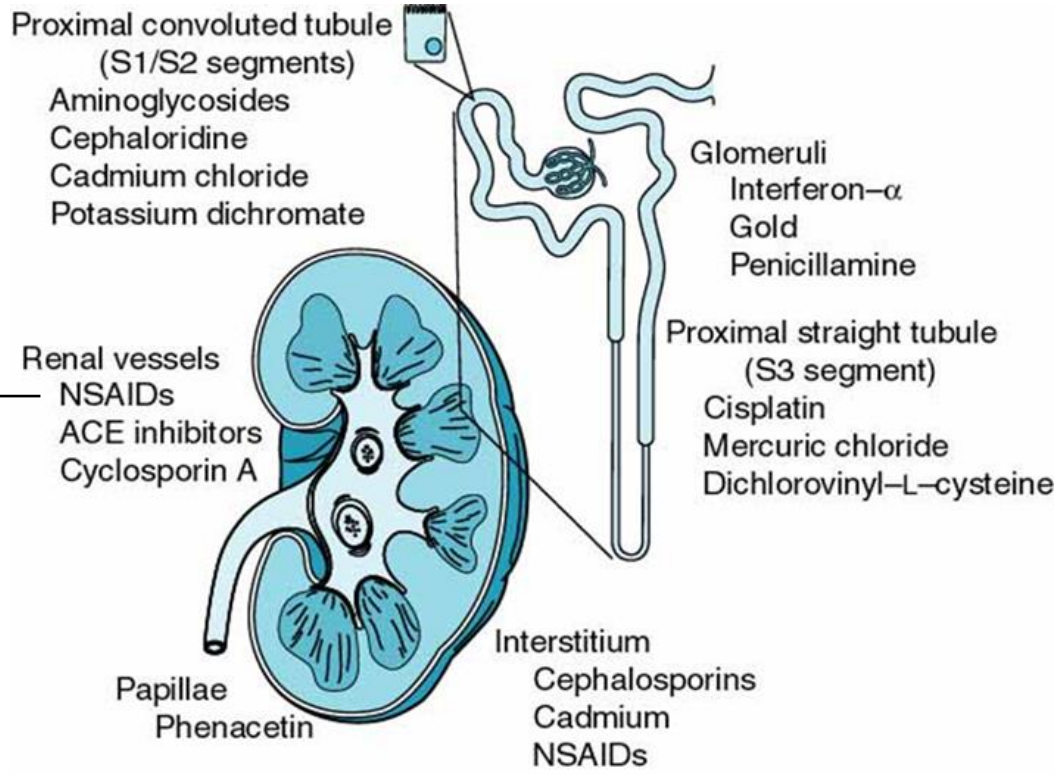
Typical renal AKI: renal nephrotoxic AKI





Rick G. Schnellmann & Katrina J. Kelly

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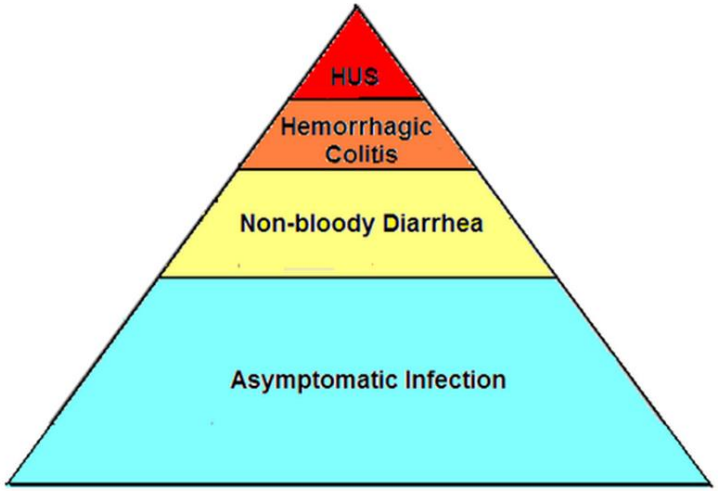
Typical renal AKI: hemolytic-uremic syndrome



Spectrum of Disease Caused by E. Coli

- is a disorder that usually occurs when an infection in the digestive system (but also other causes) produces toxic substances that destroy red blood cells
  - hemolytic anemia → hemoglobinuria → precipitation of hemoglobin in tubules causes AKI
  - also thrombocytopenia → bleeding
- etiology
  - gastrointestinal infections
    - E. coli
    - Shigellosis dysentery
    - Salmonellosis
  - non-gastrointestinal infections
    - Pneumococcus infection
  - iatrogenic (drugs)
- HUS is most common in children
  - the most common cause of AKI/ARF in children
- HUS is more complicated in adults
  - similar to thrombotic thrombocytopenic purpura (TTP)

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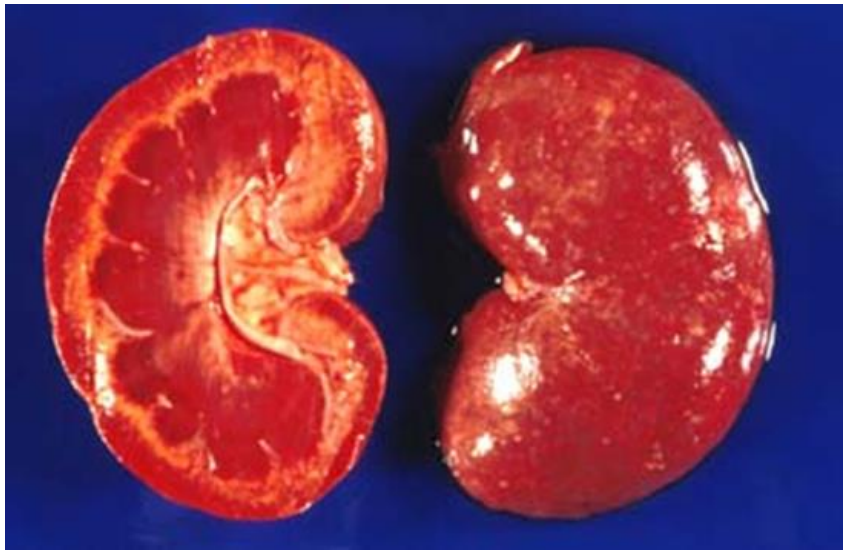
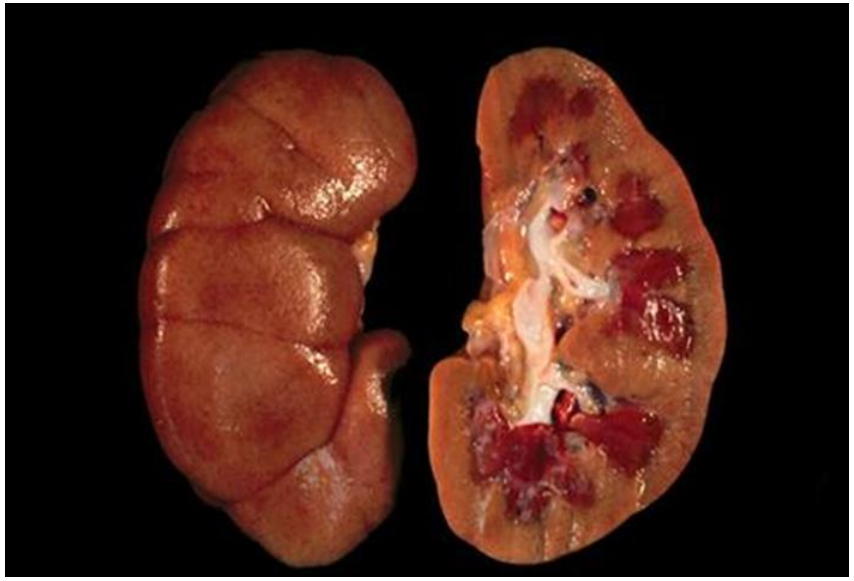
Acute tubular necrosis (ATN)





- etiology
  - ischemia
    - generates toxic oxygen free radicals and inflammatory mediators that cause swelling, injury, and necrosis
  - toxic
    - drugs
      - antibiotics, antiviral, antifungal, cytostatics
    - radiocontrast nephropathy
    - environmental toxins? (heavy metals such as mercury, arsenic)
- reasons for high vulnerability of tubules to ischemia and toxins
  - lower perfusion of medulla compared to cortex, worse energetics
  - local increase of concentration of toxins during reabsorption of water
  - additional increase of concentration of toxins by their secretion
  - intracellular toxicity due to their reabsorption
  - change of toxicity in low urine pH
- final effect mediated not only by necrosis but also by apoptosis

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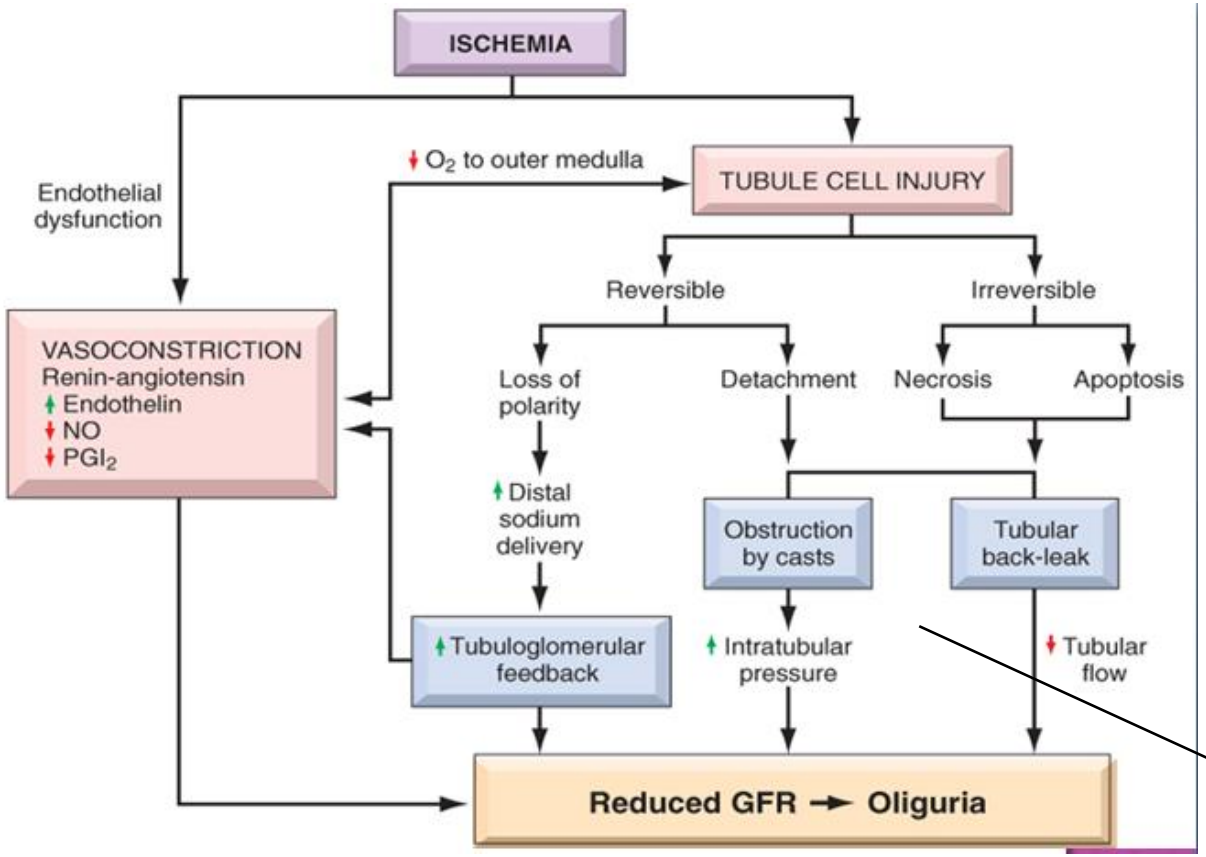
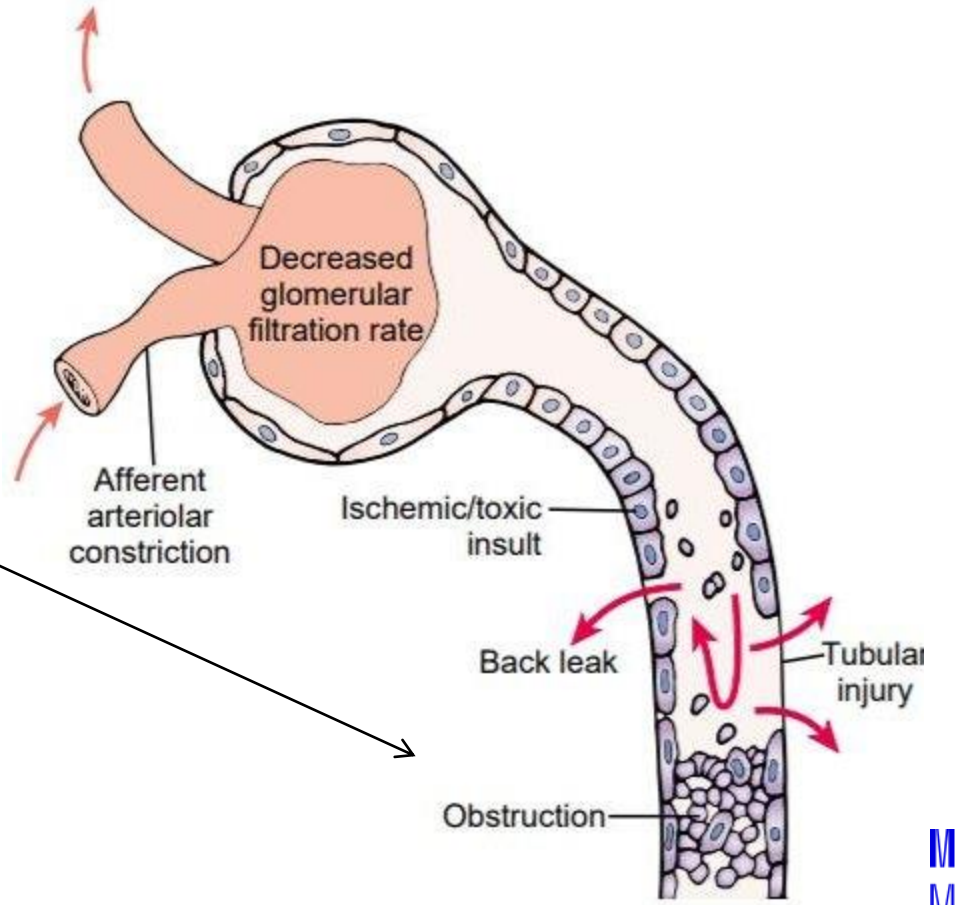
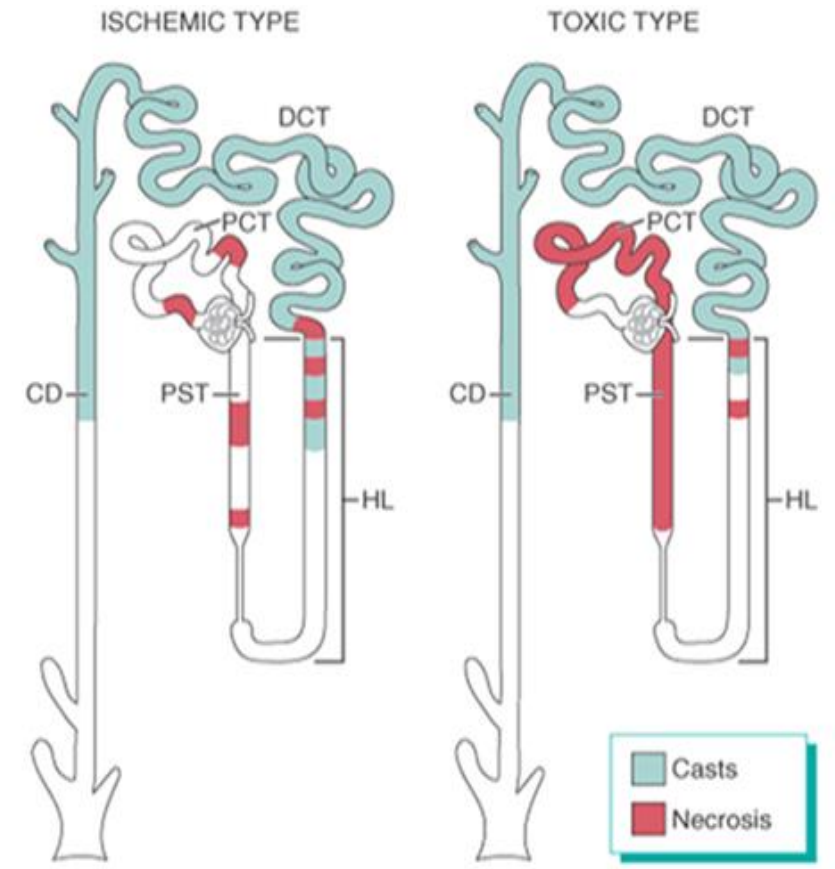
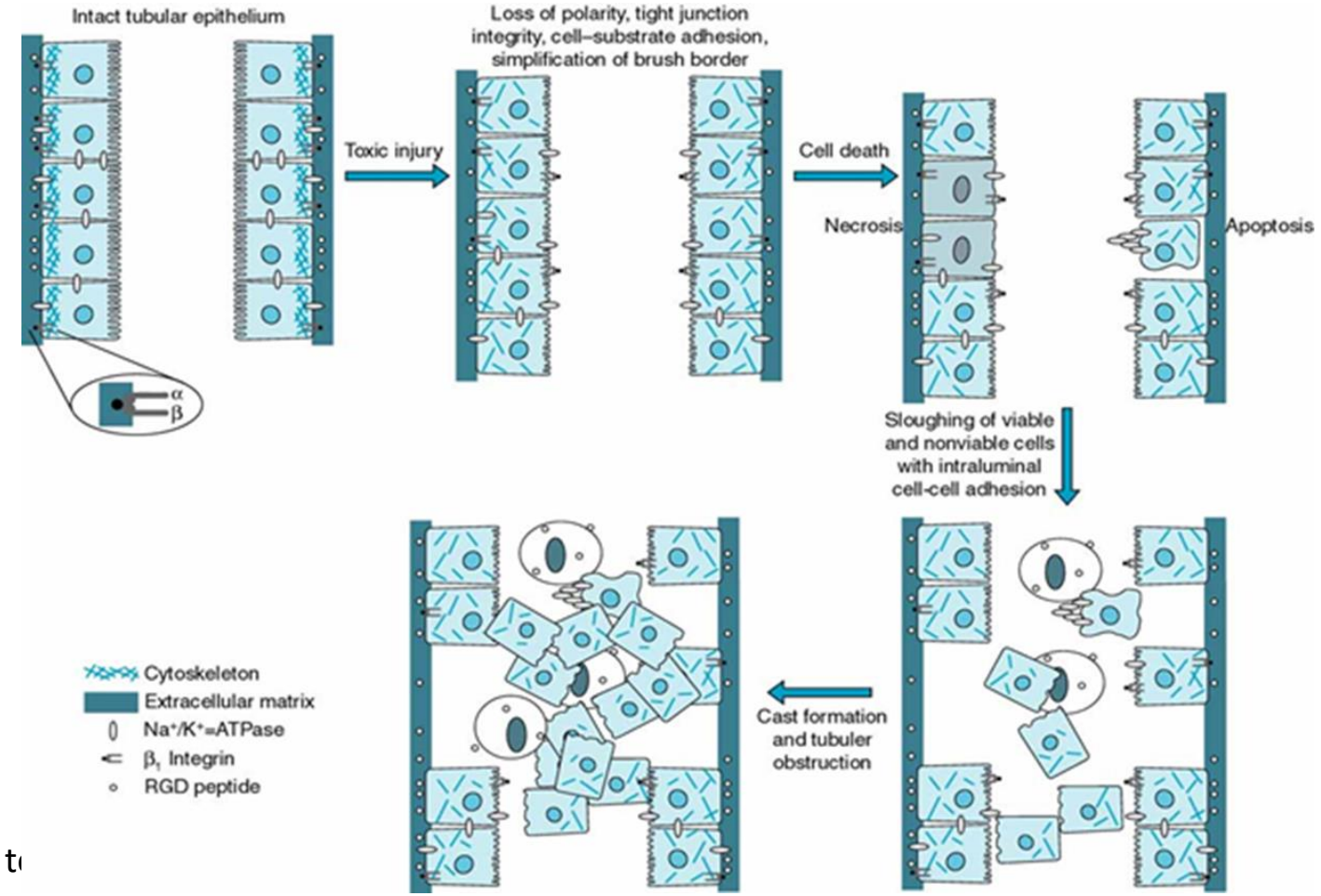
Pathogenesis and mechanisms of oliguria in ATN





Patterns of tub. damage and formation of casts in ATN





- ATN caused by nephrotoxins is usually uniform and limited t proximal tubules
- ischemic ATN tends to be patchy and may be distributed along any part of the nephron

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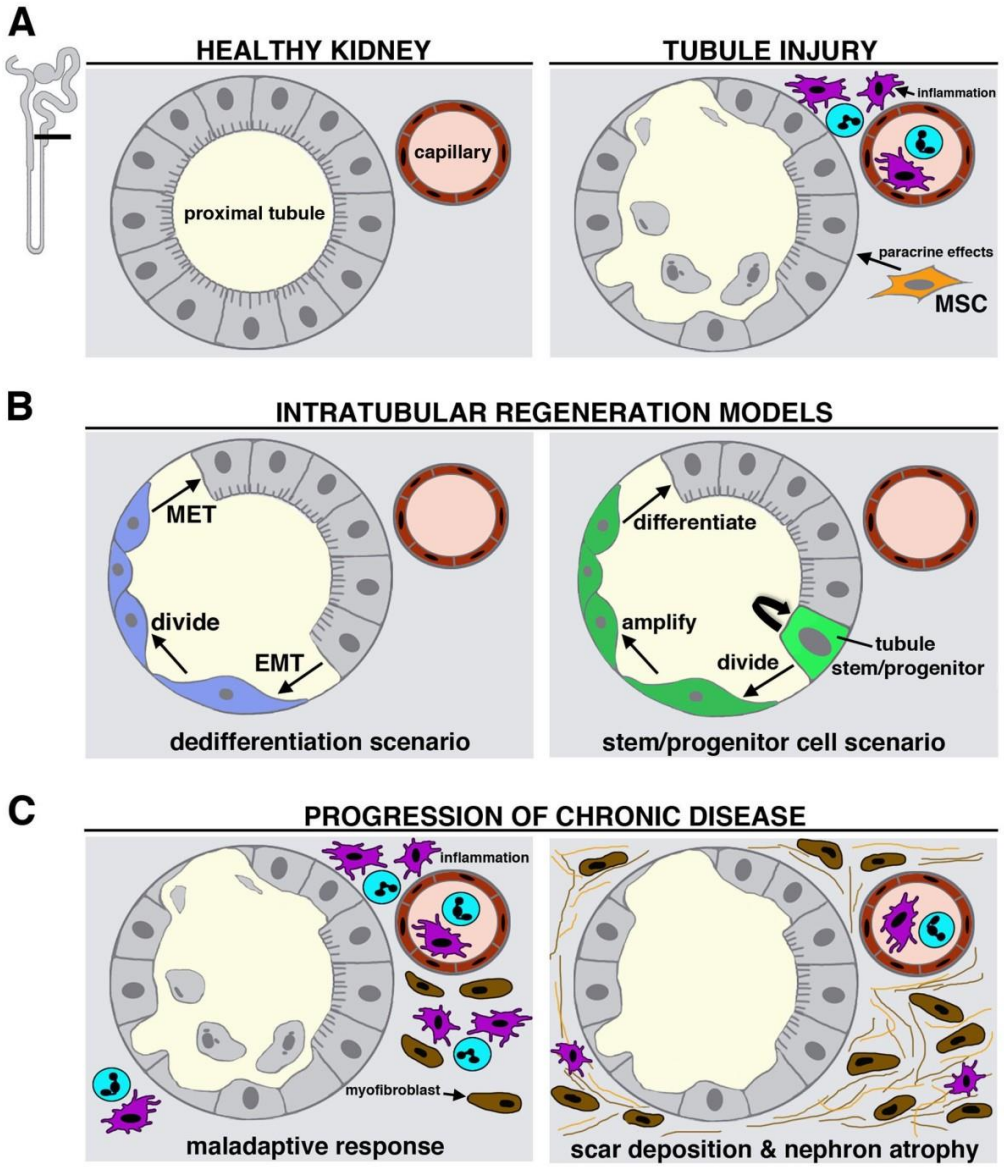
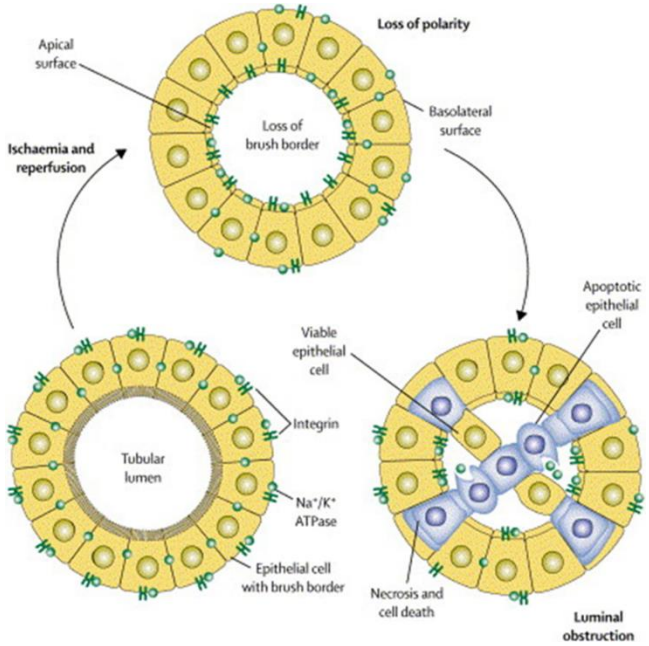
Tubular changes in ATN pathophysiology and reversibility of ATN





- morphological changes occur in the proximal tubules, including loss of polarity, loss of the brush border, and redistribution of integrins and sodium/potassium ATPase to the apical surface. Calcium and reactive oxygen species also have roles in these morphological changes, in addition to subsequent cell death resulting from necrosis and apoptosis. Both viable and non-viable cells are shed into the tubular lumen, resulting in the formation of casts and luminal obstruction and contributing to the reduction in the GFR
- tubular epithelia regenerates but it takes time and additional damage can be caused by reperfusion injury
- long term consequences of uncompleted regeneration
  - interstitial fibrosis and scaring

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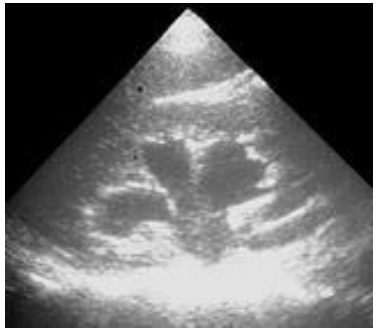
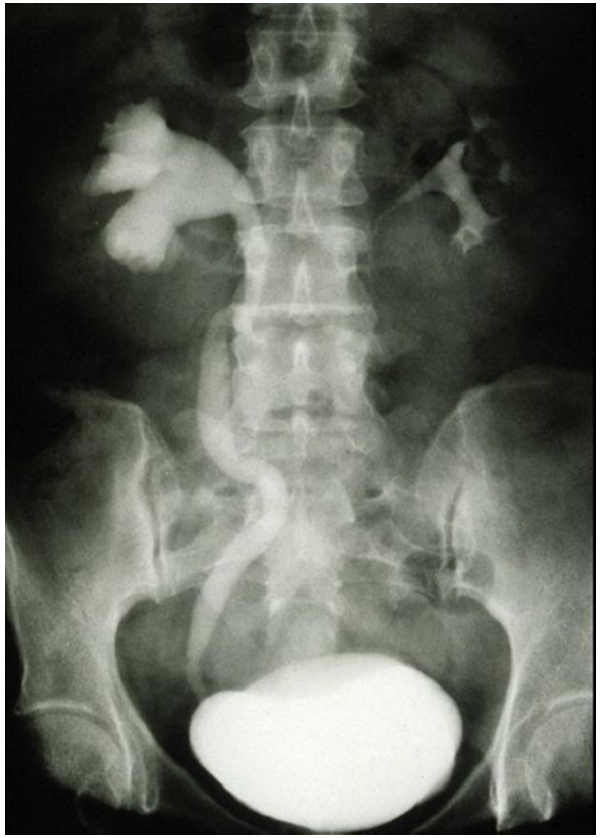
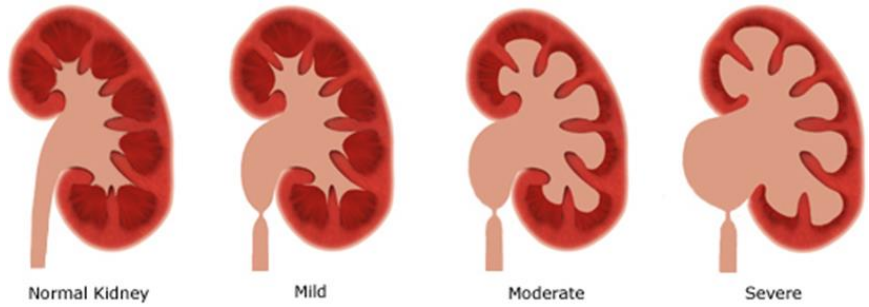
Specific etiology of AKI – (C) post-renal

- obstruction of the urinary tract below the kidneys for fluid outflow leading to waste product accumulation
  - bilateral
  - unilateral in solitary kidney or with reflex anuria in contralateral unaffected kidney
    - due to the pain during the renal colic
  - nephrolithiasis
  - benign prostate hypertrophy
  - tumors (prostate, urinary bladder, intestine, ovary…)
  - retroperitoneal fibrosis or hematoma
  - neurogenic dysfunction of bladder
- consequences (apart from AKI)
  - already after the relatively short obstruction → ↑pressure above obstruction → dilation of renal pelvis and calices → **hydronephrosis** → reflux nephropathy → infection → kidney atrophy
  - post-obstructive **profuse diuresis** (>4l/day)
  - hyperkalemic hyperchloremic renal tubular **acidosis**







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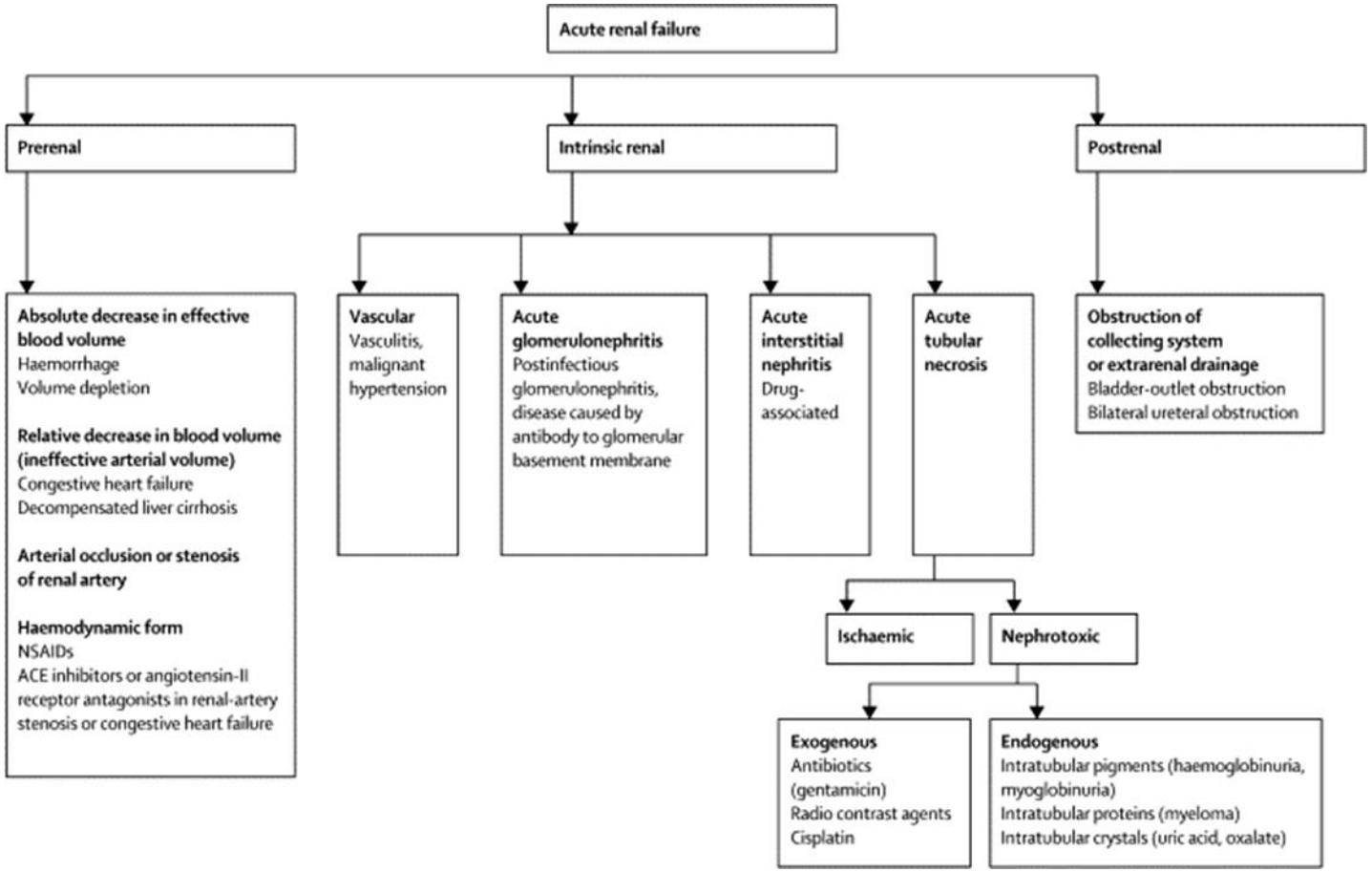
Summary of etiology of AKI



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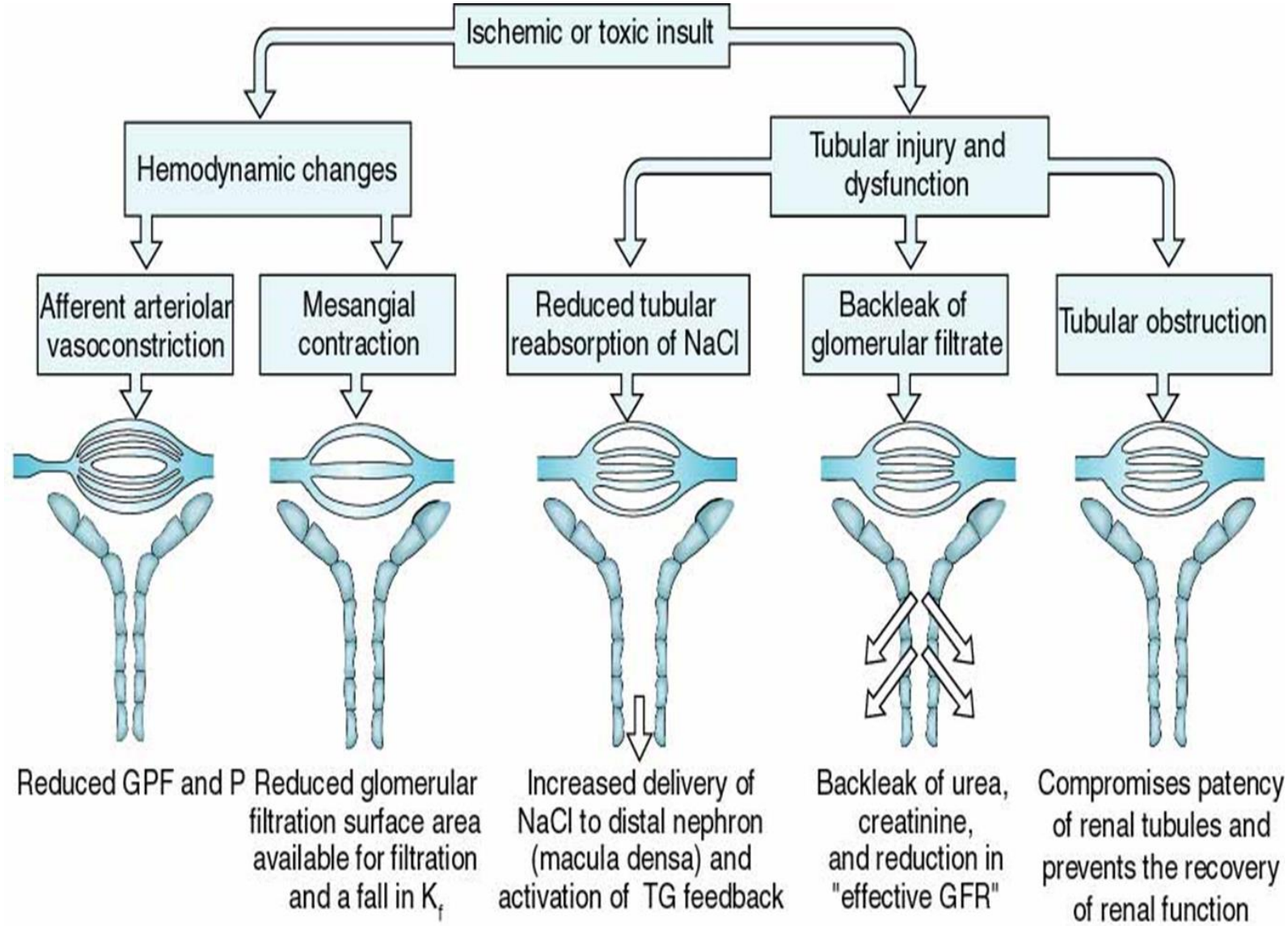
Summary of pathogenic mechanisms of AKI



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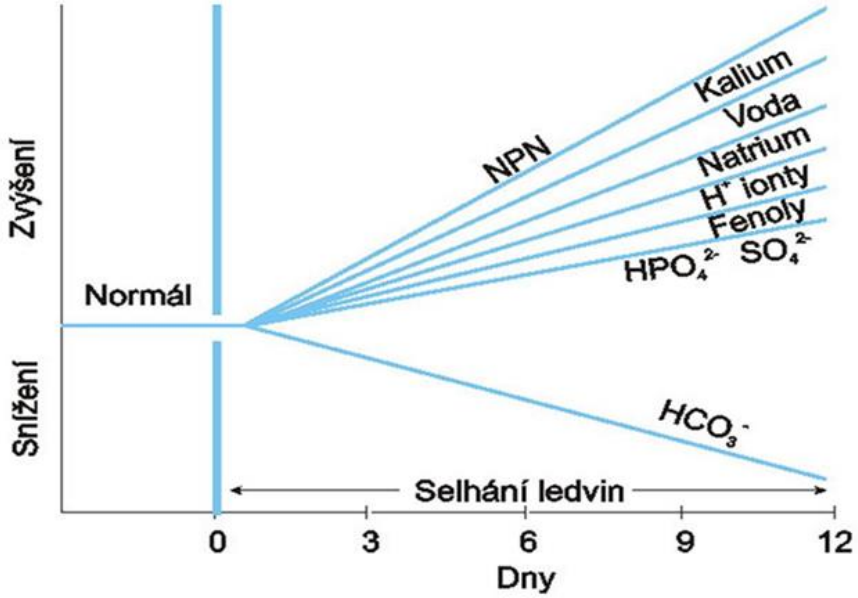
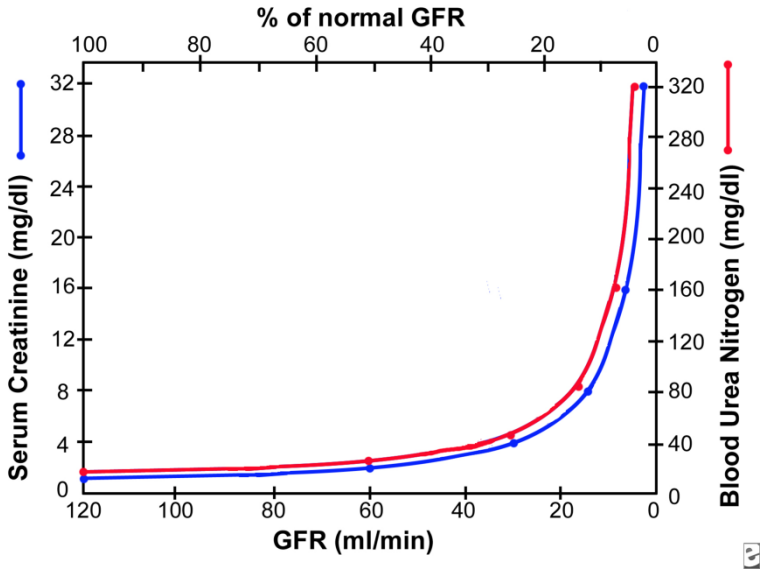
Homeostatic abnormalities during AKI

- development during several days but generally quite fast!
- ↑ serum creatinine and BUN
  - however BUN reflects more factors (GFR , protein catabolism, nutrition) than creatinine
- changes of P_{urea}/P_{creat} ratio
  - normally ~40-100:1
    - urea reabsorbed in prox. tubule while creatinine is not
    - can be normal in post-renal ARF
  - in pre-renal ARF often >100:1
    - increased reabsorption in hypovolemia
  - in renal ARF often <40:1
    - tubule damage and decreased reabsorption
- plasma concentration of K^+
    - see later for more detail
  - ↑ during oliguria phase
  - ↓ during polyuria phase
- conc. of Na^+
  - normal, ↑ or ↓ = depends on volume
- metabolic acidosis (high anion gap)
- water retention (+ metabolic water ~500ml/day)





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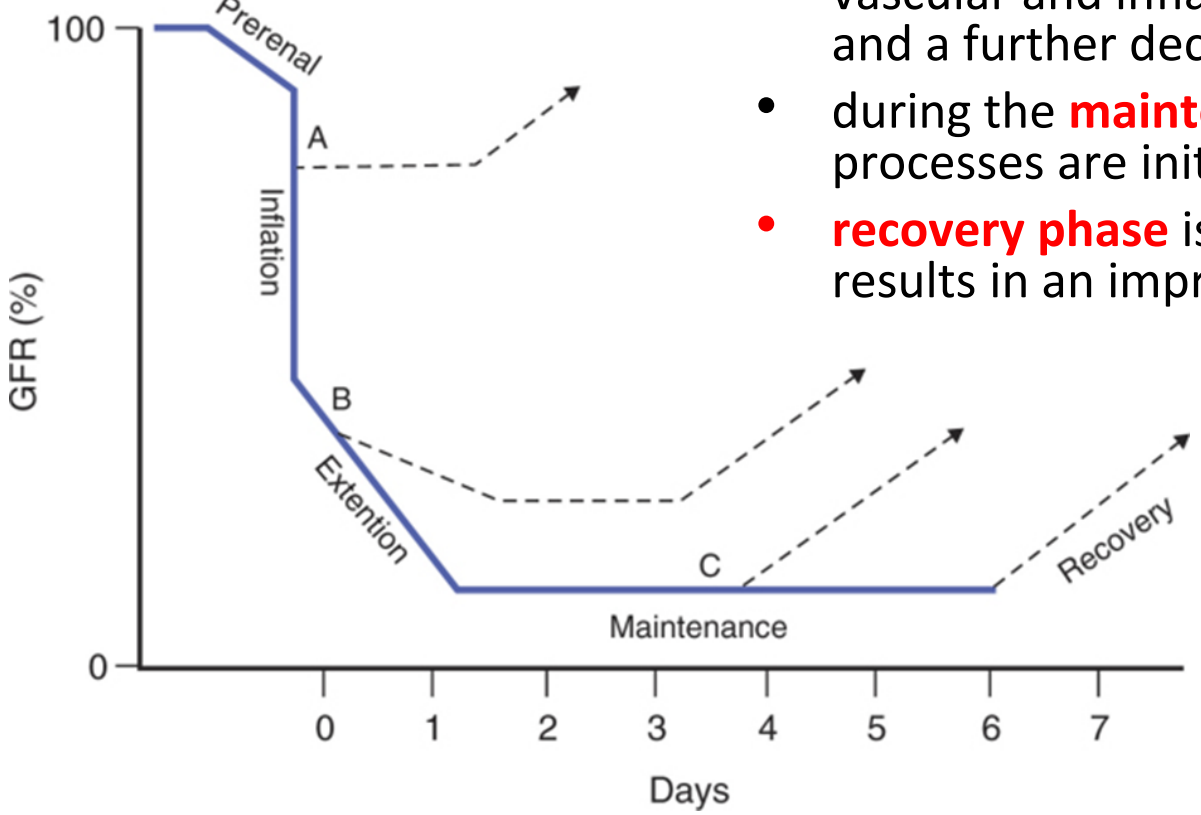
Phases of AKI



- reduction in renal blood flow causes a reduction in GFR
  - variety of cellular and vascular adaptations maintain renal epithelial cell integrity during this phase
- **initiation phase** occurs when a further reduction in renal blood flow results in cellular injury, particularly the renal tubular epithelial cells, and a continued decline in GFR
- vascular and inflammatory processes that contribute to further cell injury and a further decline in GFR usher in the proposed **extension phase**
- during the **maintenance phase**, GFR reaches a stable nadir as cellular repair processes are initiated in order to maintain and re-establish organ integrity
- **recovery phase** is marked by a return of normal cell and organ function that results in an improvement in GFR

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Risks associated with AKI

- major risks during the oliguric stage of AKI
  - **hyperkalemiaa** (>7mmol/l)
    - arrhythmias, heart arrest
  - **hypervolemia** (hyperhydration)
    - isoosmolar
    - later hypoosmolar due to dilution
      - hyponatremia → brain edema → increased intracranial pressure → brain ischemia and hypoxia → subjective symptoms (head pain, nausea, vomiting) → disorder of consciousness
    - volume and pressure overload of the heart
    - congestion or even pulmonary edema
- indication to **renal replacement therapy** (mainly an **acute hemodialysis**)
  - absolute
    - hyperkalemia (>6.5mmol/l)
    - metabolic acidosis
    - hypervolemia
    - uremia
      - see in more detail later
  - relative
    - progressive hyperazotemia (creatinine >500 µmol/l, urea >35mmol/l)
    - hypercalcemia (> 4mmol/l), hyperuricemia
    - prolonged oliguria (>3 days)

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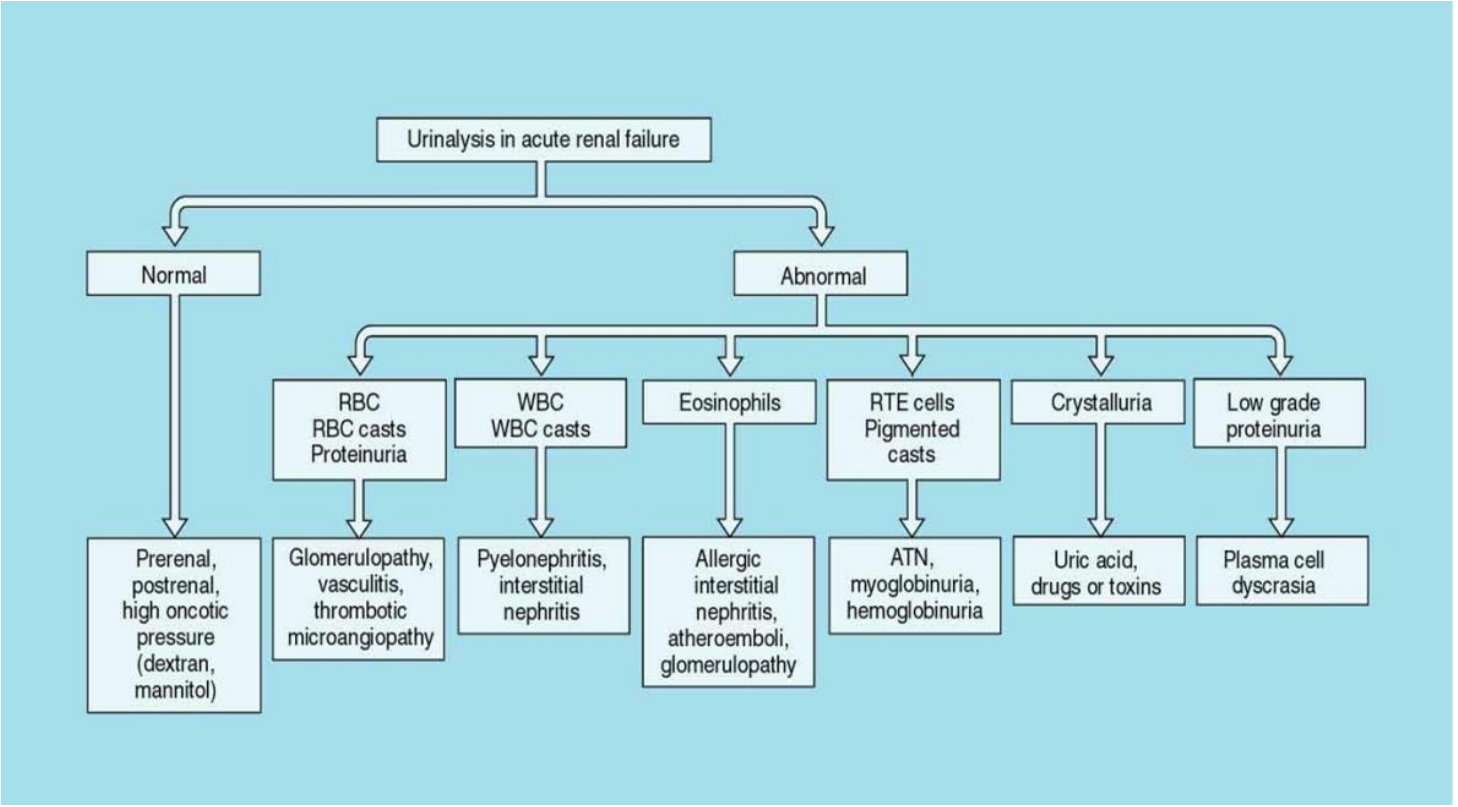
Urine analysis in AKI



- concentration of Na+ in urine:
  - pre-renal azotemia, acute GN or altered vascular resistance - tubules functioning and reabsorb Na+ from lower amount of filtrate (Na+ in urine < 20 mmol/l)
  - damage of tubules and post-renal azotemia: Na+ in urine > 40 mmol/l)
- fractional excretion of Na+
  - FE-Na+ = U-Na/S-Na, normally < 1 %
- osmotic concentration of urine
  - pre-renal azotemia: > 500 mOsm/kg
  - tubular damage: < 350 mOsm/kg

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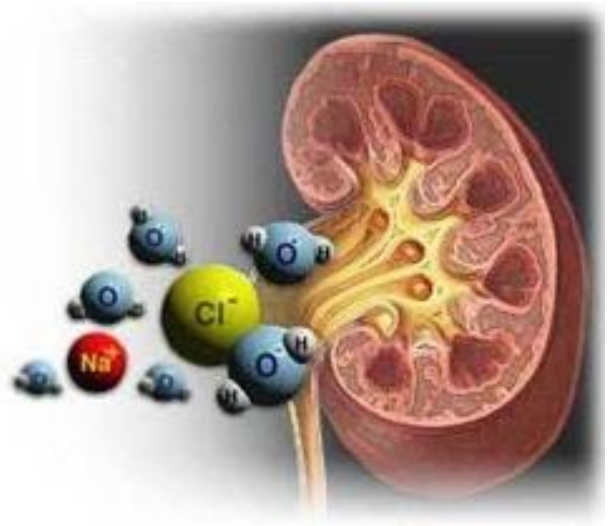

CHRONIC KIDNEY DISEASE (CKD), RENAL INSUFFICIENCY AND ESRD

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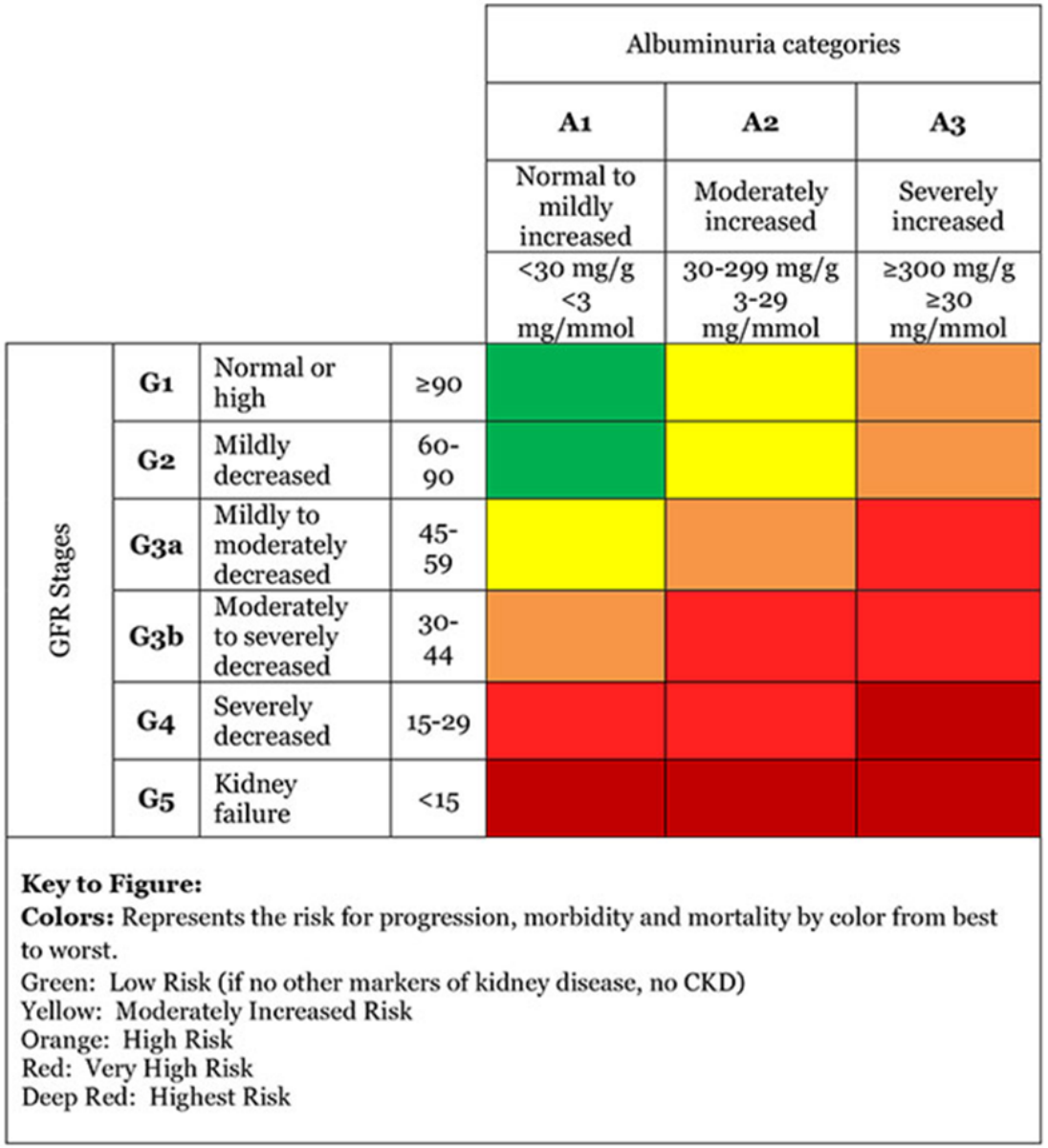
Chronic kidney disease (CKD)

- progressive, typically many years lasting decline of renal function
  - no matter of the etiology CKD defined solely based on degree of GFR decline
- basically any kind of progressive kidney disease can by the cause
  - 50% - any form of GN
  - 20% - diabetic nephropathy
  - 30% - others
    - ischemic kidney disease
    - tubulointerstitial nephritis
    - polycystic kidney disease
    - myeloma
    - hereditary nephritides
    - vascular nephrosclerosis
    - others



GFR Stages				Albuminuria categories		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30-299 mg/g 3-29 mg/mmol	≥300 mg/g ≥30 mg/mmol
	G1	Normal or high	≥90			
	G2	Mildly decreased	60-90			
	G3a	Mildly to moderately decreased	45-59			
	G3b	Moderately to severely decreased	30-44			
	G4	Severely decreased	15-29			
	G5	Kidney failure	<15			

Key to Figure:
Colors: Represents the risk for progression, morbidity and mortality by color from best to worst.
Green: Low Risk (if no other markers of kidney disease, no CKD)
Yellow: Moderately Increased Risk
Orange: High Risk
Red: Very High Risk
Deep Red: Highest Risk

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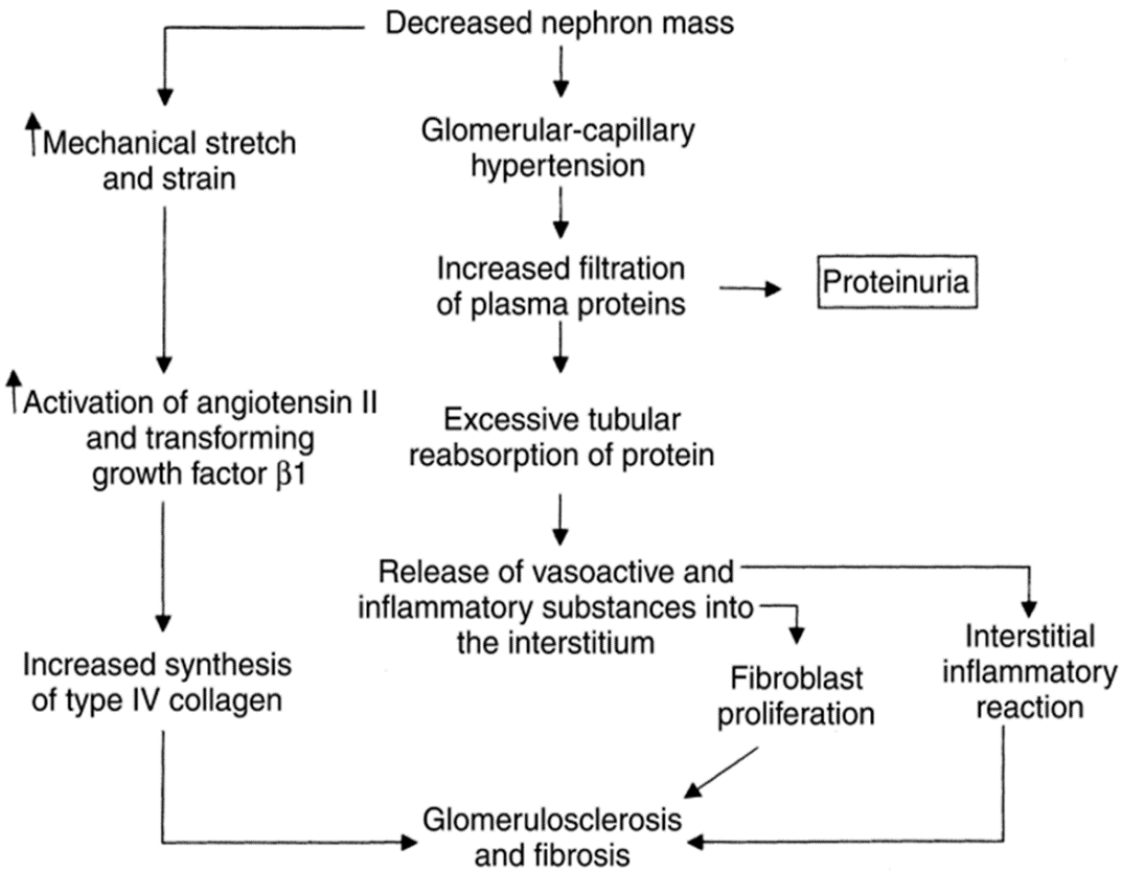
Pathogenesis of CKD – perpetual damage

- an **initial glomerular insult** is responsible for alterations of glomerular cell functions, leading to glomerulosclerosis and thus **reduction in nephron number**
  - however, symptoms appear only after the loss >75% nephrons
- this induces an increase in glomerular capillary pressure and/or glomerular volume in residual nephrons, which have to adapt (functionally and morphologically) to sustain higher workload and became damaged later, i.e. **further glomerular damage**
  - higher glomerular pressure favors **proteinuria**
- reduced nephron number is also associated with **tubular dysfunction**
  - tubular dysfunction is responsible for interstitial fibrosis and destruction of peritubular capillaries, which leads to tubular destruction
  - destruction of interstitial capillaries may also increase glomerular capillary pressure and thus enhance glomerular damage
  - similarly, **glomerulosclerosis** damages glomerular capillaries and enhances tubular hypoxia
  - proteinuria enhances tubular dysfunction and thus **interstitial fibrosis**
- along this process GFR decreases, later on renal insufficiency and event. failure develop
- CKD is associated with **high cardiovascular mortality**
  - several times higher of that in non-CKD population



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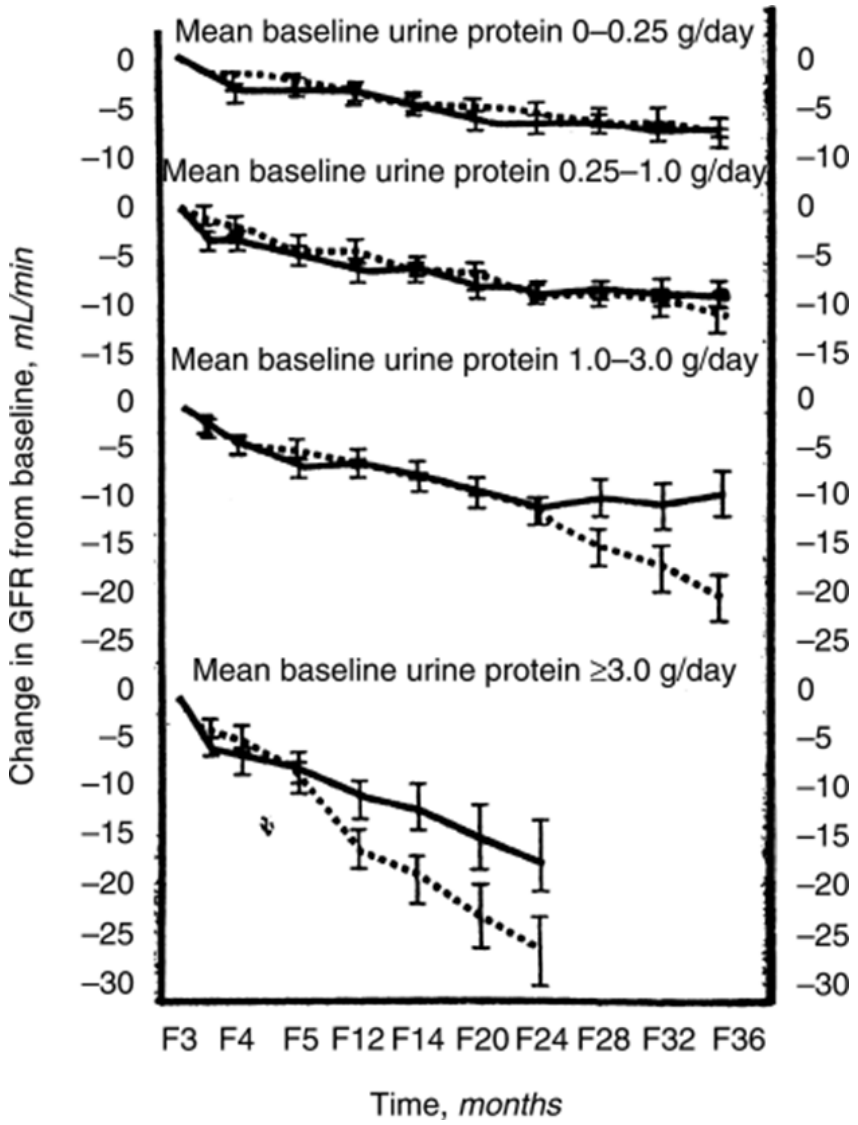
Mean decline in GFR depends on proteinuria



- mean decline in GFR (mL/min) over a 36-month period in groups with four different mean baseline 24-hour urine protein levels in non-diabetic patients with chronic renal failure in the MDRD study
  - compared in each of these four groups are the
    - normal blood pressure group (dashed line; 140/90 mm Hg; 102-107 mm Hg MAP)
    - intensive control group (solid line; 125/75 mm Hg; 92 mm Hg MAP)

Progressive renal and cardiovascular disease: Optimal treatment strategies
Matthew R Weir

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Progressive nature of CKD

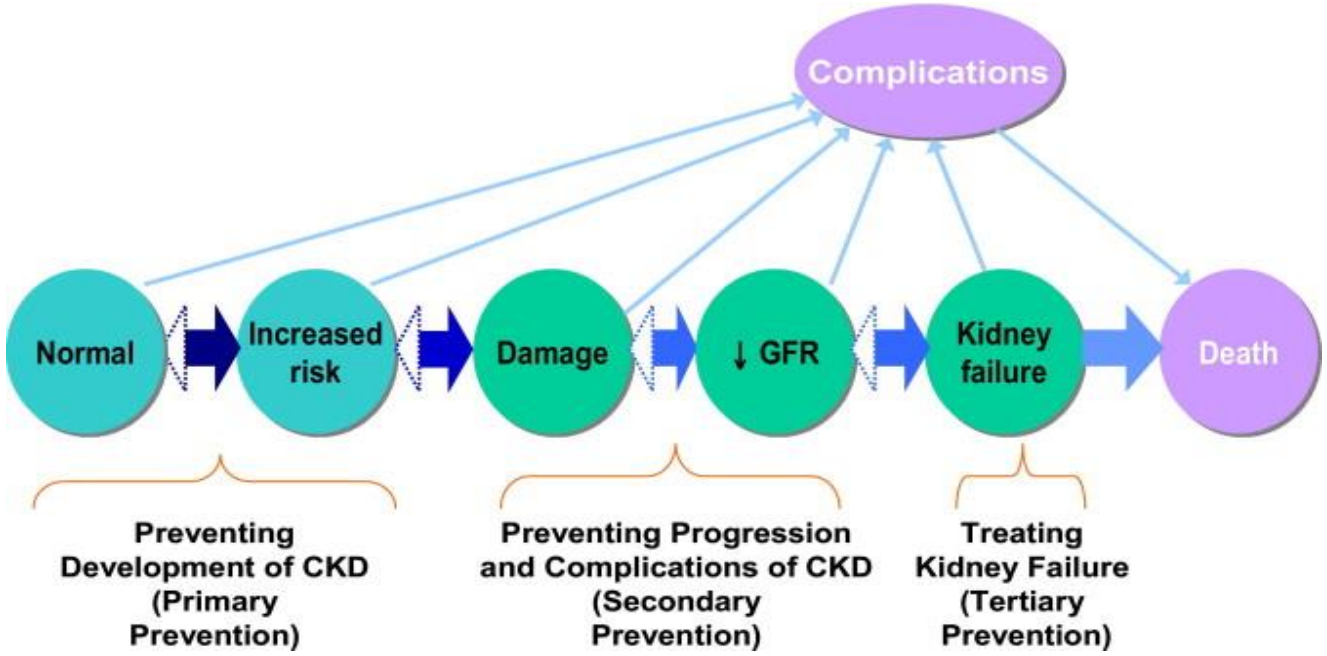
- damage and of nephrons caused by **initial specific process**

↓

- damage and loss of nephrons caused by **overload of residual nephrons** (a further non-specific process)

↓

- damage and loss of nephrons caused by **reno-parenchymal secondary arterial hypertension**
  - i.e. after the loss of critical number of nephrons caused by initial disease, further progression of CKD becomes independent in the primary pathological process
- factors determining the rate of progression
  - non-modifiable risk factors
    - primary disease
    - age, gender, ethnicity, genetics
  - modifiable risk factors
    - proteinuria
    - art. hypertension
    - glycemic
    - hyperlipidemia
    - obesity
    - hyperuricemia
    - smoking



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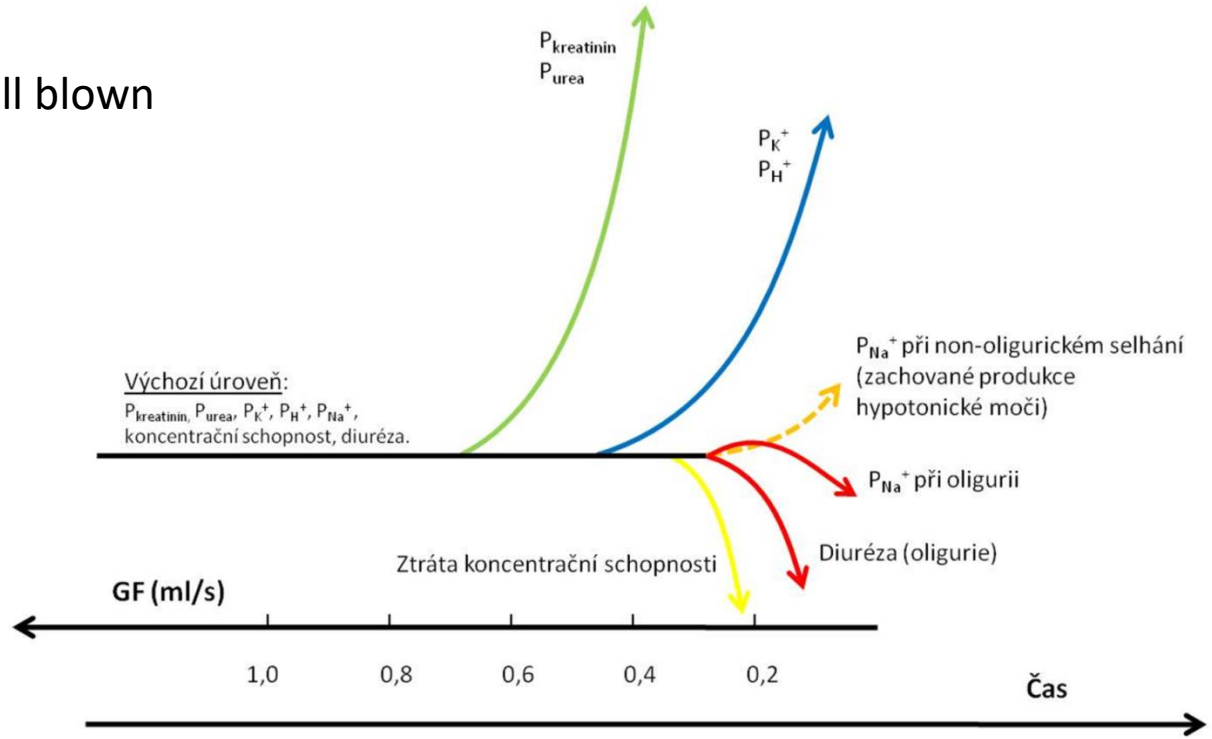
Dynamics of CKD associated abnormalities and their relationship to GFR

- ↓ of GFR by ~¼ do not causes changes of internal environment of the body (**renal functional reserve**)
  - functional adaptation of tubules to decreased GFR
- in the stage of ¼ - ¾ decrease of physiological GFR (= **renal insufficiency**)
  - gradual failure of tubular adaptation to ↓GFR and rise of plasma concentration of waste products
    - creatinine, BUN
    - uric acid
    - uremic toxins ?
- in the stage < ¾ of initial GFR **kidney failure** with full blown symptoms of **uremia**
  - changes similar to ARF
    - azotemia
    - hyperkalemia
    - hypervolemia
    - hyperphosphatemia
  - and on top of that
    - anemia
    - bone disease
    - hypertension
    - polyneuropathies



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Functional adaptation of residual nephrons

- allows to maintain homeostasis even if GFR is substantially decreased
  - **modification of intensity of tubular transport processes**, mainly maintenance of normal sodium, potassium and water balance (↓ tubular reabsorption or ↑ tubular secretion)
    - it is useful to measure fractional excretion (FE) of compounds (i.e. percentage of the given compound filtered by the kidney which is excreted in the urine)
- ↓ tubular reabsorption of **sodium and water**
  - normal reabsorption of Na ~99%
  - when ↓ GFR then ↓ reabsorption from filtered volume
    - although for normal excretion of Na GFR 4ml/min would be sufficient
  - mechanisms ???
    - ANP, prostaglandins
- ↓ tubular reabsorption of **phosphate**
  - normal renal excretion of phosphates ~10-20% of filtered amount
  - when ↓ GFR then ↓ reabsorption from filtered volume, i.e. excretion ~40% - 100%
    - if not sufficient → hyperphosphatemia
- ↑ secretion of **potassium**
  - mechanisms maintaining homeostasis of K+ until very low GFR
    - hyperkalemia develops only after extreme fall of renal function
  - secretion via extra-renal ways (GIT) contributes to the potassium balance

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Abnormalities of hormones and metabolism

- altered concentrations of many hormones in CKD influence function of many systems
  - ↓ formation/activity
    - **1, 25-dihydroxycholecalcipherol**
      - contributes to MBD (esp. osteomalacia)
    - **erythropoietin**
      - untreated anemia places patients at risk for
        - cardiovascular events (hypoxia)
        - more rapid progression of CKD
        - significantly decreased quality of life
    - prostaglandins
  - ↑ formation/activity
    - **angiotensinogen**
      - contributes to CVD morbidity and mortality
    - **parathormone**
      - contributes to MBD (esp. renal osteodystrophy)
- metabolic abnormalities in CKD/CHRI
  - metabolism of **proteins** and **amino acids**
    - malnutrition in proteinuria and decreased dietary intake of protein (necessary though)
    - increased protein catabolism in muscle
    - changes of intracellular AA concentrations in tissues as well as in plasma (↓essential, ↑non-essential)
  - saccharide metabolism (**insulin resistance**)
    - fasting hyperglycemia in 30 % h of CKD patients
    - impaired glucose tolerance in oGTT in 60%
    - ↑ plasma insulin due to peripheral resistance (post-receptor defect)
      - moreover secretion of insulin stimulated also by ↑K+ (insulin promotes transport of K+ into cells)
  - lipid metabolism - **hyperlipidemias**
    - present in ~70% of CKD patients
    - pathogenesis of secondary hyperlipidemia is complex
      - ↓ catabolism (↓LPL) and ↑ liver synthesis of lipoproteins
    - ↑ VLDL, LDL and TAG, ↓ HDL

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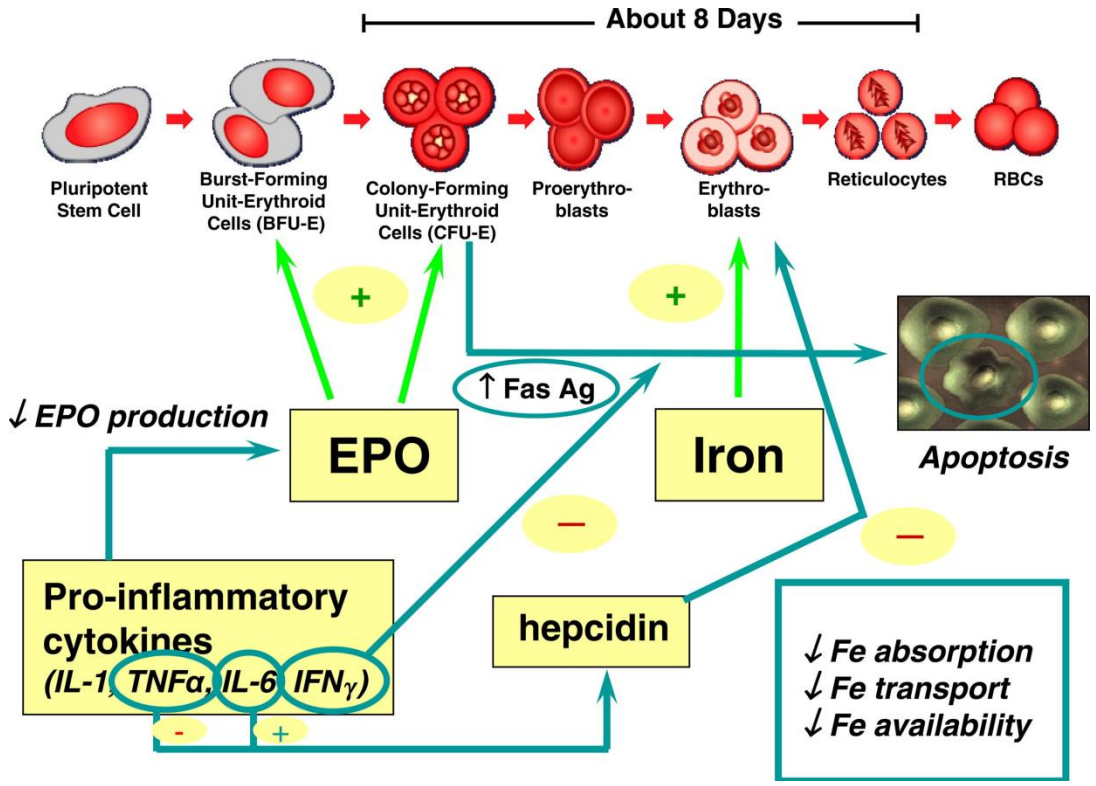
Anemia in CKD



- The cause of anemia in patients with CKD is **multifactorial**
- The most well-known cause is inadequate **erythropoietin** (EPO) production
  - EPO is produced in the peritubular capillary endothelial cells in the kidney relying on a feed-back mechanism measuring total oxygen carrying capacity
    - subsequent production of hypoxia inducible factor (HIF)
  - EPO then binds to receptors on erythroid progenitor cells in the bone marrow(BFU-E and CFU-E). With EPO present, these erythroid progenitors differentiate into reticulocytes and red blood cells (RBCs)
  - The absence of EPO leads to pre-programmed apoptosis mediated by the Fas antigen
- There are other factors in chronic kidney disease which contribute to anemia
  - **pro-inflammatory cytokines** decreasing EPO production and inducing apoptosis in CFU-E
  - inflammatory cytokines have also been found to induce the production of **hepcidin**, a recently discovered peptide generated in the liver, which interferes with RBC production by decreasing iron availability for incorporation into erythroblasts.
- **Red blood cells** also have a **decreased life span** in patients with CKD
- **Uremic toxins** have been implicated as contributing to apoptosis as the anemia will often improve after initiation of dialysis

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MINERAL BONE DISEASE (MBD) IN CKD

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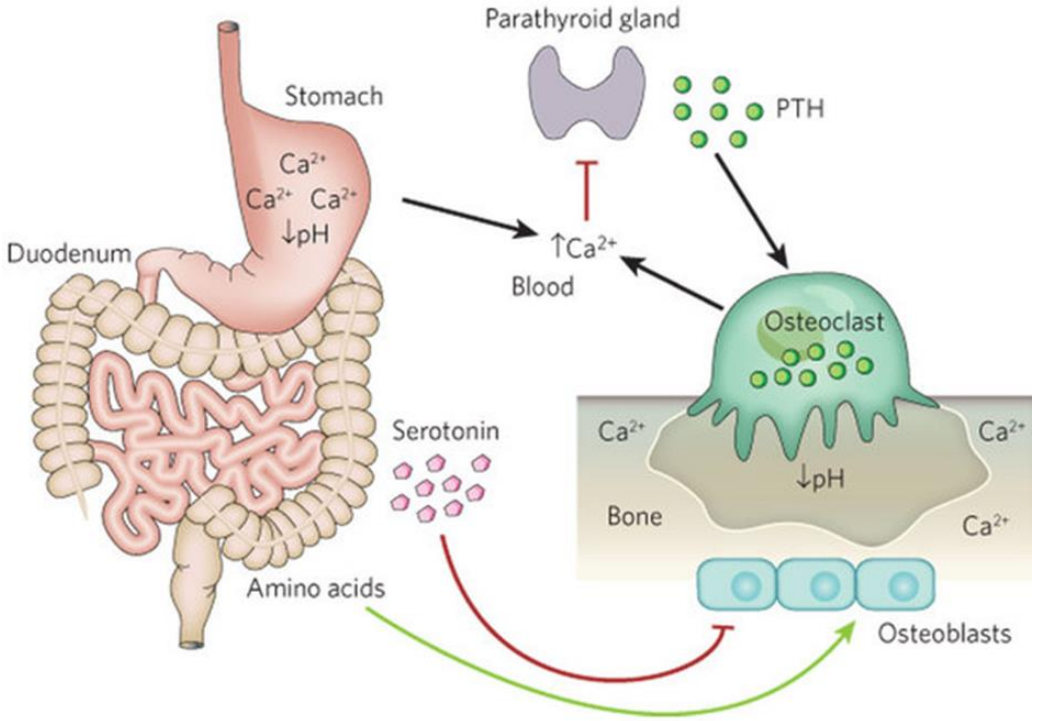
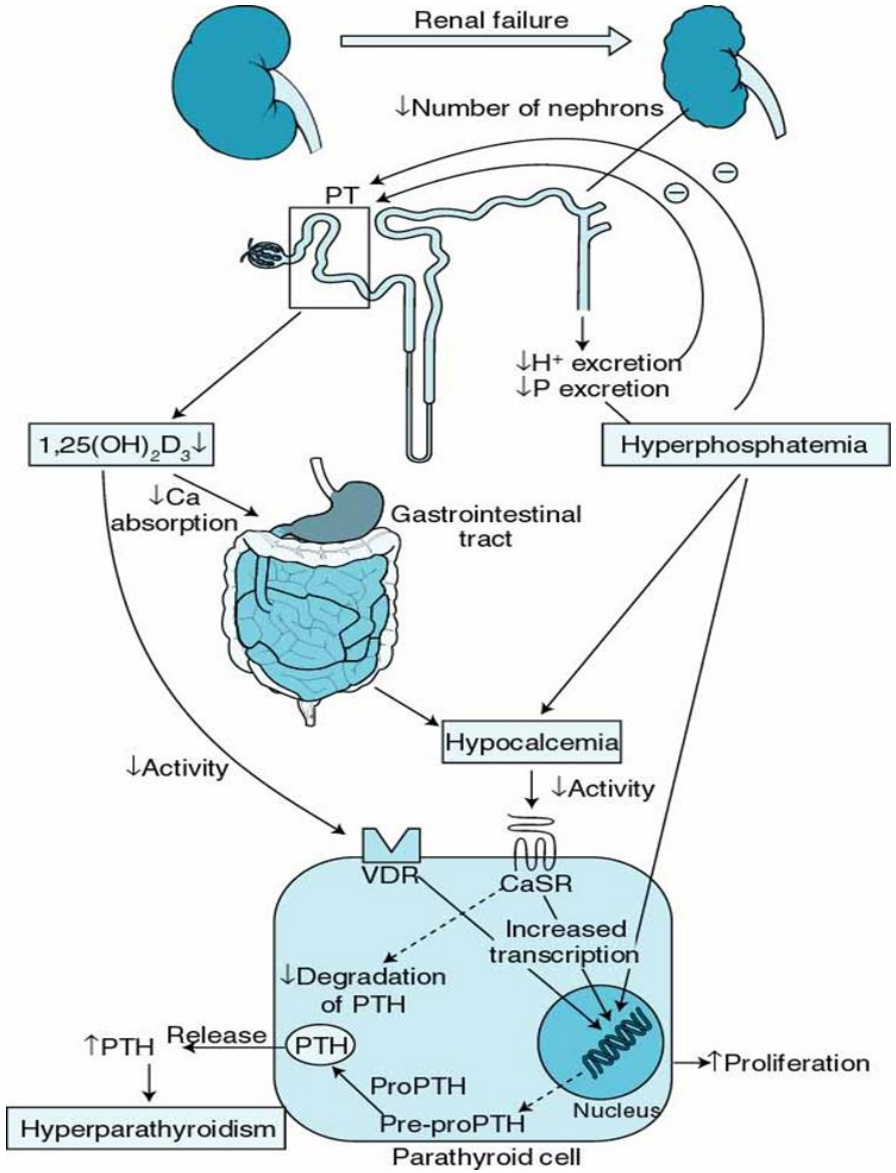
Terminology

- **osteoporosis** ("porous bones“)
  - the bone mineral density (BMD) is reduced, bone microarchitecture deteriorates, and the amount and variety of proteins in bone are altered
  - an increased risk of fracture
  - causes: old age, inactivity, menopause
    - ↓ sex steroids (esp. estrogens) → ↓synthesis of collagen (prevent mineralization)
- **osteomalacia**
  - softening of the bones caused by defective bone mineralization secondary to inadequate amounts of available phosphorus and/or calcium
  - causes: hypovitaminosis D or hypophosphatemia
    - lack of calcium or phosphate in the body
      - calcium : phosphate ratio prevents mineralization
    - ↓vitamin D → hypocalcaemia → ↑ PTH → ↑ calcaemia but ↓ phosphataemia
- **osteodystrophy**
  - bone mineralization deficiency associated with either high or low bone turnover as a consequence of hyperparathyroidism
    - primary HPTH: ↑ PTH → ↑ calcemia but ↓ phosphatemia
    - secondary (renal osteodystrophy): ↑ phosfatemia → ↓calcemia → ↑ PTH
  - in advanced stage accompanied by **osteitis fibrosa**



Hyperphosphatemia/hypocalcemia in CKD



- abnormal metabolisms of Ca, phosphorus, PTH and vitamin D in CKD
- ↓ excretion of phosphorus in kidney when ↓ GFR leads to **hyperphosphatemia** and
  - a) ↓ ionized Ca, **hypocalcaemia** stimulate production of PTH
    - altered calcium : phosphate product leads to calcium phospate precipitation and extraosseal calcifications
  - b) inhibition of 1α-hydroxylase in proximal tubular cells and ↓production of active D vit.
    - impaired intestinal absorption of Ca in GIT aggravates hypocalcaemia and this way to another ↑ of PTH
  - c) blockade of inhibitory action of vit. D on parathyroid bodies
    - less vit. D binds to VDR receptors in parathyroid bodies , ↓ inhibition of transcription of the PTH gene and ↑secretion of PTH
  - d) direct stimulatory effect on parathyroid bodies
- development of **secondary hyperparathyroidism**

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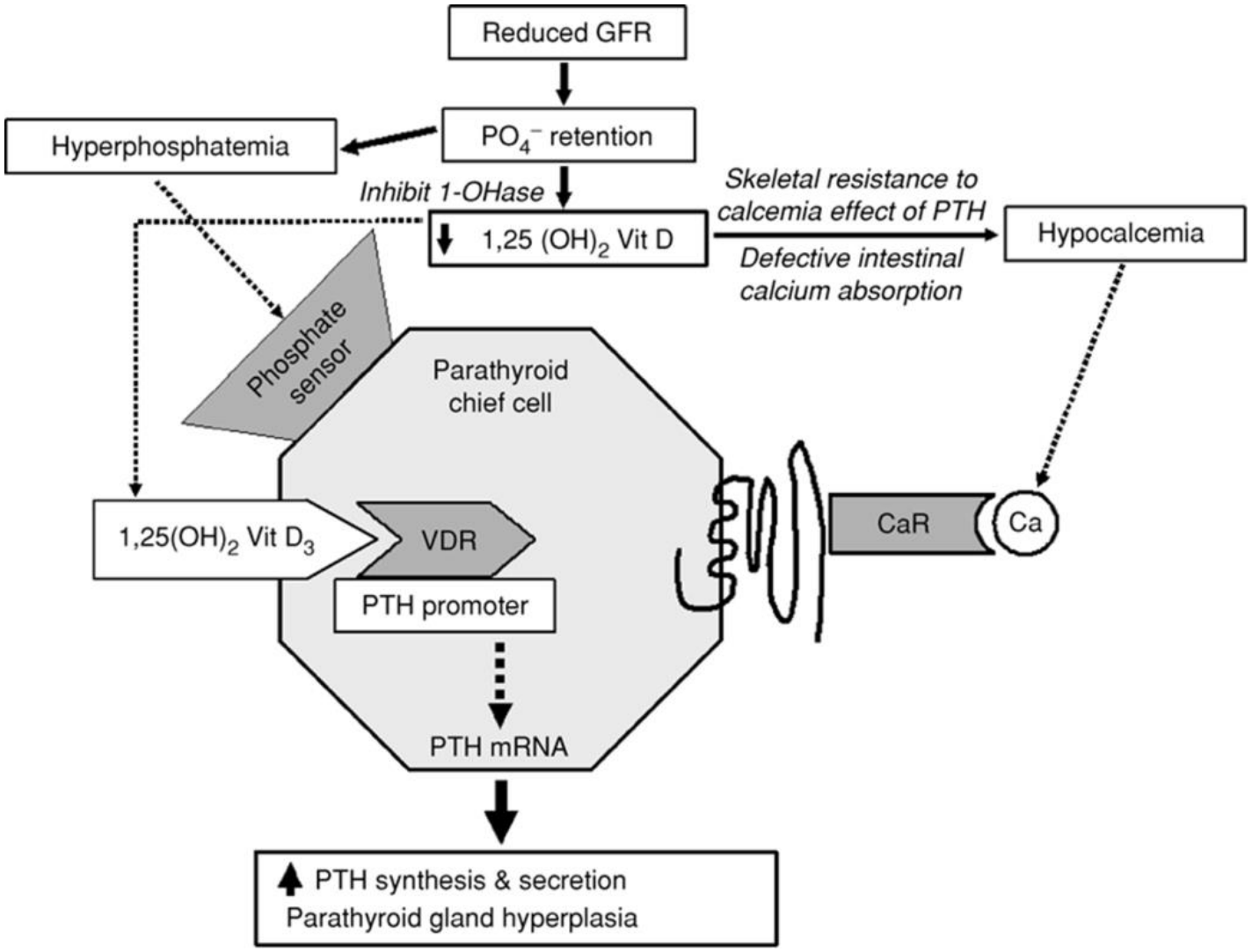
Pathophysiology of secondary hyperparathyroidism in CKD



- consequence of phosphate retention and reduced renal production of active vitamin D, resulting in hyperphosphatemia and hypocalcemia. With GFR <70 mL/min, renal excretion of phosphate can no longer keep pace with GIT absorption, and phosphorus retention occurs. Hyperphosphatemia inhibits the renal 1–alpha-hydroxylase, so that production of active 1,25 dihydroxy vitamin D_3 by the kidney is reduced. Vitamin D deficiency then leads to hypocalcemia as a consequence of defective gastrointestinal calcium absorption and skeletal resistance to the calcemic effect of PTH. The serum-ionized calcium is the most important factor regulating PTH secretion. The effects of calcium on parathyroid cells are mediated by a membrane-bound calcium-sensing receptor (CaR). Low serum calcium leads to an increase in PTH . In contrast, active vitamin D modulates PTH production in the parathyroid by binding to the cytoplasmic vitamin D receptor (VDR). The vitamin D-VDR complex binds to the PTH promoter and inhibits the transcription of PTH mRNA. Thus, vitamin D deficiency will lead to increased production of PTH message. A chronic decrease in vitamin D levels also leads to parathyroid cell proliferation and gland hyperplasia.

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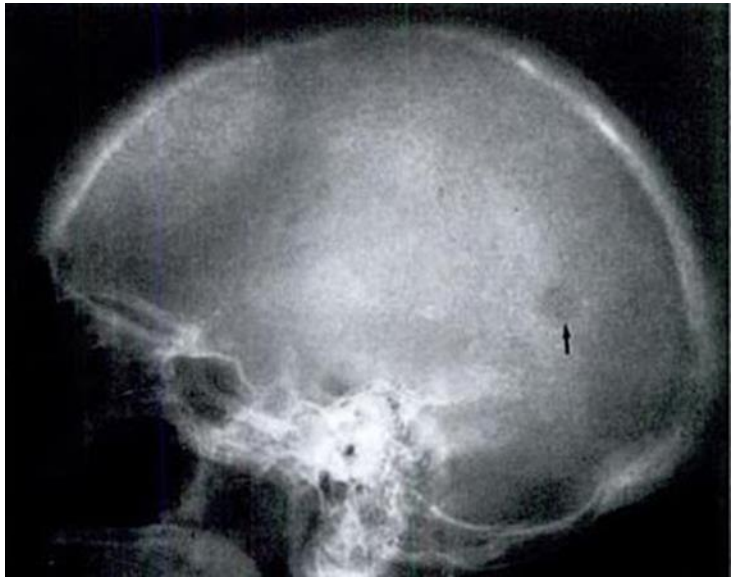
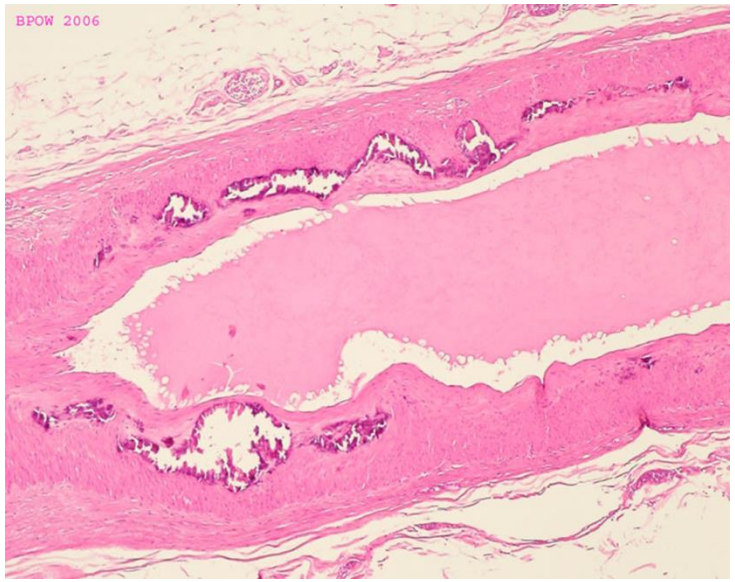
Renal osteopathy (synonym mineral bone disease, MBD)

- adverse complication of advanced CKD
- main features
  - — abnormal mineral metabolism
  - — increased bone fragility and impaired linear bone growth
    - fractures, pain, limited mobility
  - — soft tissue, vascular and valvular calcification
    - arterial calcification is an active process similar to bone formation with participation of multiple factors (osteopontin, osteoprotegerin, RANKL, RANK, FGF23 and fetuin A)
- MBD consists of a mixture of bone abnormalities
  - — osteodystrophy (+ osteitis fibrosa cystica)
  - — osteomalacia
  - — osteoporosis





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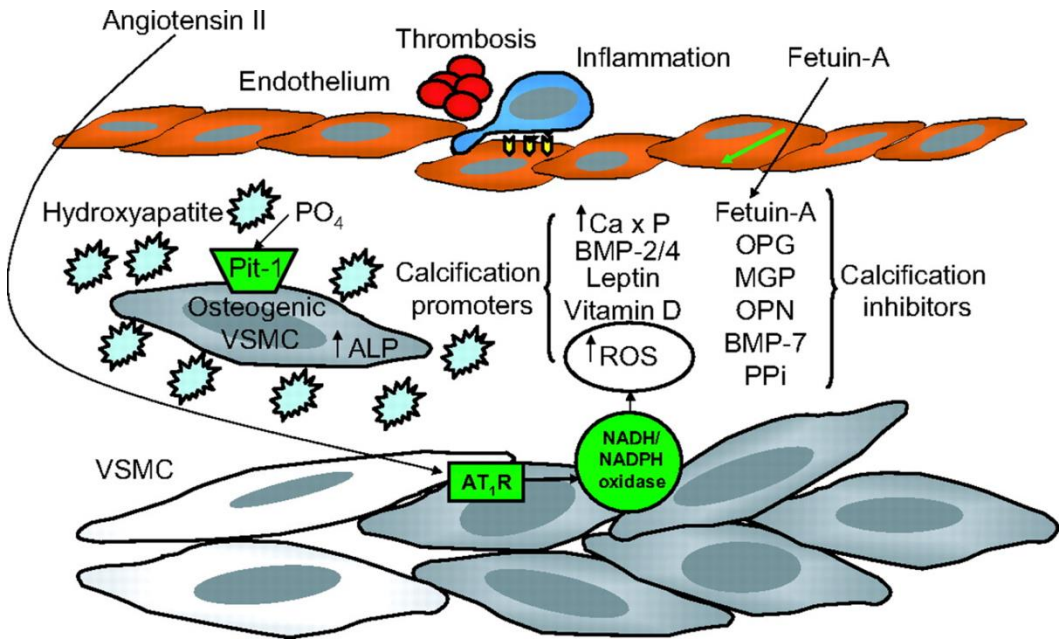
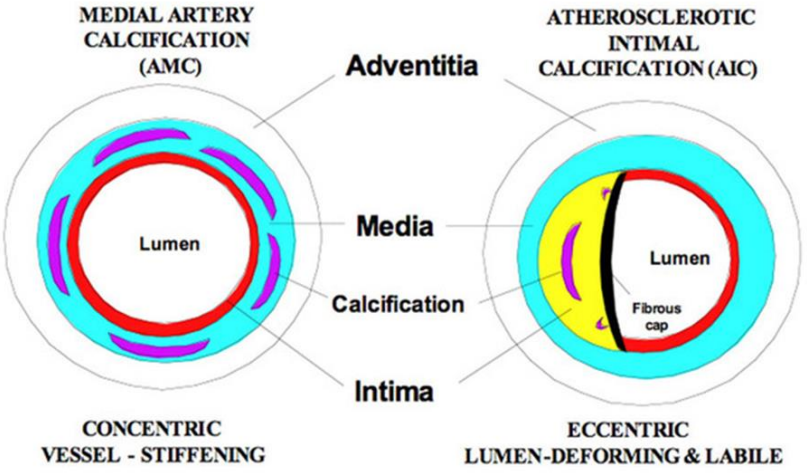
CV consequences of CKD-MBD

- causal abnormalities
  - arterial hypertension (90%)
  - hyperlipidemia, diabetes
  - sec. anemia (anemic hypoxia)
  - hyperhydration (volume overload)
  - calcification (arteries and valves)
  - uremic toxins
  - others
    - oxidative stress, hypofibrinolysis (= thrombophilia), homocystein
- manifestation
  - **LV hypertrophy**
  - **CAD**
    - compared to non-CKD patients ↑ media thickness, ↓ lumen diametr and more calcification, due to uremic neuropathy quite often „silent ischemia“
  - **arrhythmias**
    - due to hyperhydration and electrolyte dysbalances , event. pericarditis and CAD (+ myocardial ischemia during hypotension in dialysis)
- consequences
  - cardio-renal resp. reno-cardiac syndrome
    - pre-existing heart disease worsens CKD prognosis and vice versa





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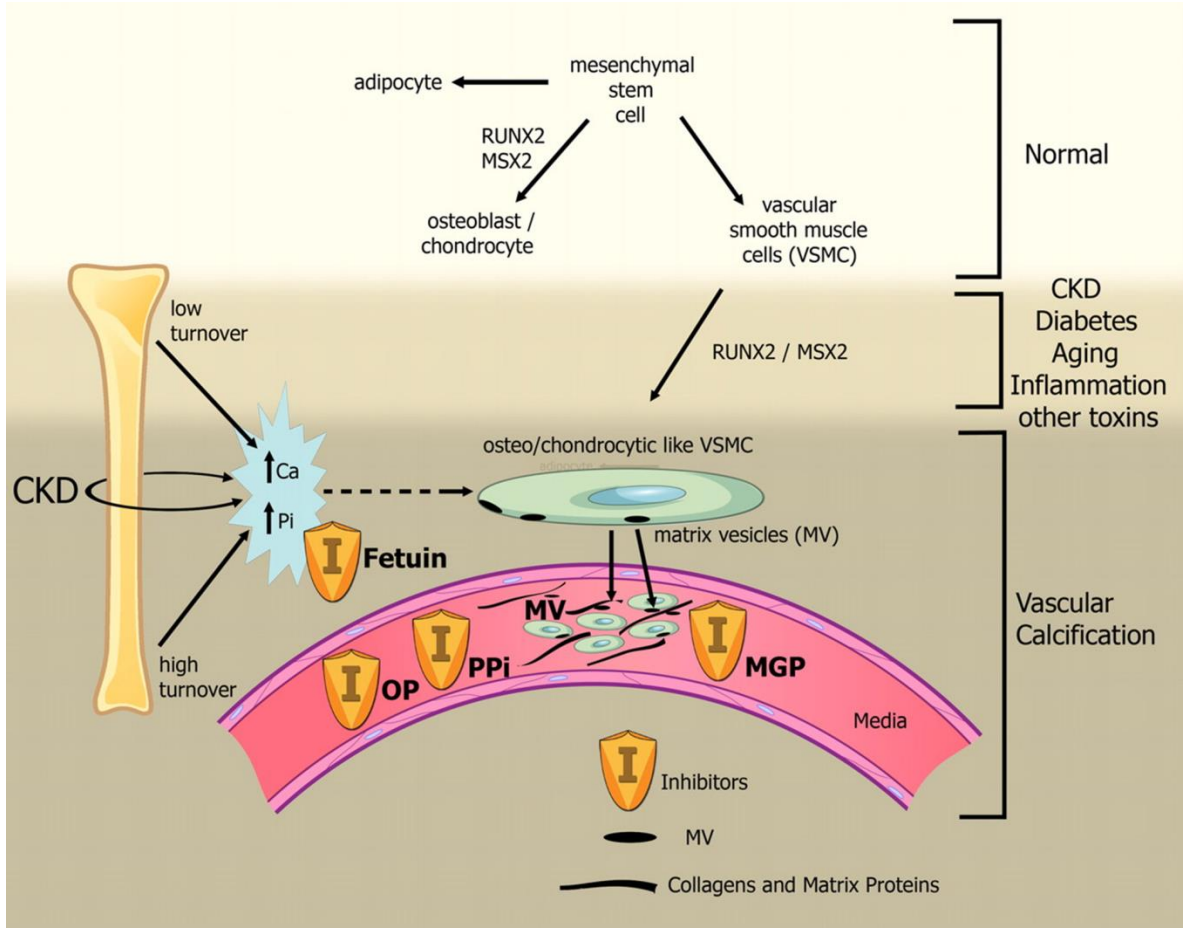
Pathogenesis of vascular calcification



- Normally, mesenchymal stem cells differentiate into adipocytes, osteoblasts, chondrocytes, and vascular smooth muscle cells (VSMCs). In the setting of chronic kidney disease (CKD), diabetes, aging, inflammation and multiple other toxins, these VSMCs can de-differentiate or transform into chondrocyte/osteoblast-like cells by upregulation of transcription factors such as Runx2 and Msx2. These transcription factors are critical for normal bone development and thus their upregulation in VSMCs is indicative of a phenotypic switch. These osteo/chondrocytic-like VSMCs then become calcified in a process similar to bone formation. These cells lay down collagen and non-collagenous proteins in the intima or media and incorporate calcium and phosphorus into matrix vesicles to initiate mineralization and further grow the mineral into hydroxyapatite. Ultimately, whether an artery calcifies or not depends on the strength of the army of inhibitors standing by in the circulation (fetuin-A) and in the arteries
- MGP = matrix gla protein; OP = osteopontin; PPi = pyrophosphate

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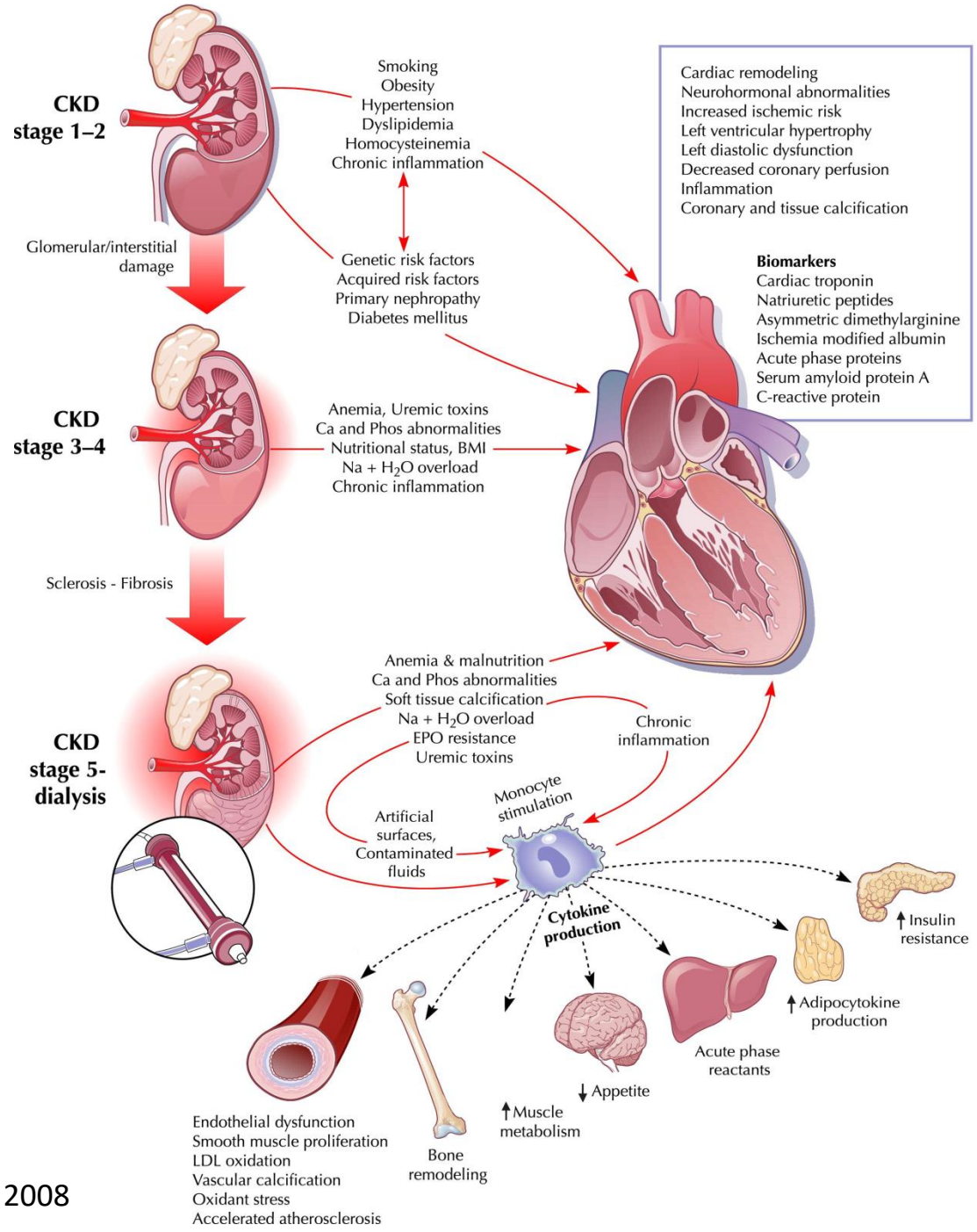
Pathophysiological interactions between heart and kidney (= reno-cardiac syndrome)

CKD contributing to decreased cardiac function, cardiac hypertrophy, or increased risk of adverse cardiovascular events)

BMI = body mass index; EPO = erythropoietin; LDL = low-density lipoprotein



Ronco C et al, JACC 2008

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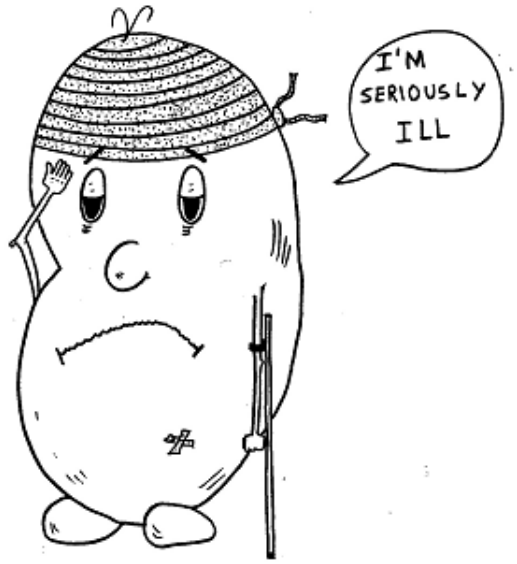

CHRONIC KIDNEY FAILURE

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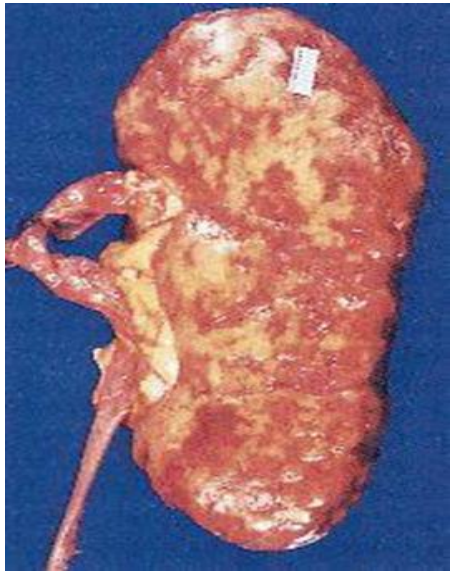
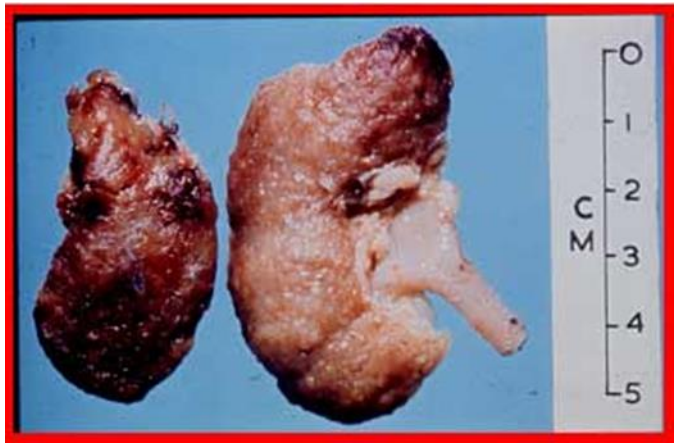
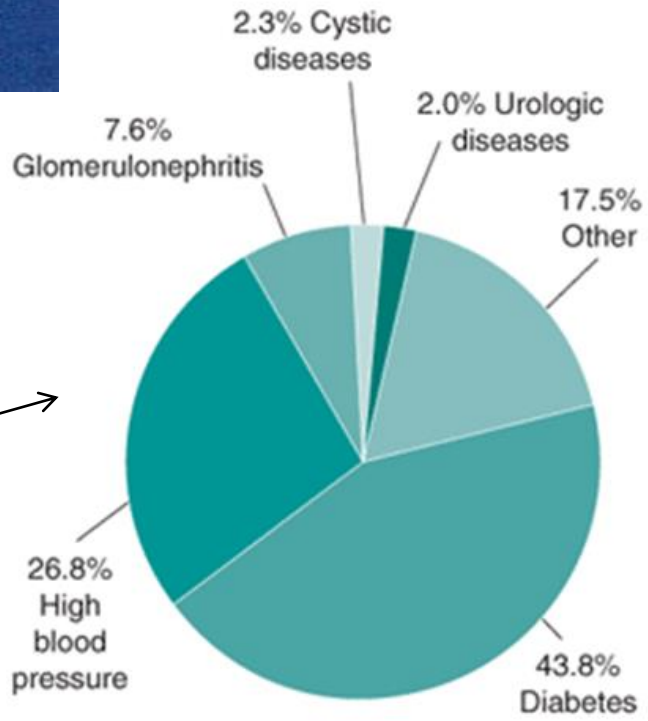
Chron. renal failure = CKD stage 5 = ESRD

- appearance of small, irregular shape, scarred, **shrunken kidney** with granular surface
- full blown symptoms of **uremia**
- it is necessary to
  - treat conservatively but aggressively (only symptomatic though)
    - ↓ fluid intake
    - ↓ Na+, K+ intake
    - ↓ protein intake
    - complications
      - anemia, MBD, hypertension, infections, …
    - modification of drug dosage!!
  - kidney replacement therapy
    - dialysis
    - transplantation
  - etiology of the most common CKD causes progressing to ESRD







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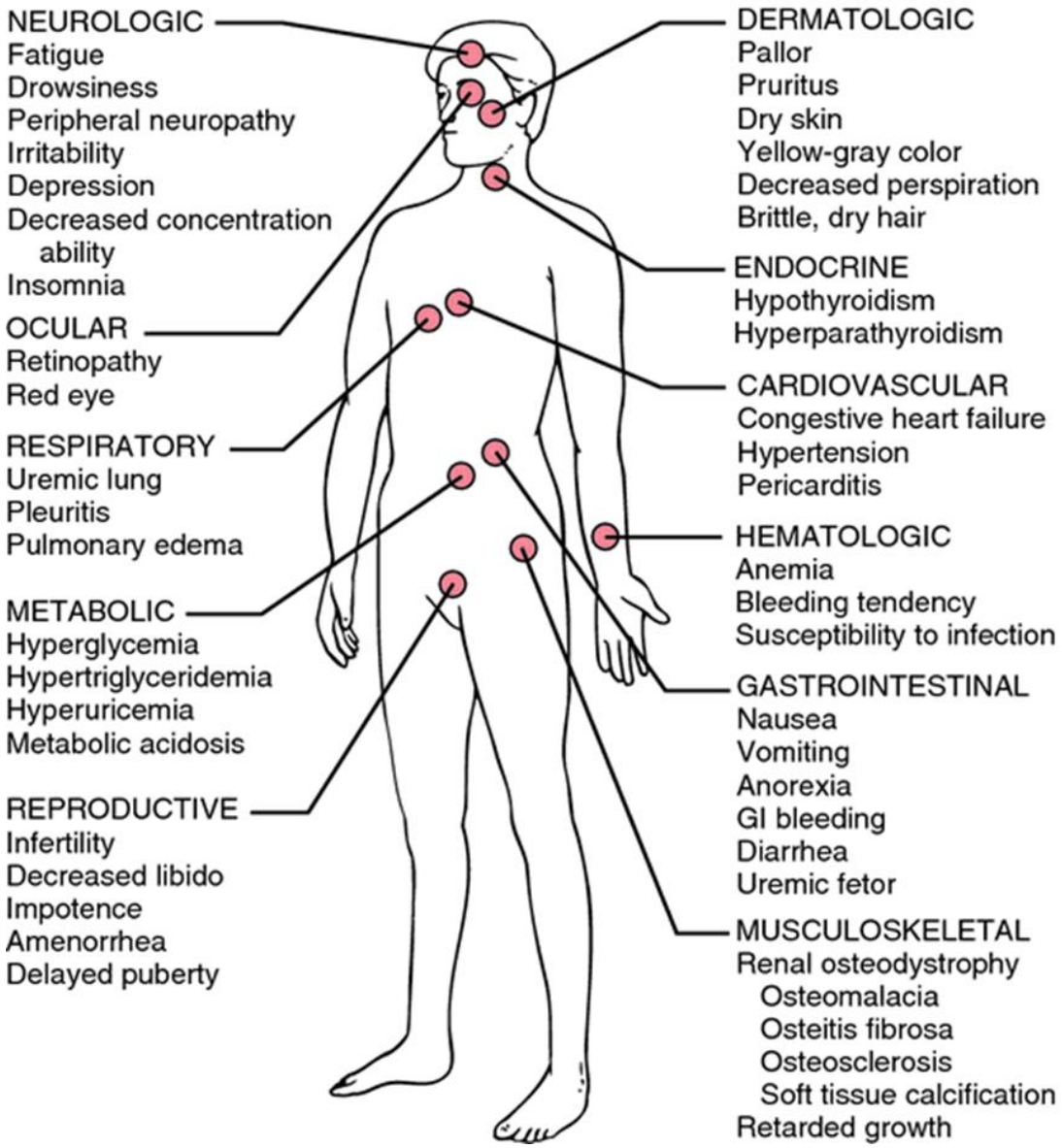
Uremic symptoms



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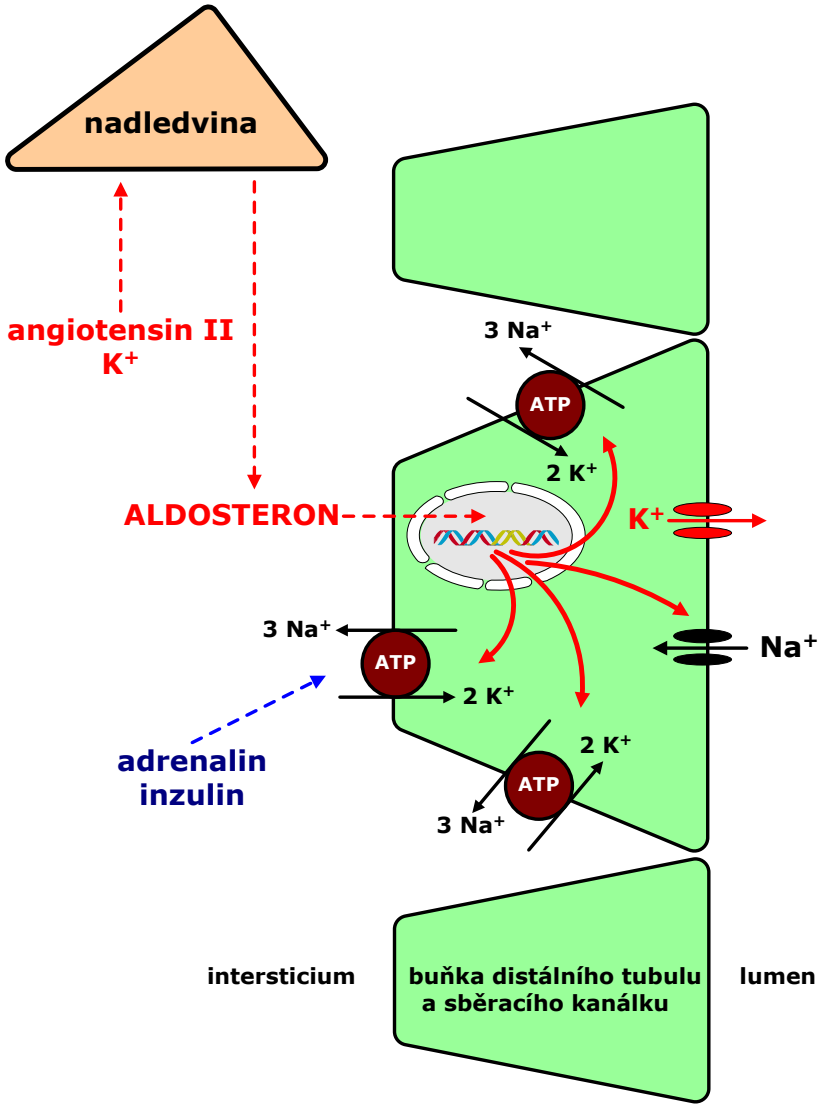
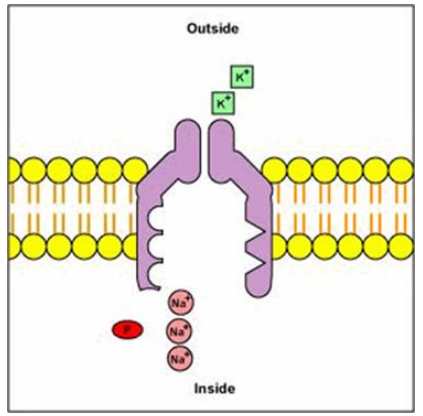
Hypercalemia

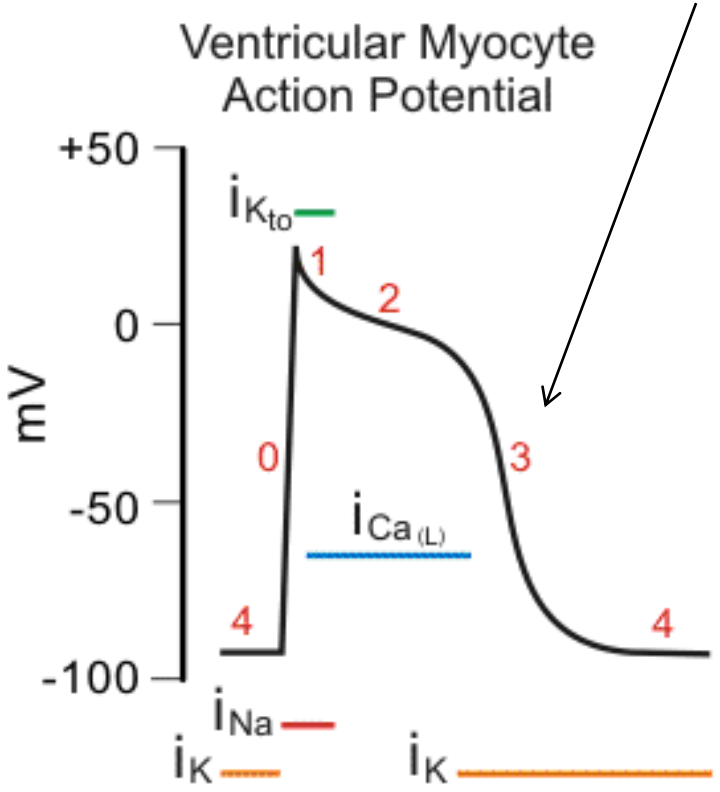
- 98% K+ in ICF
  - 35-50x more than in ECF (3.8 – 5.5 mmol/l)
  - Na+/K+ ATPase
- higher permeability of membrane for K+ that other cations
  - contribution to the resting membrane potential
    - passive K flow from the cell along the conc. gradient limited by intracellular anoints
  - changes of kalemia in ECF are slowly reflected in ICF too
- disorders of K balance in organism:
    - ↑ dietary intake with intact kidneys is not a problem
    - decreased K excretion in renal insufficiency and ESRD
- disorders of distribution – multiple factors influence K distribution between ECF and ICF:
  - disruption of cells/ hemolysis
  - osmolality
  - acidosis
- regulation of [K+] in ECF
  - (1) redistribution of K+ (from ECF to ICF)
    - pH, insulin, adrenalin
  - (2) renal excretion
    - aldosterone, [K+]



Effect of hyperkalemia on heart

- **effect depends on the magnitude of change (= how much) and speed of change (= how fast)!!!!**
  - therefore there are significant differences between acute and chronic renal failure
- hyperkalemia
  - ↑ excitability by moving the resting membrane potential closer to the threshold
    - passive K flow from the cell along the conc. gradient limited by intracellular anoints is diminished by ↑[K+] in ECF, retention of K+ in ICF and depolarisation
  - initially also quicker repolarization (phase 3)
    - activating substrate effect on Na+/K+ ATP-ase (↑ availability of K+ for exchange)
  - later when ↑↑ [K+] inhibition of repolarization
    - too low concentration gradient
  - finally when ↑↑↑ [K+] cardiac arrest
    - inhibitory effect on Na+/K+ ATP-ase (it cannot pump against extremely high concentration of K+ in ICT)
    - too close shift of resting m. potential to threshold disables opening (voltage gated) of Na+ channels





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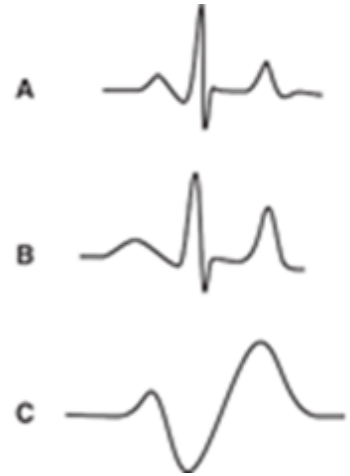
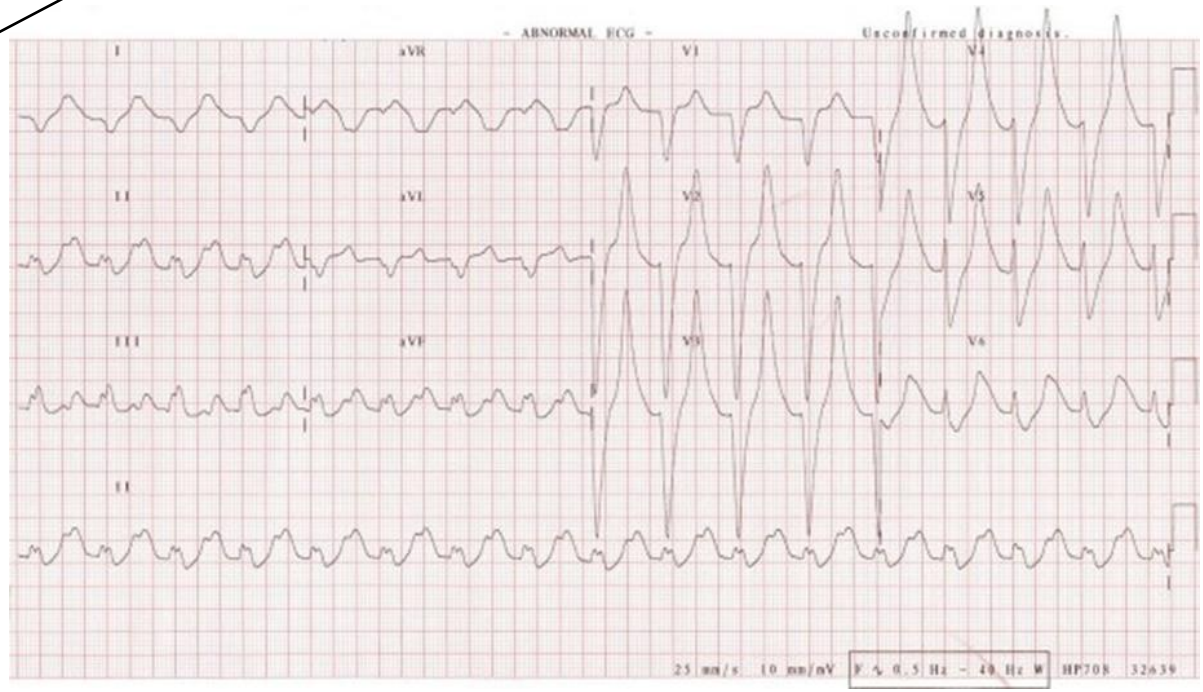
Hyperkalemia (K+ >5.5 mmol/l)

- affected all types of muscles
  - skeletal
  - smooth
  - myocardium
- signs
  - arrhythmia (ECG):
    - < 7 mmol/l
      - spiked T waves
      - widened QRS
      - prolonged PR interval
      - flattened P waves
    - > 7 mmol/l
      - lowered voltage
      - bradycardia
    - > 8 mmol/l
      - „sinusoidal“ shape of QRS
      - idioventricular rhythm
      - ventricular fibrillation, arrest
  - paresthesias, weak reflexes, paresis and obstipation





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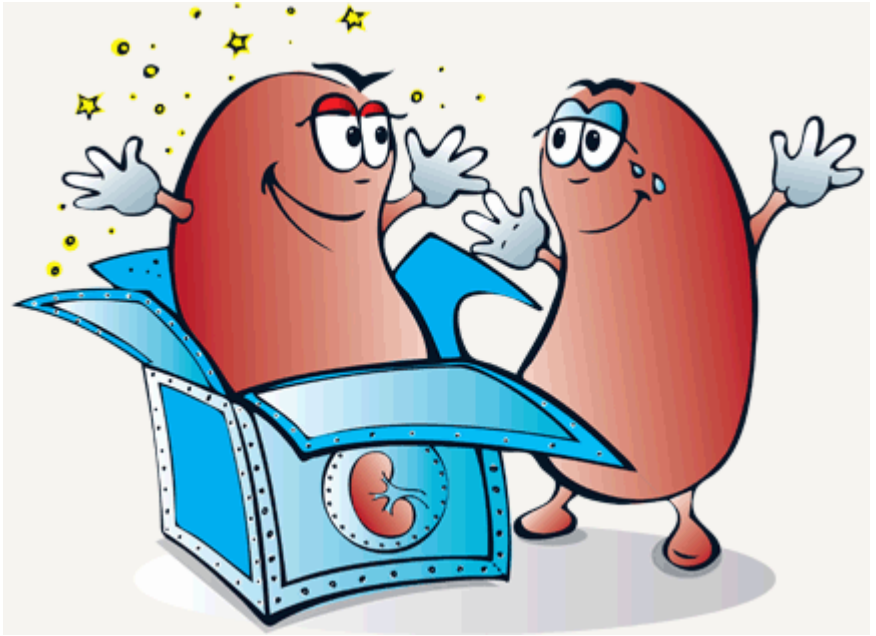

RENAL REPLACEMENT THERAPY - METHODS

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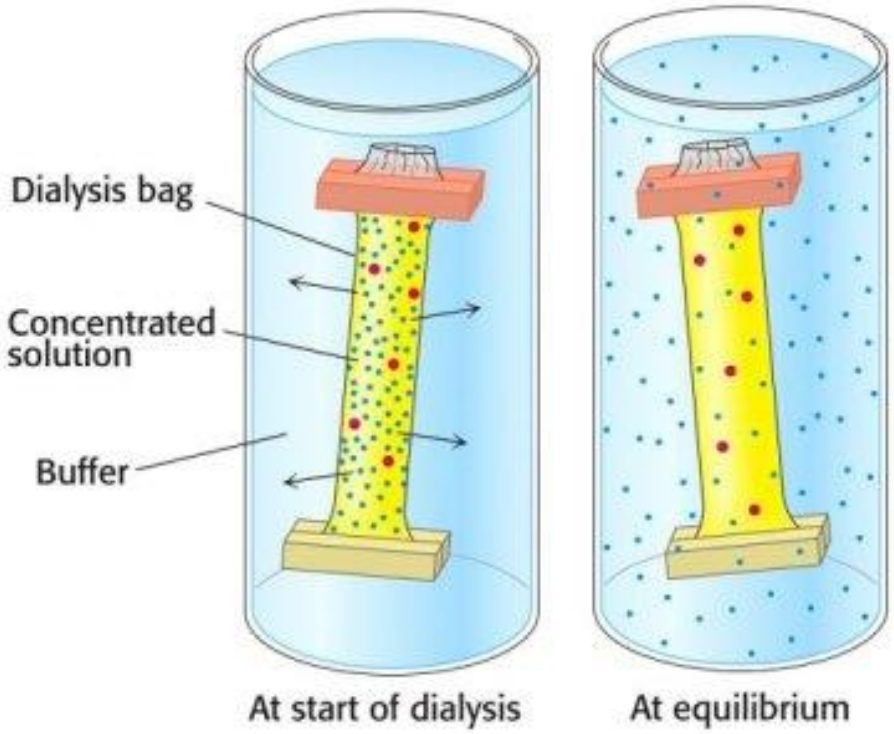
Principle of hemodialysis



- for the first time in 1943 in Netherlands
- 3 main physical principles
  - **diffusion** and **ultrafiltration** of solutes across a semipermeable membrane
  - **counter current flow** where the dialysate is flowing in the opposite direction to blood flow in the extracorporeal circuit
- standard regimen
  - three times a week, 3–4 hours per treatment schedule
- dialysis solution
  - **urea, creatinin, potassium** and **phosphate** diffuse into the dialysis solution (high in blood, low in solution)
  - concentrations of **sodium** and **chloride** are similar to those in plasma to prevent loss
  - **sodium bicarbonate** is added in a higher concentration than plasma to correct blood acidity
  - **glucose** is also added to balance glycaemia and prevent hypoglycemia

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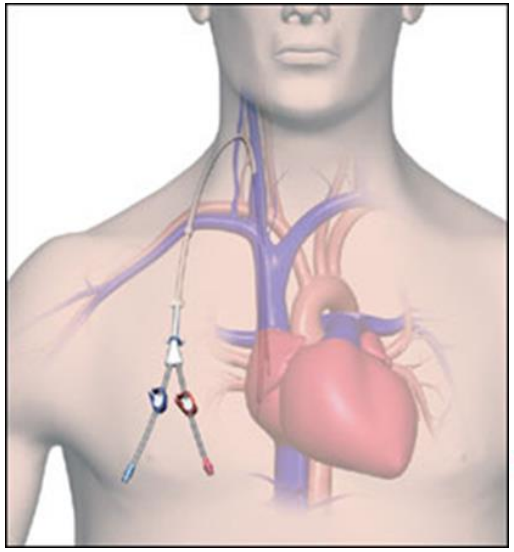
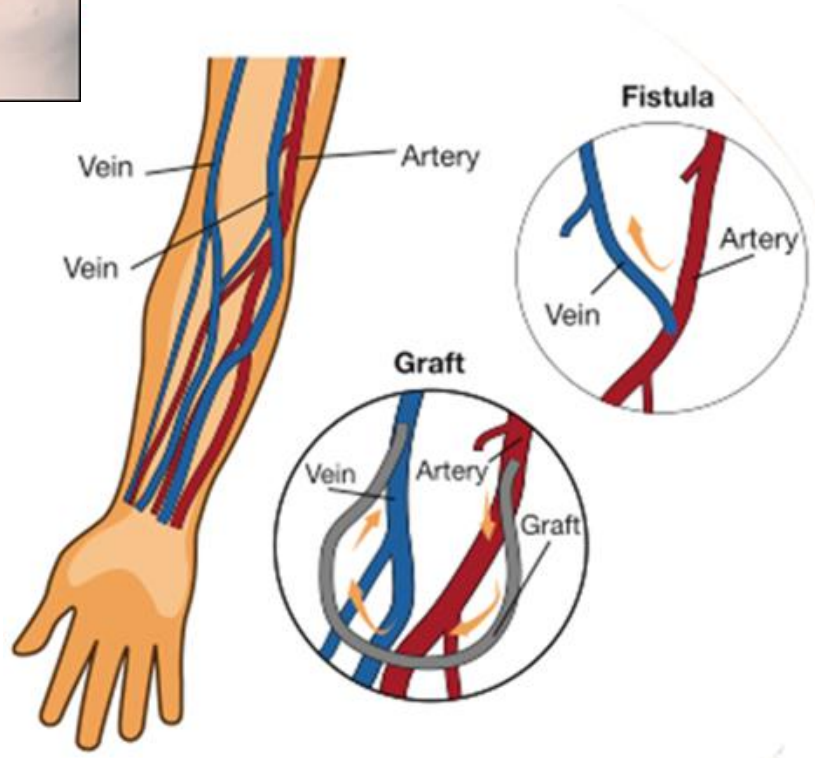
Blood stream access





- temporary – useful for limited number of procedures
  - —two-way catheter
    - v. subclavia, v. jugularis, v. femoralis
  - —risks: bleeding, thrombosis, stenosis, infection
- permanent – in patients in regular HD program
  - —arterio-venous fistule
    - between a. radialis and v. cephalica
  - —synthetic graft

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HD side-effects and complications

- **hypotension**
  - — most often, nearly 30% of dialyses
- **leg-cramps, nausea** and **headaches**
  - — second most common complication
  - — due to volume depletion during ultrafiltration or ion dysbalance
- **disequilibrium syndrome**
  - — u acute HD with high pre-dialysis BUN and too fast HD
    - sudden drop of BUN is not reflected with urea decrees in CSF
    - ↑ CSF osmolality causes intracranial hypertension and brain edema
  - — metabolic acidosis also contributes
    - during HD plasma bicarbonate (HCO_3^-) level rapidly increases, but bicarbonate cannot readily pass across the BBB, whereas carbon dioxide (CO_2) diffuses rapidly. The initial increased passage of carbon dioxide into the CSF and brain leads to a reduction in pH (Henderson-Hasselbach equation), and intracellular acidosis results in the breakdown of intracellular proteins to create idiogenic osmoles that create an osmotic gradient for water movement into the brain
  - — stop of HD and anti-edematous therapy
- **infection** (esp. endocarditis and osteomyelitis)
- long term (neuropathies, amyloidosis)

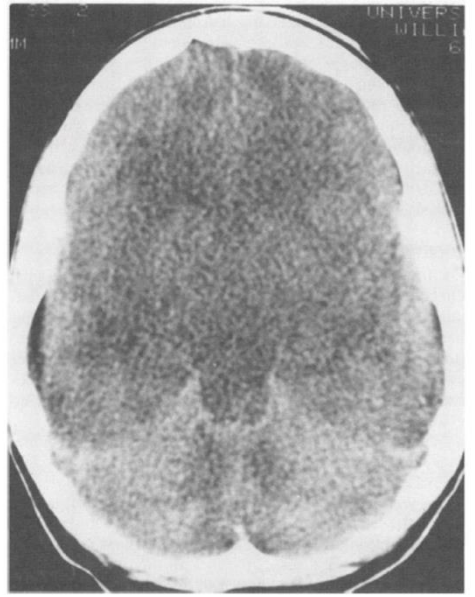

Figure 1.—An enhanced computed tomographic scan of the head shows diffuse cerebral edema.

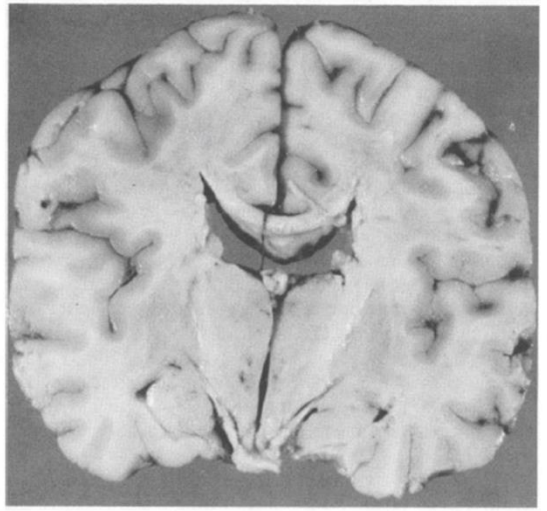

Figure 2.—A coronal section of the brain shows severe cerebral edema.

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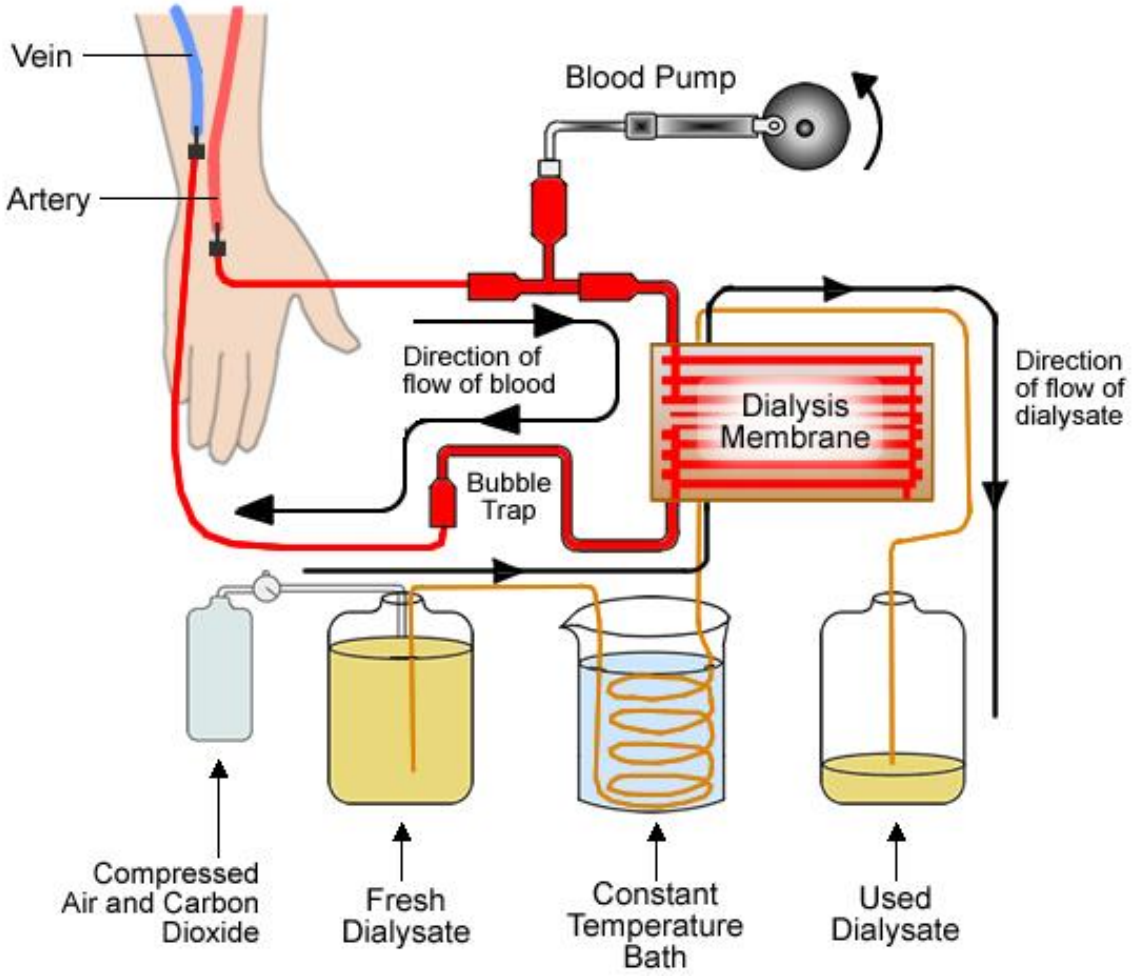
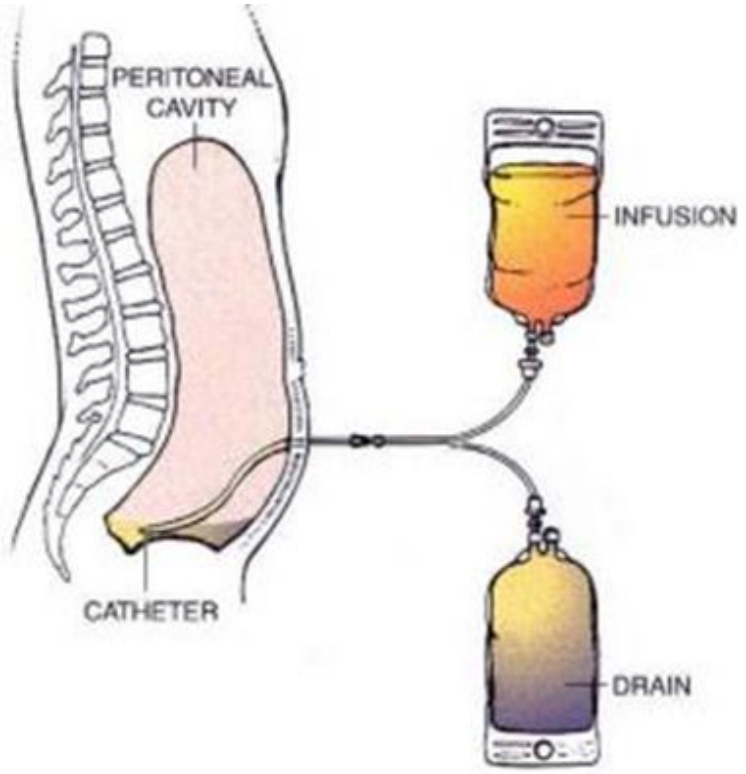
HD vs. peritoneal dialysis





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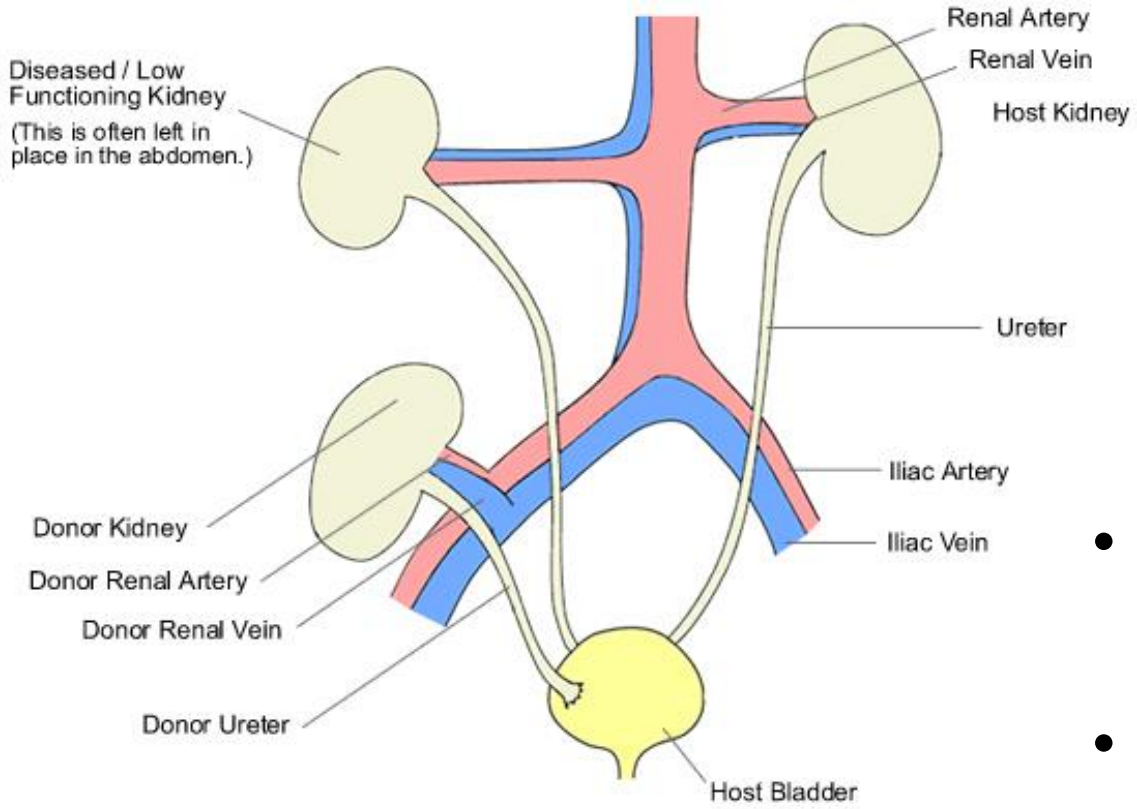
Kidney transplantation



- necessity to obtain donor kidney
  - cadaverous
  - from living donor (often relative)
- immunological compatibility
  - risk of rejection
    - hyper-acute
    - acute
    - chronic
  - risks associated with immunosuppressive therapy

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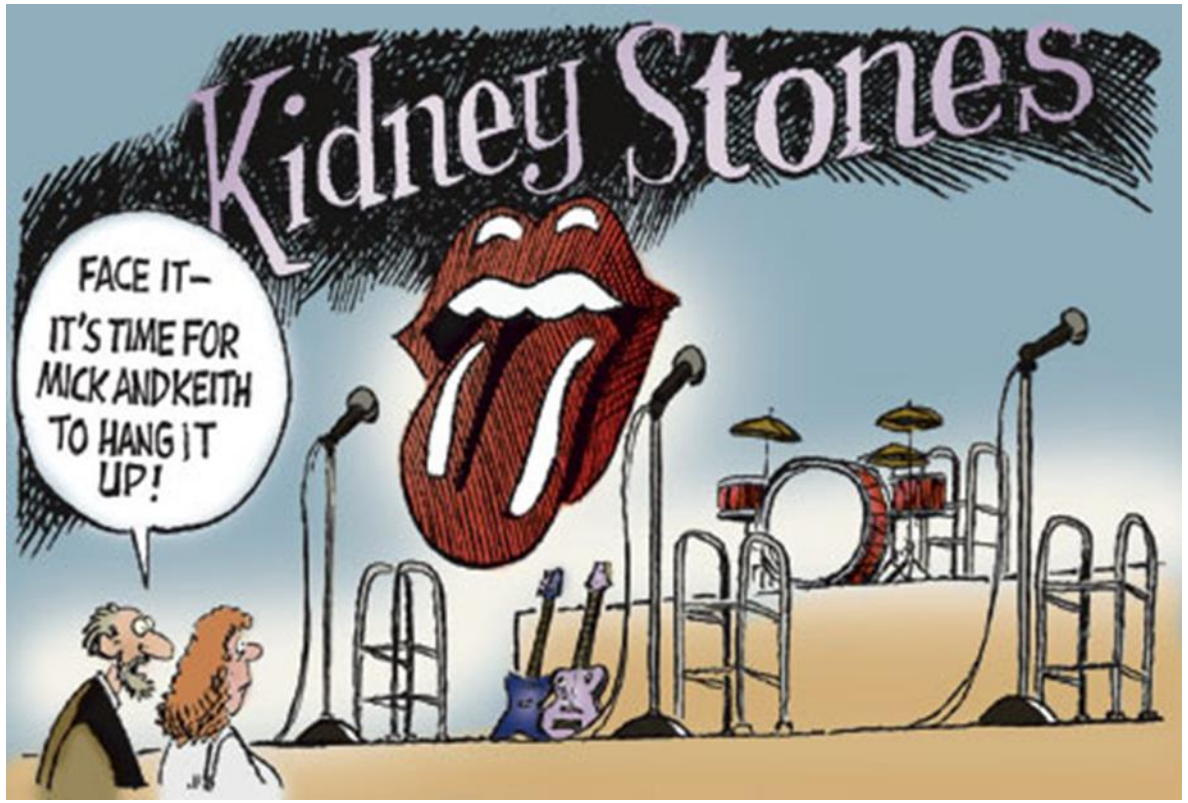
Kidney Stones
FACE IT–
IT'S TIME FOR
MICK AND KEITH
TO HANG IT
UP!

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