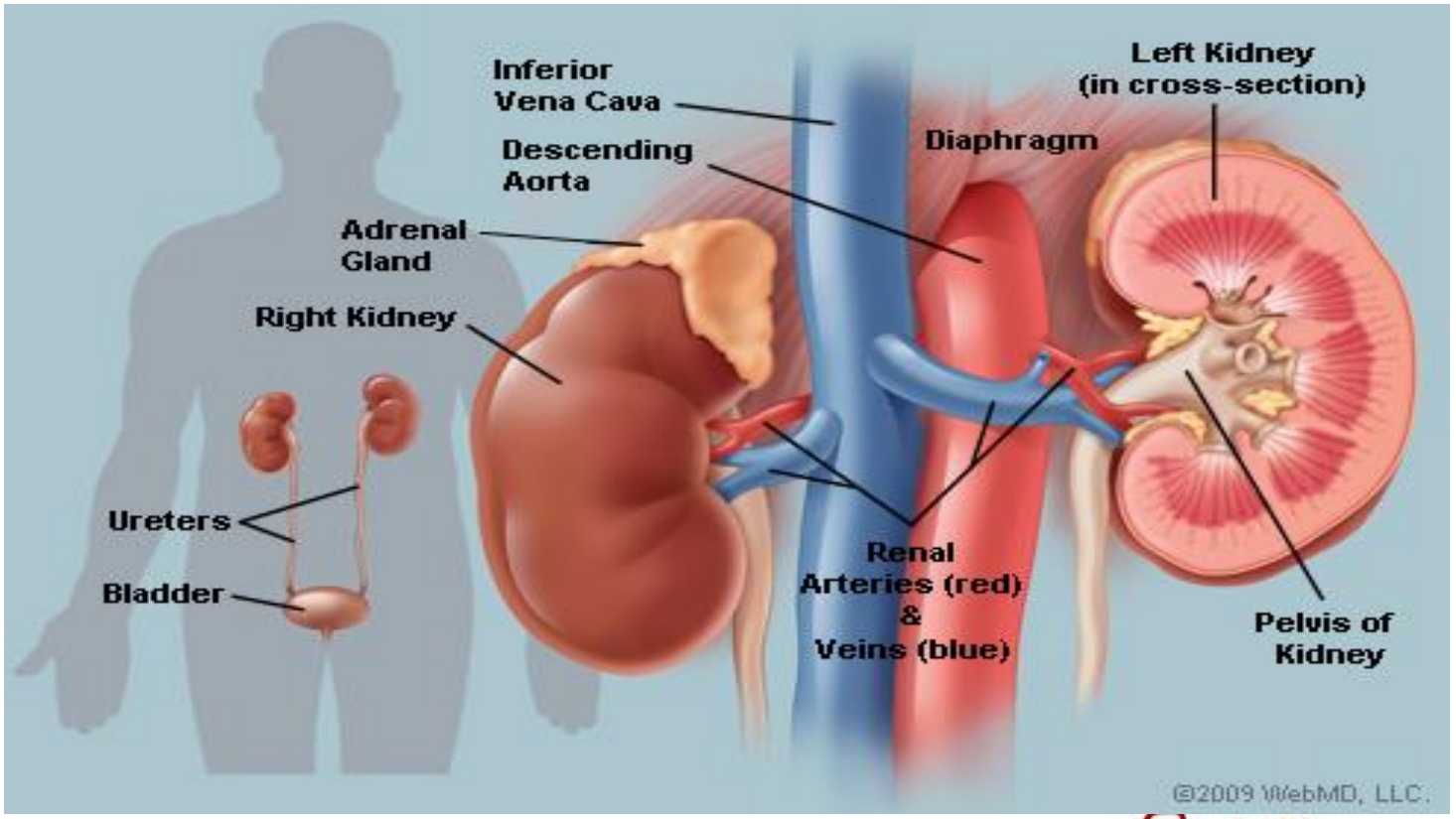
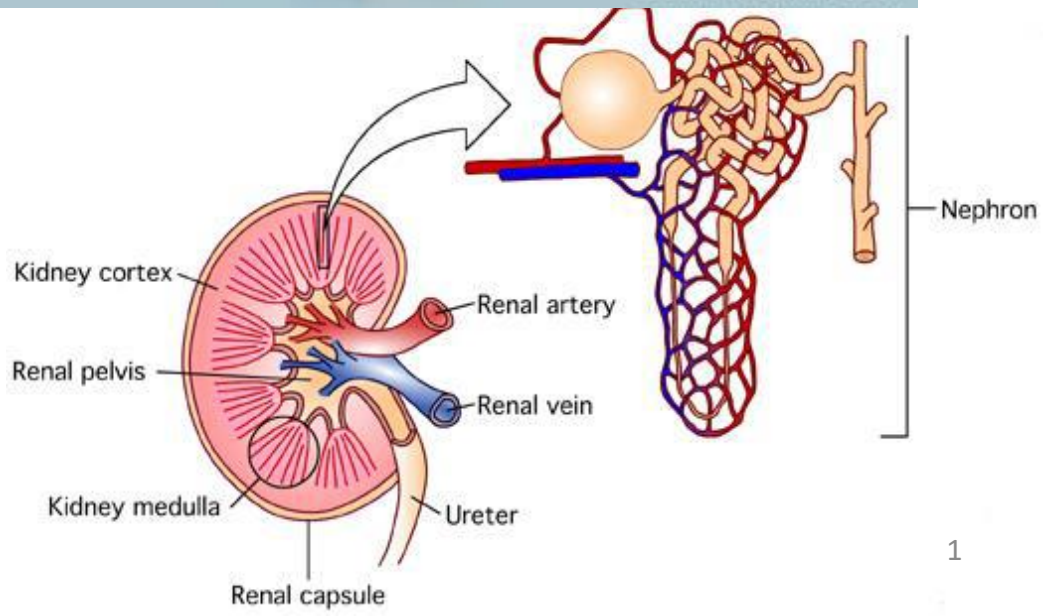


Pharmacotherapy of Renal Disorders



Acute Kidney Injury (AKI)

- AKI is characterized by a rapid/abrupt decrease in GFR and the resultant accumulation of nitrogenous waste products, with or without a decrease in urine output.
- AKI is diagnosed when one of the following criteria is met
  - SCr rises by ≥ 0.3mg/dl within 48 hrs **or**
  - A 50% increase in baseline SCr within 7 days **or**
  - Urine output is < 0.5ml/kg/hr for >6 consecutive hrs

Staging classification of AKI

Stage	Increase in serum Creatinine	Urine out put
1	≥ 0.3 mg/dl increase or 1.5 to 2-fold from baseline	< 0.5 ml/kg/hr for > 6-12 hrs
2	>2- to 3-fold increase from baseline	< 0.5 ml/kg / hr for ≥12 hrs
3	>3-fold from baseline or serum creatinine ≥ 4.0 mg/dl with an acute increase of at least 0.5 mg/dl	< 0.3 ml/kg/ hr for ≥24 hrs or Anuria for ≥12 hrs

- Classifications based on…….Urine output
  - Anureic: < 50mL/24 hr (worse outcome)
  - Oliguric: 50-500 mL/24 hrs
  - Nonoliguric: >500 mL/24 hrs….better outcome

- Other classifications
  - Community-acquired AKI
  - Hospital acquired AKI
  - ICU acquired AKI

Risk factors

- **Volume depletion**
  - Sepsis, hemorrhage, vomiting, diarrhea, poor fluid intake, diuretic use
  - Poor renal perfusion
- **Pre-existing CKD**
- **Nephrotoxic drugs**:
  - AG, Contrast media, NSAID, ACEI, ARBS, Cyclosporine and tacrolimus
- Cimetidine, TMP: inhibit kidney tubular secretion of SCr
- **Co-morbidities** (e.g., liver failure, heart failure, diabetes)
- Advanced age

Pathophysiology and Classification of AKI

- AKI is classified into three basic categories based on the location and type of damage
  - Pre-renal AKI (occurs in approximately 10% to 25% of patients diagnosed with AKI)
  - Intrinsic/intrarenal AKI, and
  - Post-renal AKI (accounts for less than 10% of cases of AKI)

Pre-Renal AKI

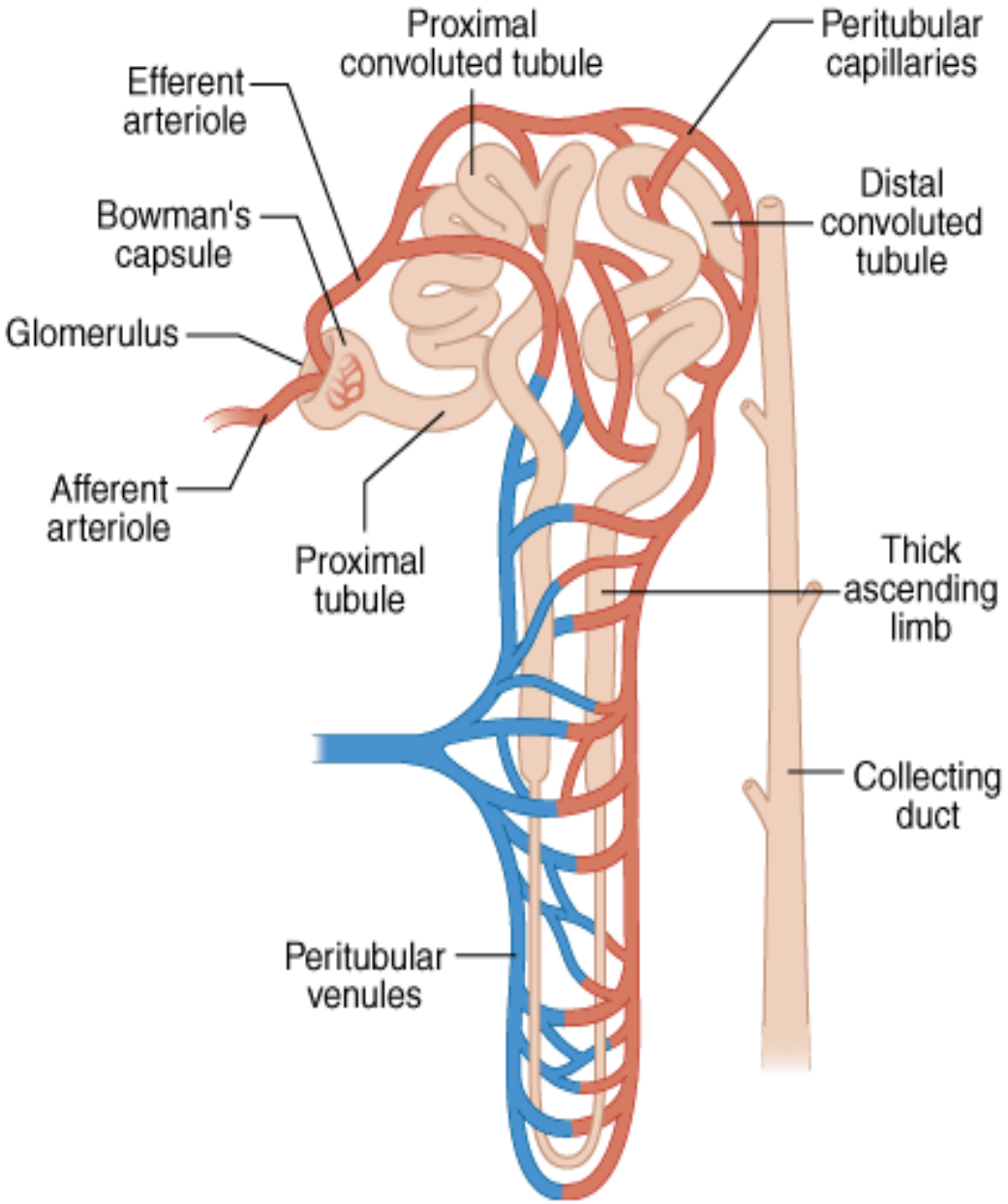
- Characterized by **hypoperfusion** of the kidneys due to
  - Intravascular **volume depletion** from hemorrhage, dehydration, or GI fluid losses
  - Conditions of **reduced cardiac output** (CHF or MI) and hypotension
  - Renovascular **obstruction** (e.g., renal artery stenosis), **hyperviscosity** syndromes (e.g., multiple myeloma), or systemic **vasoconstriction** (e.g., hepatorenal syndrome)
- ↓blood flow/pressure to kidneys lead to
  - ↓ intraglomerular pressure
  - ↓ in GFR, and
  - hypoxia/ischemia within the kidneys
- Early volume restoration can prevent progression & improve recovery b/c no structural damage to the kidney has occurred

Functional AKI

- Is a type of pre-renal azotemia resulting from hemodynamic changes at the glomerular level
- Caused by reduced glomerular hydrostatic pressure
- Mostly medication related– ACEI/ARB, NSAID
  - NSAIDs impair PG-mediated dilation of afferent arterioles
  - ACE inhibitors & ARBs inhibit angiotensin II–mediated efferent arteriole vasoconstriction
  - All of these agents can reduce intraglomerular pressure, with a resultant decrease in GFR
- Prompt discontinuation of the offending drug can often return renal function to normal

Renal blood flow

- Blood → afferent arteriole → glomerular capillary → coalesce to form an efferent arteriole → a second capillary network (peritubular capillaries) surrounding the cortical tubules.
- Thus, nephron has two capillary beds separated by the efferent arteriole that regulates hydrostatic pressure in both capillary beds.
- The peritubular capillaries empty into small venous branches, which coalesce into larger veins to eventually form the renal vein.



Intrinsic-AKI

- Caused by diseases that can affect the structure of the nephron, such as the tubules, glomerulus, interstitium, or blood vessels.

Acute Tubular Necrosis (ATN)

- ATN: most common cause of intrinsic AKI, particularly in hospitalized patients
- ATN signifies the death of tubular epithelial cells, which slough off and may then be visualized in urine
  - this cellular debris, described as "**muddy brown casts**" is very specific to ATN & is important for diagnosis
- Causes:
  - Prolonged ischemia: extreme form of pre-renal AKI. Prerenal AKI can progress to intrinsic AKI if the underlying condition is not promptly corrected
  - A direct toxic effect of agents such as AGs, cisplatin, radio-contrast media may cause tubular cell apoptosis

Acute Interstitial Nephritis (AIN)

- AIN is a hypersensitivity reaction
- Commonly caused by pharmacotherapy and less commonly triggered by an infection.
  - The first agent associated with AIN was methicillin
  - Antimicrobials and allergy causing drugs cause AIN
  - Identify causative agent & D/C as soon as possible

Post-Renal AKI

- Obstruction of urine flow at any portion of the urinary tract from the tubules, ureters, bladder, to the urethra
  - Kidney stones, benign or malignant masses, misplaced indwelling catheters, or hypertrophic prostatic disease can block urine flow
- Result in backflow of urine into the kidney
  - this reverse pressure can damage the kidneys, causing AKI or, if left untreated, may result in CKD
- As with pre-renal AKI, post-renal AKI
  - may resolve completely or
  - cause significant long-term kidney damage depending on the duration of the insult and quick reversal and supportive care

Clinical Presentation

- Dependent on the underlying etiology
  - Increased blood pressure
  - Jugular venous distention (JVD)
  - Peripheral edema, pulmonary edema, ascites
  - Hypotension or orthostatic hypotension (prerenal AKI)
  - Rash (intrinsic AKI due to acute interstitial nephritis)
  - Pruritus
  - Hiccup
  - A, N, V
  - Bladder distention (postrenal bladder outlet obstruction)
  - Prostatic enlargement (postrenal AKI)
  - Urine discoloration (cola-colored urine is a blood in urine i.e. commonly associated with acute glomerulonephritis)
  - Change in mental status (flapping tremor/asterixis, seizure)

History

- General: PO intake, urine output, body weight, and baseline creatinine measurement (to assess how current increase)
- Prerenal:
  - Thirst, orthostatic dizziness
- Intrarenal:
  - Nephrotoxic medications, radiocontrast, other toxins; fever, arthralgias, & pruritic rash ----allergic interstitial nephritis
  - Edema, hypertension, and oliguria with nephritic urine sediment points to glomerulonephritis or vasculitis
  - Flank pain suggests occlusion of the renal artery or vein.

History

- Postrenal:
  - Colicky flank pain that radiates to the groin suggests a ureteric obstruction such as a stone.
  - Nocturia, frequency, and hesitancy suggest prostatic disease
  - Suprapubic and flank pain are usually secondary to distension of the bladder and collecting system.
  - Ask about anticholinergic drugs that could lead to neurogenic bladder

Physical Exam

- **Prerenal signs**: Tachycardia, orthostatic hypotension, dry mucous membranes, decreased skin turgor; look for stigmata of associated comorbidities such as liver & heart failure, sepsis.
- **Intrinsic renal signs**: Pruritic rash
- **Postrenal signs**: Suprapubic distension, flank pain, and enlarged prostate

Investigations

- **Urinalysis**: Dipstick for blood & protein; microscopy for cells, casts, and crystals
- **BUN and creatinine**
- **Serum electrolytes**
- **ECG** – to look for evidence of hyperkalemia
- **Imaging**
  - Renal ultrasound: r/o urinary tract obstruction (postrenal causes) and assess kidney size or identifies presence of kidneys, hydronephrosis, and nephrolithiasis
  - Doppler-flow kidney US: r/o renal artery stenosis/thrombosis
  - Abdominal x-ray: Rules out renal calculi
- Pathological Findings
  - Kidney biopsy

- Generally, the first noticeable signs of AKI are elevations of BUN, SCr, & possibly Δs in urine output
- Cases of isolated ↑ in BUN or SCr not resulting from a decreased GFR are termed "pseudorenal failure."

- Although both parameters may increase in any type of AKI, BUN/SCr ratio increases >20 in prerenal AKI
  - kidney absorbs high urea (not creatinine) with water by passive diffusion in the proximal tubule to compensate for hypoxia or poor perfusion

- AKI in CKD may develop when an abrupt rise in the pt's S_{Cr} occurs (increase by $\geq$ 1mg/dl from baseline)
- In hospitalized pts, changes in urine output may be helpful in characterizing the cause of the pt's AKI
  - Acute anuria is typically caused by either complete urinary obstruction or a catastrophic event (e.g., shock or acute cortical necrosis).
  - Oliguria, which often develops over several days, suggests prerenal azotemia, whereas nonoliguric renal failure usually results from acute intrinsic renal failure or incomplete urinary obstruction.

- Evaluating the urine sodium concentration and percent excreted (FeNa) is helpful in differentiating between a pre-renal AKI and ATN.
- In pre-renal, kidneys should excrete very little Na as a compensatory mechanism to increase water reabsorption.
- Normally the kidneys excrete approximately 1% to 2% of the total sodium intake (normal FeNa value).
- * $FE_{Na} = [(U_{Na} \times S_{Cr})/(S_{Na} \times U_{Cr})] \times 100$

  Where U= urine and S=serum

  * *< 1 prerenal, >2% renal*

- Urinary Na < 20
- Urine Osms > 500
- Highly concentrated urine (>500 mOsm/kg [>500 mmol/kg]) suggests stimulation of antidiuretic and intact tubular function. These findings are consistent with prerenal azotemia.
- Common lab abnormalities in AKI:
  - Increased: K^+, phosphate, Mg, uric acid
  - Decreased: Hematocrit (Hct), Na, Ca

Creatinine Clearance

- Cockroft-Gault equation: To Calculate Creatinine Clearance
  - $\frac{(140 - \text{age}) \times \text{wt in kg}}{72 \times \text{serum creatinine}}$ (x 0.85 for women)

	Prerenal /Functional	Intrinsic	Postrenal
History/ Presentation	**Volume depletion** Renal artery stenosis Hypercalcemia NSAID/ACEI use Cyclosporine	Ischemic failure **Nephrotoxic** Vascultitis Glomerulenephritis	**Kidney stones** **BPH** Cancers
Physical examination	Hypotension Dehydration Ascites Edema	Hypersensitivity Rash, Fever, edema	**Distended bladder** **Enlarged prostate**
Serum BUN/SCr ratio	**> 20:1**	15:1	15:1

	Prerenal /Functional	Intrinsic	Postrenal
Urine Concentrated?	**Yes** Low urine Na (<20 mEq/L) Low FENa (<1%) High Uosm	No Urine Na >40 mEq/L FENa >2% Low Uosm	No Urine Na>40 mEq/L FENa >2% Low Uosm
Urine Sediment	Normal	**Muddy-brown granular casts; tubular epithelial casts**	Variable, may be normal
Urinary WBC	Negative	**2-4+**	Variable
Urinary RBC	Negative	**2-4+**	1+
Proteinuria	Negative	**Positive**	Negative

Prevention of AKI

- The best treatment of AKI is *prevention*!
- Sometimes, the risk is predictable, such as decreased perfusion 2^0 to coronary bypass surgery or 2^0 to adm'n of a radiocontrast dye prior to a diagnostic procedure
  - In these situations, the potential insult to the kidneys cannot be avoided but may be preventable with aggressive hydration and removal of any additional insults.
- In outpatient, educate pt on preventive measures
  - optimal daily fluid intake (~2 L/day) to avoid dehydration, especially if they are to receive nephrotoxic medication
- In inpatient
  - adequate hydration, standardized hemodynamic support in critically ill, & avoidance of nephrotoxic medications

Treatment of AKI

- A primary goal in the care of patients with AKI is ameliorating identifiable underlying causes of AKI such as hypovolemia, nephrotoxic drugs, or ureter obstruction.
- Prerenal and postrenal AKI can be reversed if the underlying problem is promptly identified and corrected, whereas treatment of intrinsic renal failure is more supportive in nature.
- Prerenal azotemia: Correct primary hemodynamic
  - Normal saline if volume depleted
  - Pressure management if needed (↓BP)
  - Blood products if needed (↓Hgb)
- Postrenal azotemia – relieve obstruction
  - Consult Urology….BPH, Prostate Cancer
- The ultimate goal is to have the pt's renal function restored to pre-AKI baseline

- Intrinsic AKI: no universal therapy
  - Avoid insult
  - Consider fluid bolus…..perfusion/urine production
  - Loop diuretics for oliguric/euvolemic or hypevolemic
    - Furosemide ……..40-80 mg IV every 6-8 hrs or
    - Furosemide infusion 40-80 mg IV bolus; then, 10-20 mg/hr iv
  - Acidosis……. restrict dietary protein
    - HCO_3 to maintain arterial pH > 7.2
  - Dialysis if needed

Complications of ARF

Fluid accumulation leads to

- Hypertension
- Hyperkalemia
- Hyperphosphatemia vs. hypocalcemia
- Acidosis
- Anemia……..decreased EPO production
- Uremic bleeding……BUN interferes w/platelet function

AKI & Indications for Dialysis

- BUN greater than 100 mg/dL
- Potassium greater than 6 mEq/L
- Magnesium greater than 9.7 mg/dL
- Metabolic acidosis with a pH less than 7.15
- Diuretic-resistant fluid overload
- Pulmonary edema and anuria
- Uremic complications - pericarditis, encephalopathy and bleeding
- Toxins which can be removed by dialysis

- **Follow-Up Evaluation**
  - Monitor the pt's weight, urine output, electrolytes (such as potassium), and BP to assess efficacy of the diuretic regimen
  - Monitor SCr to evaluate whether kidney function is worsening or improving

Chronic Kidney Disease (CKD)

- CKD is defined as abnormalities in the structure or function of the kidney, present for 3 months or more.
- Markers of structural abnormalities include
  - Albuminuria (30 mg/24 hours or more or
  - Albumin: creatinine ratio (ACR) of more than 30 mg/g
  - Hematuria or casts in urine sediment
  - Electrolyte and other abnormalities caused by renal tubular disorders
  - Abnormalities detected by histology or imaging
  - History of kidney transplantation
- Functional abnormalities are indicated by a decline in GFR less than 60 mL/min/1.73m^2
- CKD is a progressive disease that eventually leads to ESKD.
- The decline in kidney function in CKD is often irreversible, treatment of CKD is aimed at slowing the progression to ESKD.

Stages of CKD

Stage of CKD	GFR or maker of kidney damage	GFR in ml/min/1.73 m^2
1	Normal or high	≥ 90
2	Mildly decreased	60-89
3a	Mildly to moderately decreased	45–59
3b	Moderately to severely decreased	30–44
4	Severely decreased	15-29
5	Kidney Failure	<15 or Dialysis

Risk Factors

- Risk Factors Associated with CKD
- **Susceptibility**
  - Advanced age
  - Reduced kidney mass
  - Low birth weight
  - Racial/ethnic minority
  - Family history of kidney disease
  - Low income or education
  - Systemic inflammation
  - Dyslipidemia

- **Initiation**
  - Diabetes mellitus
  - Hypertension
  - Autoimmune disease
  - Polycystic kidney disease
  - Drug toxicity
  - Urinary tract abnormalities (infections, obstruction, stones)
- **Progression**
  - Hyperglycemia: Poor blood glucose control (in patients with diabetes)
  - Hypertension: Elevated blood pressure
  - Proteinuria
  - Tobacco smoking
  - AKI

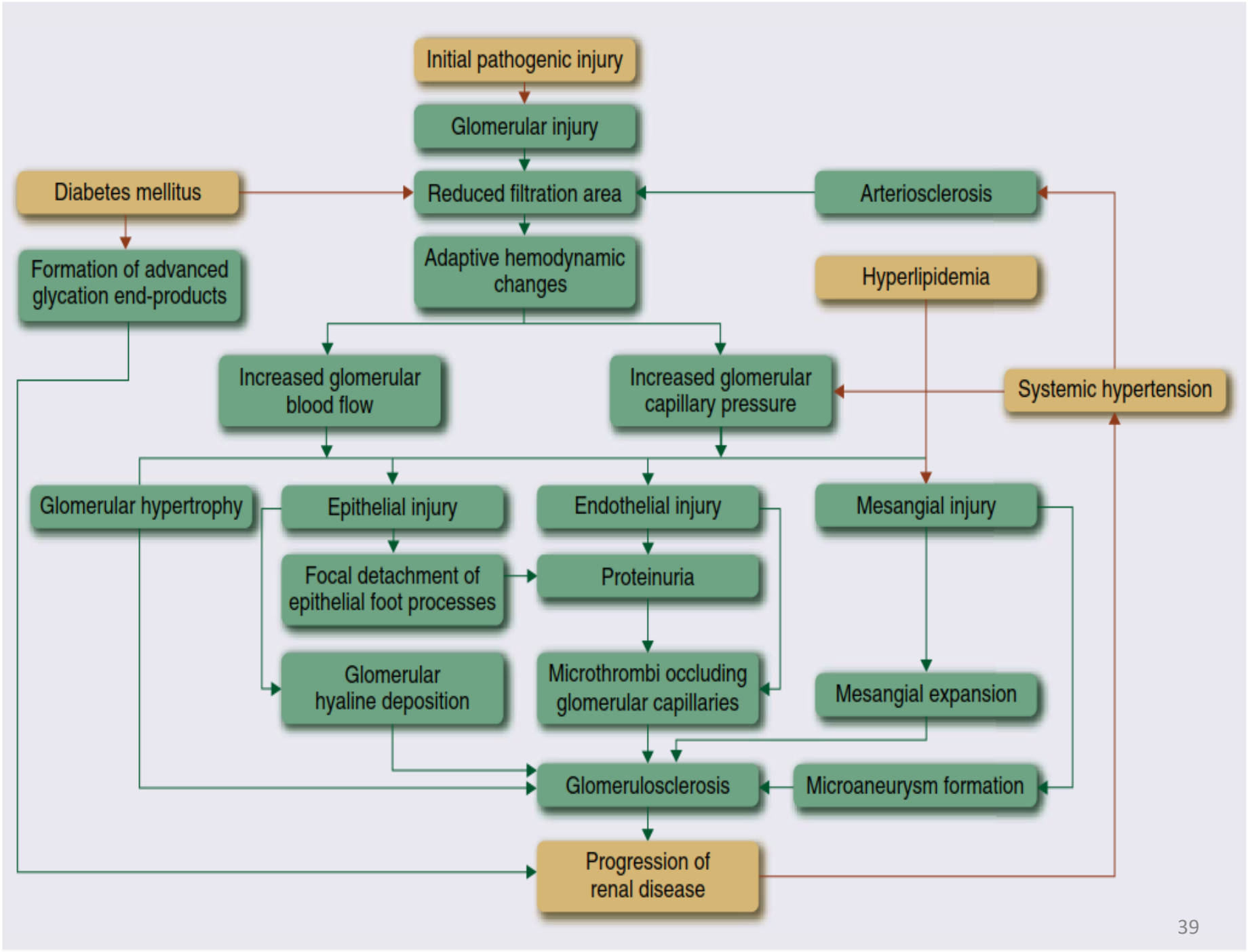
Pathophysiology of CKD

Progressive destruction of nephrons leads to:

a. Decreased glomerular filtration, tubular reabsorption & renal hormone regulation
b. Remaining functional nephrons hypertrophy to increase glomerular filtration and tubular function in an attempt to compensate for the loss of kidney function.
c. Functional and structural changes occur
d. Inflammatory response triggered
e. Healthy glomeruli so overburdened they become stiff, sclerotic and necrotic

- Regardless of the initial cause of kidney damage, the result is a decrease in the number of functioning nephrons.
- The remaining nephrons hypertrophy to increase glomerular filtration and tubular function in an attempt to compensate for the loss of kidney function.
- Initially, these adaptive changes preserve many of the clinical parameters of kidney function, including creatinine and electrolyte excretion.
- However, as time progresses, angiotensin II is required to maintain the hyperfiltration state of the functioning nephrons.
- Angiotensin II is a potent vasoconstrictor of both the afferent and efferent arterioles but has a preferential effect to constrict the efferent arteriole, thereby increasing the pressure in the glomerular capillaries.

- Increased glomerular capillary pressure expands the pores in the glomerular basement membrane, altering the size-selective barrier and allowing proteins to be filtered through the glomerulus.
- Proteinuria increases nephron loss through various complex mechanisms.
- Filtered proteins are reabsorbed in the renal tubules, which activates the tubular cells to produce inflammatory and vasoactive cytokines and triggers complement activation.
- These cytokines cause interstitial damage and scarring in the renal tubules, leading to damage and loss of more nephrons.
- Ultimately, the process leads to progressive loss of nephrons to the point where the number of remaining functioning nephrons is too small to maintain clinical stability, and kidney function declines.


Initial pathogenic injury
Glomerular injury
Diabetes mellitus
Reduced filtration area
Arteriosclerosis
Formation of advanced glycation end-products
Adaptive hemodynamic changes
Hyperlipidemia
Increased glomerular blood flow
Increased glomerular capillary pressure
Systemic hypertension
Glomerular hypertrophy
Epithelial injury
Endothelial injury
Mesangial injury
Focal detachment of epithelial foot processes
Proteinuria
Glomerular hyaline deposition
Microthrombi occluding glomerular capillaries
Mesangial expansion
Glomerulosclerosis
Microaneurysm formation
Progression of renal disease

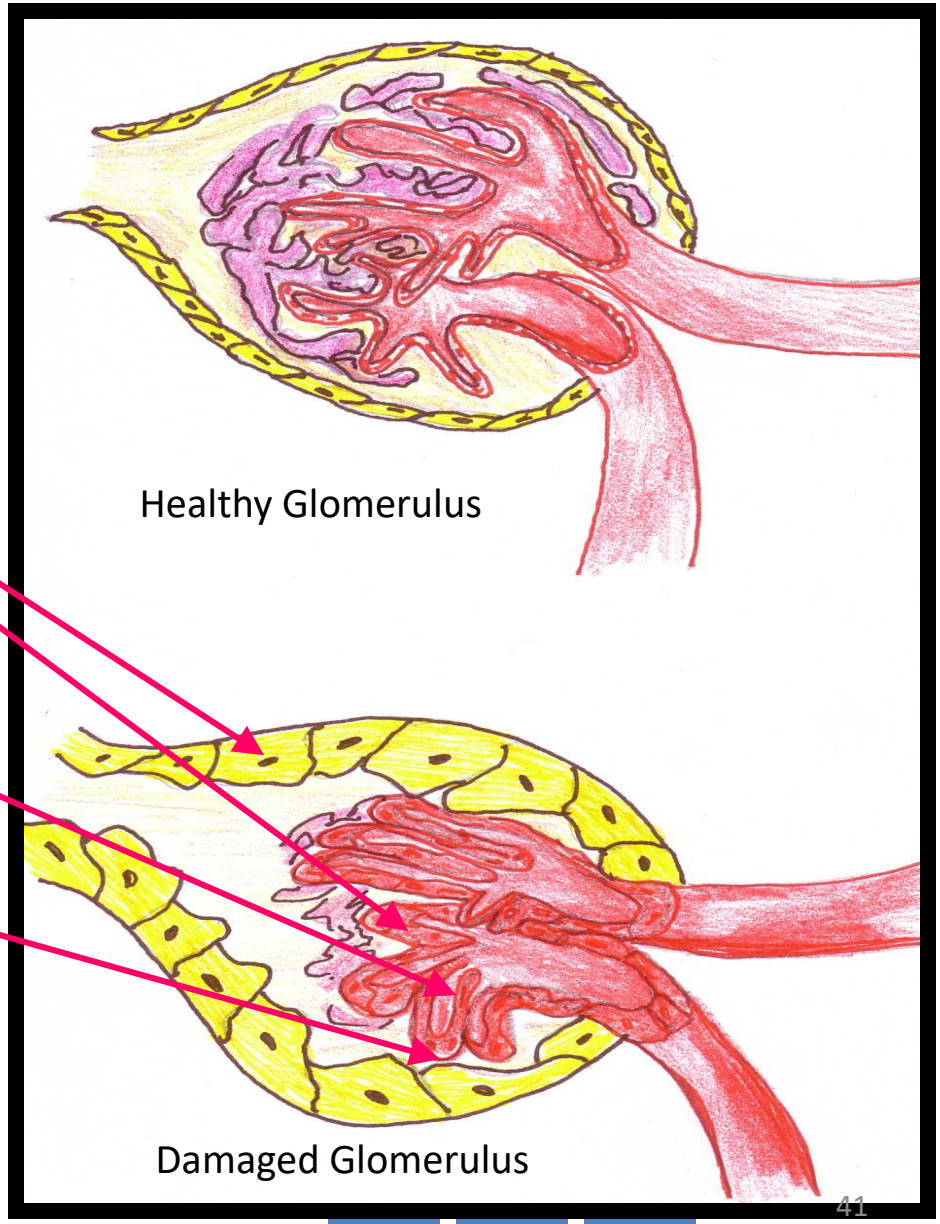
Functional Changes of CKD

The Kidneys are unable to:

- Regulate fluids and electrolytes
- Balance fluid volume and renin-angiotensin system
- Control blood pressure
- Eliminate nitrogen and other wastes
- Synthesize erythropoietin
- Regulate serum phosphate and calcium levels

Structural Changes of CKD

- Epithelial cell damage
- Glomerular and parietal basement membrane damage
- Vessel wall thickening
- Vessel lumen narrowing leading to stenosis of arteries and capillaries
- Sclerosis of membranes, glomeruli and tubules
- Reduced glomerular filtration rate
- Nephron destruction



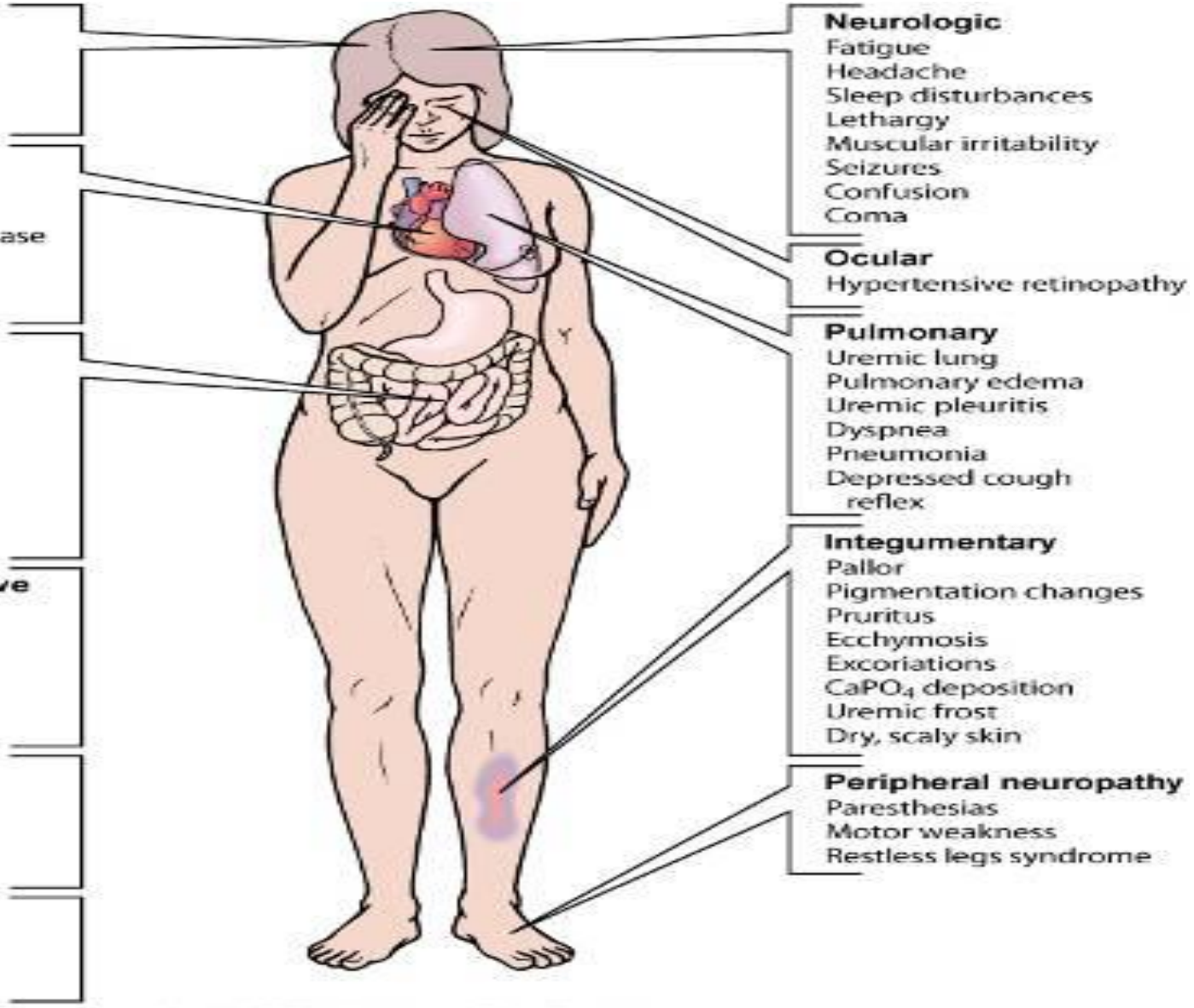
- Because CKD often presents without symptoms, assessment for CKD relies on appropriate screening strategies in all pts with risk factors for developing CKD.
- Screening for CKD should be performed in all people with an increased risk for developing CKD, including pts with DM, hypertension, genitourinary abnormalities, autoimmune disease, increased age, a family history of kidney disease, or following AKI.
- Assessment for CKD includes measurement of SCr, urinalysis, blood pressure, serum electrolytes, and/or imaging studies.

- A key part of CKD assessment is analysis for proteinuria, which is the primary marker of structural kidney damage, even in pts with normal GFR.
- Protein excretion can be assessed by measuring urine albumin-to-creatinine ration (ACR), urine protein-to-creatinine ratio, or urinalysis with a reagent strip test.
- A urinary protein excretion of 30 mg/day or more or an ACR or 30mg/g or more on a random untimed urine sample is considered to be significant in the context of CKD.
- Albuminuria should be assessed with GFR at least annually in people with CKD.
- Assessment of protein excretion is important in pts with DM, even without CKD.

Clinical presentations

- Generally asymptomatic in the early stages
- Nocturia
- Hematuria
- Flank pain
- Edema
- Signs of uremia
- Muscle pain, lethargy/fatigue
- Anorexia, nausea, vomiting, hiccup, SOB, palpitations, cramping, pruritus
- Paresthesia, depression, anxiety
- If asymptomatic may have elevated Scr or an abnormal urinalysis

Manifestations of Chronic Uremia



Diagnostic Tests

Lab

- Calculate GFR
- Analyze urine:
  - Urine microscopy: WBC/RBC casts, dysmorphic RBCs
  - Proteinuria/albuminuria: 24-hr urine collection is gold standard. Spot urine protein-to-creatinine ratio equally as good:
  - 30–300 mg/day of albuminuria is classified as microalbuminuria (risk factor for CVD)

- Blood:
  - Normochromic, normocytic anemia
  - Increased bleeding time
- Chemistry:
  - Elevated BUN, Scr
  - Elevated potassium
  - Increased parathyroid hormone
  - Decreased active vitamin D
  - Reduced calcium
  - Elevated phosphate
  - Hyperlipidemia
  - Metabolic acidosis

Imaging

- U/S: Small, echogenic kidneys; obstruction (e.g., hydronephrosis); cysts; kidneys may be enlarged with HIV and diabetic nephropathy.
- Doppler U/S to assess for renovascular disease, thrombosis
- CT scan (non-contrast): Obstruction; calculi; cysts; neoplasm; renal artery stenosis

Diagnostic Procedures/Surgery

- Renal biopsy
- Major indications for biopsy: hematuria, proteinuria, unexplained renal failure

MDRD Equation to Predict GFR

- Prediction based on age, gender, race & Scr.
- Developed to follow GFR as part of the Modification of Diet in Renal Disease (MDRD) study.
- Validated

$$GFR/1.73m^2 = 186 \times [S_{cr}]^{-1.154} \times [age]^{-0.203} \times [0.742 \text{ if female}] \times [1.212 \text{ if AfAm}]$$

- Cockcroft-Gault Equation

$$\text{CrCl (mL/minute)} = \frac{(140 - \text{age}) \times \text{BW}}{(\text{Scr}) \times 72} \ (\times 0.85 \text{ if women})$$

  - Age, in years
  - BW=actual body weight (kg): Often substituted with ideal body wt, or adjusted body wt when body wt is significantly greater than ideal body wt.
  - Scr=serum creatinine concentration, mg/dL

Treatment: Chronic Kidney Disease

- The primary goal is to slow & prevent progression of CKD.
- Objectives
  - Detect chronic kidney disease early
  - Decrease the decline in kidney function
  - Prevent, detect and manage complications
  - Improve quality of life and survival
- Non pharmacologic
  - General health advice e.g. smoking cessation, wt reduction for obese individuals
  - Restrict salt intake
  - Avoid nephrotoxins e.g. NSAIDs, Ags, amphotericin B
  - Restrict dietary protein

- Nutritional Management
  - pts who have GFR < 25 mL/minute/1.73 m^2 who are not receiving dialysis should restrict protein intake to **0.6 g/kg/day**
  - Malnutrition is common in pts with ESRD for various reasons, including decreased appetite, hypercatabolism, and nutrient losses through dialysis. For this reason, pts receiving dialysis should maintain protein intake of **1.2 to 1.3 g/kg per day**.

- Interventions to slow the progression should be considered in all pts with CKD
- Interventions proven to be effective include:
  - Strict glucose control in diabetes;
  - Strict blood pressure control;
  - ACEI and ARBs
- Interventions that may be effective include:
  - Dietary protein restriction
  - Lipid-lowering therapy
  - Correction of anemia

- Prevention measures:
  - Volume depletion
  - IV contrast
  - Avoid using nephrotoxic antibiotics
    - aminoglycosides and amphotericin B
    - NSAIDs, including COX 2 inhibitors
  - Use protective drugs
    - ACEI, ARBs
- eGFR should be obtained at least yearly in CKD, and more often in pts with:
  - GFR <60 mL/min/1.73 m2
  - Fast GFR decline in the past
  - Risk factors for faster progression
  - Ongoing treatment to slow progression
  - Exposure to risk factors for acute GFR decline

COMPLICATIONS OF CKD

- Hypertension
- Fluid and electrolyte disorders
- Anemia
- Metabolic bone disease/ Osteodystrophy
- Cardiovascular disease
- Malnutrition
- Metabolic acidosis
- Dyslipidemia

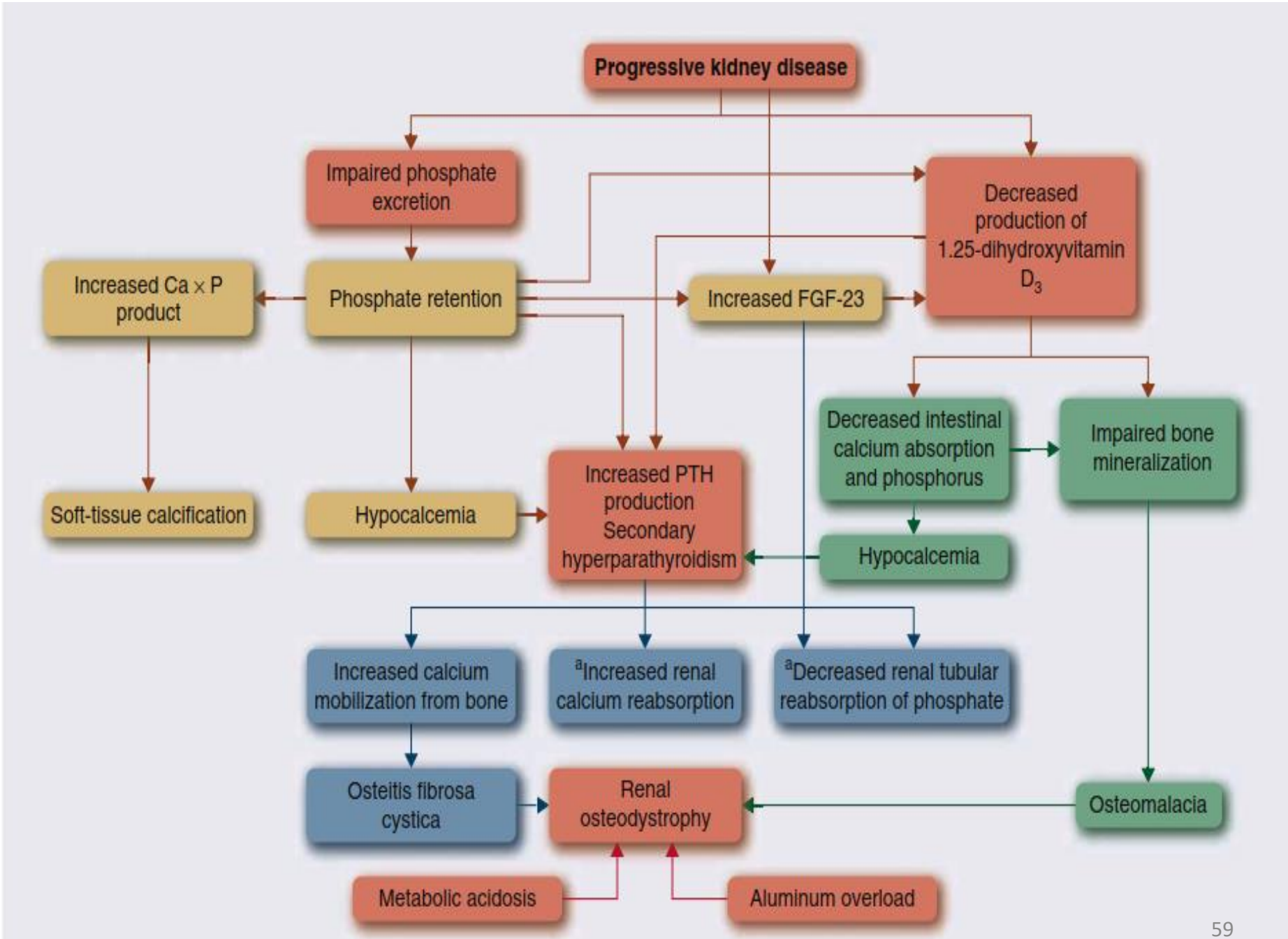
- Pts with CKD who have an AER less than 30 mg/day should achieve a BP target of less than or equal to 140/90 mm Hg.
- If AER is 30 mg/day or greater, the BP goal is less than or equal to 130/80 mm Hg.
- The first-line antihypertensive agents for pts with an AER of 30 mg/day or more are ACEIs or ARBs, because of their ability to also lower protein excretion.

Recommendations for BP and Management in CKD

Patient Group	Goal BP (mm Hg)	First Line	Adjunctive
+ Diabetes	<140/90	ACEI or ARB	Diuretics then CCB or BB
– Diabetes + Proteinuria	<130/80	ACEI or ARB	Diuretics then CCB or BB
– Diabetes – Proteinuria	<140/90	No specific preference: Diuretics then ACEI, ARB, CCB, or BB	

Hyperphosphatemia

- Common for pts receiving dialysis therapy
- Pathogenesis
  - a decreased glomerular filtration rate of phosphorus
  - an increased tubular reabsorption of phosphorus
- Consequences
  - stimulation of parathyroid hormone
  - suppression of vitamin D3 production
  - vascular calcification: Ca x PO4 >55
- Treatment approach:
  - dietary restriction of phosphate (meat, dairy products, peas, beans, cola soft drinks).


Progressive kidney disease
Impaired phosphate excretion
Decreased production of 1.25-dihydroxyvitamin D_3
Increased Ca × P product
Phosphate retention
Increased FGF-23
Decreased intestinal calcium absorption and phosphorus
Impaired bone mineralization
Soft-tissue calcification
Hypocalcemia
Increased PTH production Secondary hyperparathyroidism
Hypocalcemia
Increased calcium mobilization from bone
[a]Increased renal calcium reabsorption
[a]Decreased renal tubular reabsorption of phosphate
Osteitis fibrosa cystica
Renal osteodystrophy
Osteomalacia
Metabolic acidosis
Aluminum overload

Secondary Hyperparathyroidism and CKD- Mineral and Bone Disorder

- In CKD pts, ↓P excretion disrupts balance of Ca & P homeostasis. Parathyroid gland release PTH in response to ↓ serum Ca & ↑serum P levels.
- Actions of PTH include:
  - ↑ Ca resorption from bone
  - ↑ Ca reabsorption from proximal tubules in the kidney
  - ↓P reabsorption in the proximal tubules in the kidney
  - Stimulating activation of vitamin D by 1-α-hydroxylase to calcitriol (1,25-dihydroxyvitmin D3) to promote Ca absorption in the GIT & increased calcium mobilization from bone

- All of these actions are directed at increasing serum Ca levels and decreasing serum P levels
- As kidney fails & GFR falls < 60, both P excretion & calcitriol production ↓, causing PTH levels to begin to rise highly, leading to secondary hyperparathyroidism(sHPT).
- The most dramatic consequence of sHPT is alterations in bone turnover & the development of CKD-MBD.
- The increased serum P binds to Ca in the serum, which leads to deposition of crystals throughout the body.
- The calcium-phosphorus (Ca-P) product reflects serum solubility.

- A Ca-P product >75 mg^2/dL^2 promotes crystal deposition in joints & eye, leading to arthritis & conjunctivitis, respectively
- Soft tissue deposition primarily affects coronary arteries of the heart, lungs, and vascular tissue and is associated with a Ca-P product >55 mg^2/dL^2
- The Ca-P product increases mortality & is a risk factor for calcification of vascular and soft tissues.
- Therapy: dietary phosphorus restriction, phosphate binding agents, vitamin D therapy, calcimimetics (cinacalcet)

- The first-line treatment for the management of hyperphosphatemia is dietary phosphorus restriction to 800 to 1000 mg/day in pts with Stage 3 CKD or higher.
- When serum phosphorus levels cannot be controlled by dietary restriction, **phosphate-binding agents** are used to bind dietary phosphate in the GI tract to form an insoluble complex that is excreted in the feces.
- Calcium-based phosphate binders, including calcium carbonate and calcium acetate
- Sevelamer, lanthanum, and iron-based phosphate binders do not contain calcium, magnesium, or aluminum. These agents are particularly useful in pts with hyperphosphatemia who have elevated serum calcium levels or who have vascular or soft tissue calcifications.

- **Vitamin D** regulates calcium and phosphorus absorption from the GI tract and kidney, PTH secretion, maintaining muscle, cardiovascular, immune and brain function, and glucose control.
- In CKD, a decrease in renal metabolism of vitamin D decreases circulating concentrations of the activated form of vitamin D.
- Vitamin D deficiency becomes evident as early as Stage 2.
- PTH levels rise as early as Stage 3 as a result of low calcitriol concentrations.
- Exogenous vitamin D decreases PTH synthesis and secretion.
- This is particularly useful when reduction of serum phosphorus levels does not sufficiently reduce PTH levels.

- **Cinacalcet** is a calcimimetic that increases the sensitivity of receptors on the parathyroid gland to serum calcium levels to reduce PTH secretion, but has no effect on intestinal absorption of calcium or phosphorus, and may even lower serum calcium levels.
- Thus, cinacalcet is beneficial for pts with elevated PTH levels who have increased calcium or phosphorus levels or cannot use vitamin D therapy.
- Cinacalcet should also be used with caution in pts with seizure disorders because low serum calcium levels can lower the seizure threshold.

Treatment Of Metabolic Acidosis In CKD

- Goal
  - Serum HCO_3 > 20 mEq/L and blood pH > 7.35
- Agents
  - Sodium bicarbonate tablets - (650 mg ≈8 mEq HCO_3-)
  - Sodium citrate (Shohl's solution)
- Dose of HCO_3 1.0–1.5 mEq/kg/day
  - Dependent upon initial serum HCO_3- and degree of renal insufficiency

Anemia in CKD

- The progenitor cells of kidney produce 90% of hormone erythropoietin (EPO), which stimulates RBC production.
- Reduction in nephron mass decreases renal production of EPO, the primary cause of anemia in CKD pts.
- The development of anemia of CKD results
  - decreased oxygen delivery and utilization
  - increased cardiac output and left ventricular hypertrophy (LVH)
  - increased cardiovascular risk and mortality in pts with CKD

Evaluation of Anemia

- Hemoglobin and/or hematocrit
- Red-blood-cell indices
- Reticulocyte count
- Iron studies
- Test for occult-blood in stool

Anemia Treatment & Eligibility

- **Eligibility**
  - Scr 2 mg/dl or above or
  - CrCl (45 ml/min or below) or GFR (<60 mL/min) and
  - Hemoglobin (11g/dl or below) or
  - Hematocrit (33% or below) or
  - Symptoms of anemia

- **Treatment:**
  - The ESAs currently available: epoetin alfa, darbepoetin alfa
  - 2-4 weeks needed to see a rise in Hgb
  - Iron supplementation is necessary….iron dextran or ferric gluconate, or iron sucrose
- The first-line treatment for anemia of CKD involves replacement of iron stores with iron supplements.
- When iron supplementation alone is not sufficient to increase Hgb levels, ESAs are necessary to replace erythropoietin.
- ESAs are synthetic formulations of EPO.
- Use of ESAs increases the iron demand for RBC production and iron deficiency is common, requiring iron supplementation to correct and maintain adequate iron stores to promote RBC production.

Hyperlipidemia

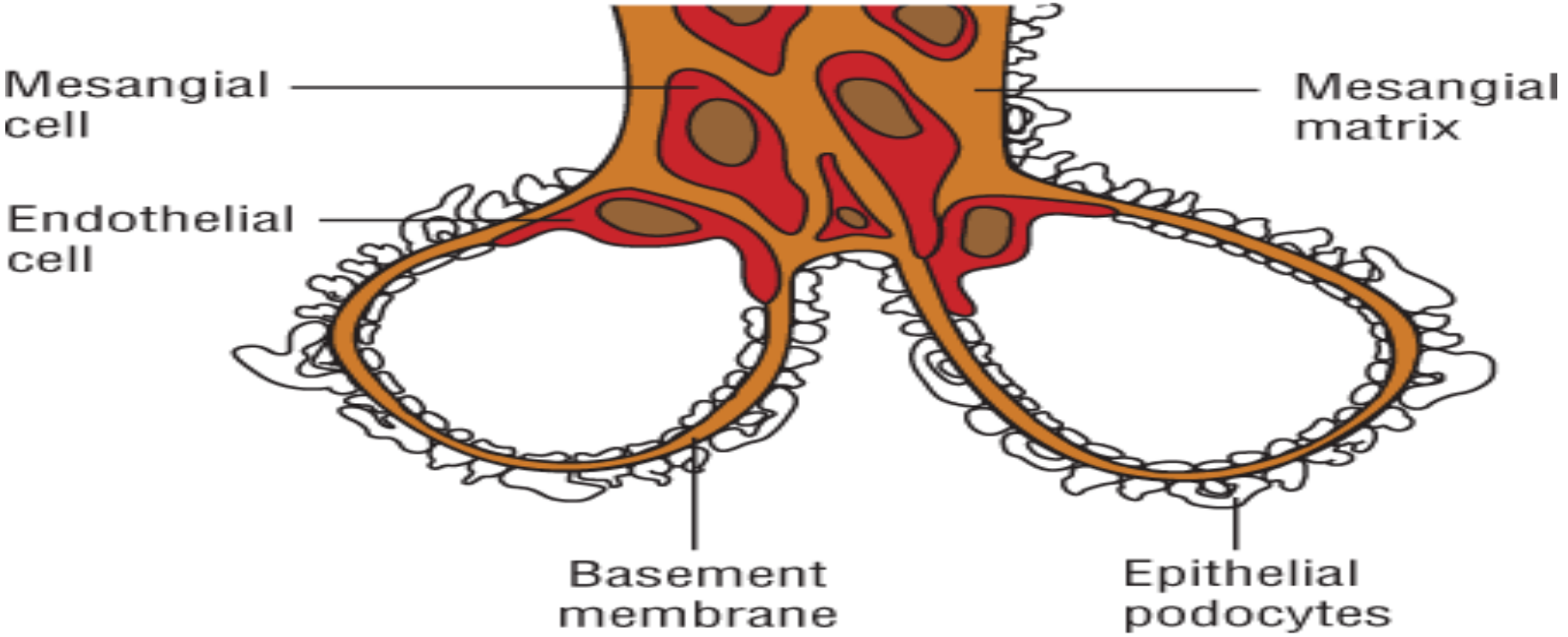
- CKD is a CHD risk equivalent and the goal LDL-C level should be
  - <100 mg/dL in all pts with CKD
- The most frequently used agents for the treatment of dyslipidemia in pts with CKD are the
  - Statins
  - the fibric acid derivatives (fibrates)

Indications for Dialysis

- Planning for dialysis should begin when CrCl falls less than 30 mL/minute/1.73 m^2 (stage 4 CKD),
  - Dialysis is initiated in most pts when the GFR falls below 15 mL/minute/1.73 m^2
- When progression to ESRD is inevitable
- Symptoms that may indicate the need for dialysis: persistent anorexia, N, V, fatigue, and pruritus
- Declining nutritional status, declining serum albumin levels
- Uncontrolled hypertension, and
- Volume overload, which may manifest as CHF, and
- Electrolyte abnormalities, particularly hyperkalemia

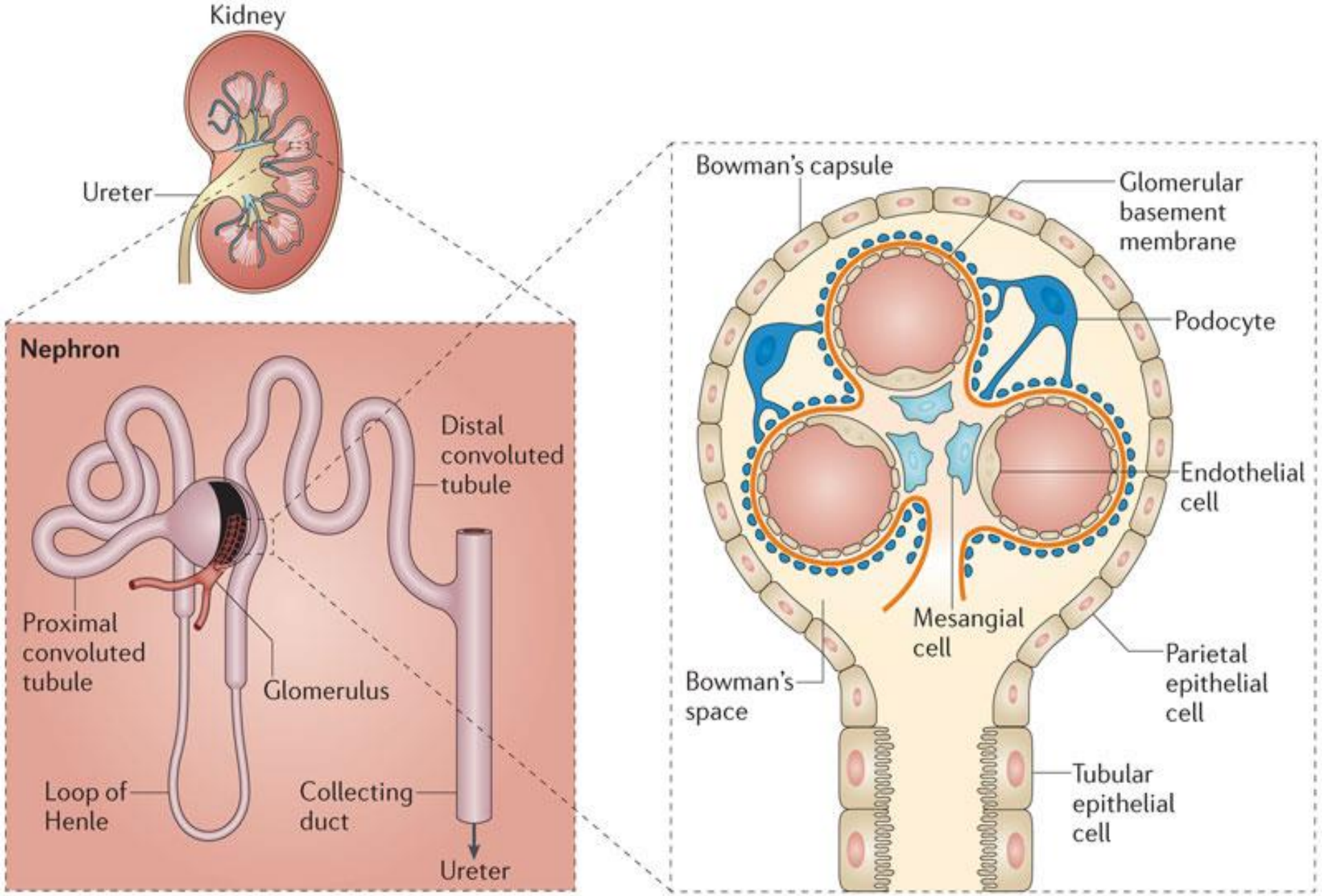
Glomerulonephritis

- A collection of glomerular diseases mediated by different immunologic pathogenic mechanisms, resulting in varied clinical presentation and therapeutic outcomes.
- The third most common cause of ESRD
- **Glomerulus: i**s enclosed by Bowman's capsule and consists of two components:
  - the filtration barrier (**capillary wall**) and the **mesangium**
- The **capillary wall** consists of three layers:
  - **fenestrated endothelium, glomerular basement membrane (GBM) and epithelial cell layer**
  - The epithelial cells (podocytes) have specialized foot processes embedded in the outer layer of the GBM.
    - It is across this barrier that fluid flows and ultimately becomes the ultrafiltrate



Source: DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey LM: *Pharmacotherapy: A Pathophysiologic Approach, Ninth Edition:* www.accesspharmacy.com

- The **mesangium**, which consists of mesangial cells embedded in an extracellular matrix,
  - provides support for the glomerular capillaries and also modulates blood flow through the capillaries



Nature Reviews | Immunology

- The ease of solute passage through the glomerular membrane is impacted by both the size and charge of the solute.
- Fixed, negatively charged sites are found within all three layers of the glomerular capillary wall: the endothelium, the epithelium, and the GBM.
- The movement of negatively charged molecules is thus restricted more than that of neutral or positively charged molecules.
- Different glomerular diseases affect this size- and charge-selective barrier to different extents; consequently, glomerulopathies present with varied clinical features and solute-excretion patterns.

Pathophysiology

- The glomerular lesion may be
  - diffuse (involving all glomeruli)
  - focal (involving some but not all glomeruli), or
  - segmental, also known as local (involving part of the individual glomerulus)
- The pathologic manifestations may also be described as
  - proliferative (overgrowth of epithelium, endothelium, or mesangium),
  - membranous (thickening of GBM), and/or
  - sclerotic

- The glomerular capillary wall is particularly susceptible to immune-mediated injury.
- Parenchymal damage can be induced as a result of humoral- and cell-mediated immune reactions.
- These humoral and cellular mediators can alter the permeability, blood flow, and function of the glomeruli.
- Vascular constriction and occlusion follow and result in the eventual destruction of the glomeruli.

Clinical Presentation

- Two classifications: nephritic or nephrotic syndrome
- Nephritic syndrome reflects glomerular inflammation and frequently results in hematuria
  - White cells and cellular/granular casts are found in urine
- Nephrotic syndrome reflects noninflammatory injury to glomerules and results in few cells or cellular casts in the urine
  - Initially, there may be limited/no reduction in renal function
- Hematuria occurs when RBCs leak through openings of GBM
- Presence of proteinuria indicates a defect within GBM
- Hypertension is common in glomerular diseases due to renal salt retention causing plasma volume expansion
  - Increased activity of angiotensin II is often the cause for patients with chronic glomerular diseases

Clinical Presentation Nephritic & Nephrotic Syndromes

- General:
  - The pts are generally not in acute distress
- Symptoms:
  - The pts may not experience any major symptoms
- Nephritic Signs
  - Hematuria
  - Hypertension and edema as renal function declines
- Nephrotic Signs:
  - Edema
  - Weight gain
  - Fatigue

Laboratory Tests

- Urinalysis
  - nephrotic nature of glomerular disease
    - Proteinuria
      - >3.5 g/day/1.73 m^2 or >50mg/kg/day or urinary dipstick 3+ to 4+
    - Lipiduria
  - nephritic nature of glomerular disease
    - Hematuria
    - Pyuria (presence of white blood cells in the urine)
    - Cellular, granular casts
- Hypoproteinemia (hypoalbuminemia: serum albumin< 3g/dL)
- Hypercoagulable state for some pts
- Hyperlipidemia
- GFR: to determine extent of glomerular damage

	Nephrotic Features	Nephritic Features
Minimal-change nephropathy	++++	–
Membranous nephropathy	++++	+
Diabetic glomerulosclerosis	++++	+
Amyloidosis	++++	+
Focal segmental glomerulosclerosis	+++	++
Mesangioproliferative glomerulonephritis	++	++
Membranoproliferative glomerulonephritis	++	+++
Proliferative glomerulonephritis	++	+++
Acute poststreptococcal glomerulonephritis	+	++++
Crescentic glomerulonephritis	+	++++

Treatment

Non-pharmacologic Therapy

- In nephrotic syndrome
  - dietary measures: restriction of **sodium** to 50 - 100 mEq/day, **protein** to 0.8 -1 g/day, **lipid** diet less than 200 mg cholesterol, total **fat** less than 30% of daily calories
  - Smoking cessation
- Plasmapheresis: plasma proteins, presumably including the pathogenic immune factors are removed from the pt

Pharmacologic Therapy

- Immunosuppressive Agents
  - Corticosteroids
  - Cytotoxics …alkylating agents
  - Calcineurin Inhibitors … cyclosporine
  - Mycophenolate
  - Rituximab
- Levamisole
- Diuretics
- ACEI/ARB
- NSAID
- Statins
- Anticoagulant

- Management of glomerulonephritis involves
  - specific pharmacologic therapy for glomerular disease
  - supportive measures to for pathophysiologic sequelae like hypertension, edema, and progression of renal disease
- For nephrotic syndrome pts, supportive therapy should address management of extrarenal complications of heavy proteinuria:
  - hypoalbuminemia, hyperlipidemia, and thromboembolism
- Significant proteinuria cause rapid decline of renal function, thus reduction of proteinuria is critical to delay the rate of progression toward ESRD

Monitoring Parameters

- Renal function
  - SCr
  - 24-hr urine collection for CrCl determination, urinary protein excretion
  - Urine protein-to-creatinine ratio
- Clinical signs and symptoms
  - Nephrotic syndrome
    - Proteinuria
    - Serum lipid concentrations
    - Edema
  - Blood pressure
  - General well-being: appetite, energy level
- Kidney biopsy to assess disease progression and response to therapy
- Assessment of drug therapy adverse reactions and toxicities

Nephritic presentations

Hematuria

Urinalysis

Complete blood count

Minimal-Change Nephropathy (Nil disease or minimal-change disease)

- Common in children, 85% to 90% of all cases of nephrotic syndrome in children1- 4 years of age
  - Accounts <50% after age 10 years and <20% of all cases of idiopathic nephrotic syndrome in adults
  - Secondary causes include drugs (e.g., NSAIDs, lithium, interferon), lupus, Hodgkin's disease and leukemias
- The pathogenesis of MCD is unknown
- Absence of definitive pathologic changes observed under microscopy
- Altered cell-mediated immunologic response, specifically T-cell dysfunction
- Activated lymphocytes are thought to secrete lymphokines that reduce production of anions in the GBM
- The permeability of the GBM to plasma albumin is increased through a reduction of electrostatic repulsion
- Most responsive to initial treatment with corticosteroids especially in children

Steroids

- In children, proteinuria will disappear in 50% of pts after 1 wk & in 90% of pts after 4 wks of Rx:
  - prednisone 60 mg/m²/day for 4-6 wks. Then 40 mg/m²/day every other day for 4-6 wks
- For adults, prednisone 1 mg/kg/day is given initially for 4 wks with a reduction to 0.75 mg/kg every other day for the next 4 wks
  - proteinuria will disappear in 50% to 60% of pts after 8 wks of treatment, and
  - complete remission will be attained in 80% of pts after 28 wks of therapy

Relapse

- Around 85% of the pts who respond to initial steroid therapy (steroid sensitive) will experience a relapse of proteinuria, mostly within 6 to 12 months after disease onset
- 60 mg/m^2/day of prednisone is given until the urine is free of protein for 3 days, to be followed by 4 wks of alternate-day prednisone at 40 mg/m^2 per dose
- First/initial/infrequent relapse: is relapse after initial steroid therapy
- **Frequently relapsing NS**: four or more relapses per year
- **Steroid dependent:** relapsing during taper or within two wks of discontinuation of steroid therapy

Resistance

- Approximately 10% to 20% of children that are responsive to steroid will experience 3 or 4 relapses
- Half of them will relapse frequently and become steroid dependent, requiring continuous low-dose alternate-day prednisone to maintain an extended relapse-free period
- A small number of pts eventually develop resistance to steroids, and a biopsy done at that time often reveals another pathology such as FSGS
- **Steroid-resistant**: persistent proteinuria
  - after initial steroid therapy (for eight wks) or
  - one wk after iv methylpredinisolone pulse treatment (given for pts who are not in remission after 4 wks of daily steroid therapy)

Cytotoxics

- Considered for steroid resistant pts, as well as for those who require large doses of steroids to sustain remission (steroid dependent)
- Cyclophosphamide at 2 mg/kg/day for 10-12 wks given alone or with prednisone (50-75 mg/m^2)
  - very effective in inducing remission and restoring steroid responsiveness for pts who were previously steroid dependent and then became steroid resistant
- Azathioprine
  - treatment for 6-12 months is often needed before any favorable response is apparent
- Toxicities of cyclophosphamide: infection, gonadal fibrosis which results in sterility, hemorrhagic cystitis, alopecia, and a potential to develop malignancy in those on long-term treatment

Calcineurin Inhibitors

- Calcineurin inhibitors (cyclosporine, tacrolimus):
  - competitively binds to & inhibits calcineurin, a calcium and calmodulin dependent phosphatase, to **block T-cell activation**
  - decreases lymphokine production by activated T lymphocytes and thereby reduces proteinuria by reversing the lymphokine-induced alterations in the anionic charge and permeability of the GBM to albumin
  - used to treat pts with frequently relapsing or steroid-dependent NS

- **Cyclosporine**
  - Dose: 5 mg/kg/d for adults and 100-150 mg/m²/d for children
  - Adverse events: rise in Scr, hypertrichosis, gingival hyperplasia
  - Long-term therapy: HTN and progressive renal failure. Thus do not give for >4 months in the absence of any beneficial effect
- **Tacrolimus:** similar efficacy & risk of nephrotoxicity like cyclosporine
  - less cosmetic side-effects (hypertrichosis, gum hypertrophy)
- Due to adverse effects, cyclosporine is indicated for
  - Frequent relapse or steroid dependent, after failing to cyclophosphamide
  - If cyclophosphamide is contraindicated or when gonadal toxicity is a concern
  - Steroid dependent when a "steroid holiday" is needed for catch-up growth and puberty
  - Steroid-resistant disease

Levamisole

- Immunostimulant, promote maturation of young T cells and restore function of T cells and phagocytes when the immune system is depressed
- Have steroid-sparing effect and maintain remission in children who had frequent relapse steroid-dependent nephrotic syndrome
- As effective as cyclophosphamide in reducing relapse rate and steroid dosages
- Adverse effect: mild neutropenia, which is reversible, and GI upsets

Mycophenolate Mofetil

- Immunosuppressant that can suppress T- and B-cell lymphocyte proliferation, B-lymphocyte antibody production, and expression of adhesion molecules
- Has steroid-sparing effects and is useful in frequently relapsing, steroid-dependent and steroid-resistant pts, in those who fail cytotoxic therapy

Supportive therapy

- Symptomatic therapy with **diuretics** to control edema, in conjunction with a low-salt diet
- NSAIDs and ACEIs may to reduce the proteinuria
- Because of the overall favorable outcome of the disease and the relatively uncommon progression into chronic renal failure
  - aggressive use of cytotoxic agents is not indicated even for most pts with frequent relapses

Focal Segmental Glomerulosclerosis (FSGS)

- Can be idiopathic (primary) or secondary to a variety of causes.
- Accounts for less than 20% of the cases of idiopathic nephrotic syndrome in children and approximately 40% in adults
- Sclerotic lesions are characteristically found in some of the glomeruli (focal) and usually involve only a portion of the glomeruli (segmental)
- Almost all the pts present with proteinuria, and many of them have all the features of nephrotic syndrome
- The presenting clinical features in nephrotic adults with minimal-change nephropathy can be indistinguishable from that of FSGS, and renal biopsy is therefore critical in the diagnosis of adults with nephrotic syndrome

- A course of prednisone 1 to 2 mg/kg/day with tapering after 3 to 6 months of treatment.
- If the pt develops a relapse after an adequate response to the initial treatment, a second course of steroids is generally sufficient
- If relapse occurs frequently, cytotoxic agents or cyclosporine would be indicated
- **Close follow-up and good BP control with ACEIs are necessary to minimize disease progression.**
- Cyclosporine or mycophenolate may be used in steroid-resistant pts.

Lupus Nephritis (LN)

- It's glomerulonephritis from systemic lupus erythematosus (SLE)
- Immune complex deposits found in various regions of the glomerulus, interstitium and vasculature outside the glomerulus.
- The hallmark feature in the pathogenesis of SLE is B-cell hyperactivity and the dysregulated production of autoantibodies against multiple antigens in the body
- Females have a higher risk for developing lupus
- Hematuria
- Proteinuria
- Hypertension
- Active urinary sediments (RBC casts, dysmorphic RBCs, and hematuria) are suggestive of the diffuse proliferative lesion

Treatment of LN

- Corticosteroids are the cornerstone of therapy
- For severe LN, primarily the diffuse proliferative type cyclophosphamide may be needed to reduce or prevent the progression to ESRD
- Optimal BP control is important.
- ACEIs or ARBs are commonly used to reduce proteinuria and BP

Acute Induction Treatment

- Steroids and Cytotoxic Agents
  - Oral prednisone of up to 1 mg/kg, followed by tapering over 6 to 12 months or pulse IV methylprednisolone followed by low-dose oral steroids
  - Combined use of IV cyclophosphamide and methylprednisolone is more effective than either agent alone in inducing remission
  - Mycophenolate mofetil is considered an alternative to cyclophosphamide as initial therapy

Chronic Maintenance Treatment

- Steroids and cytotoxic agents
- Oral steroid is commonly used as a component of maintenance treatment (≤10 mg/day prednisolone)
  - Alternate-day regimens often used in children to minimize growth retardation.
  - Monthly pulse IV steroids with cyclophosphamide had more sustained remission, fewer relapses, and no significant increase in side effects
- Pts on mycophenolate or azathioprine found to have better outcome & less side effects than cyclophosphamide
  - mycophenolate should not be used during pregnancy since many lupus pts are women of child-bearing age

- Calcineurin Inhibitors
  - Cyclosporine may reduce proteinuria
  - comparable efficacy and safety with azathioprine in preventing relapse for pts with diffuse proliferative LN
  - recommended for those intolerant of the side effects of azathioprine or mycophenolate
- Hydroxychloroquine
  - can inhibit the receptors that contribute to autoimmunity.
  - have retinal toxicity, thus all pts should have annual eye examination, especially after 5 years of continuous use

Rapidly Progressive Glomerulonephritis (RPGN)

- A clinicopathologic syndrome of rapid loss of renal function—usually a greater than 50% decrement of the GFR within 3 months.
- The predominant histologic finding of RPGN is extensive crescent formation, usually in more than 50% of the glomeruli.
- Different etiologic factors are implicated as the cause of RPGN: toxins, drugs, viral and bacterial infections, neoplasms, autoimmune mechanisms
- Damage in the glomerular capillary wall by both humoral and cellular pathways of inflammation is common
- The disruption of the capillary wall allows movement of macrophages and other plasma constituents into Bowman's space and stimulates the formation of crescents, which are composed mainly of parietal epithelial cells, as well as macrophages and fibroblasts

Clinical Presentation of RPGN

- Progressive renal insufficiency with complaints of tea-colored urine, malaise, anorexia, low-grade fever, and migratory polyarthropathy
- Urinalysis commonly shows nephritic sediments with hematuria, RBC casts, and proteinuria

Treatment of RPGN

Antiglomerular Basement Membrane Glomerulonephritis (Type I)

- Steroids and cyclophosphamide
- Plasma exchanges remove the pathogenic anti-GBM antibodies in circulation and are conducted for 2 wks or until the antibodies disappear
- Prednisolone 1 mg/kg/day, tapered over 6 months and cyclophosphamide 2 to 3 mg/kg/day for 3 months are then given to prevent new antibody production

Immune-Complex–Mediated Glomerulonephritis (Type II)

- Pulse doses of methylprednisolone (30 mg/kg/day, every other day × 3), followed by
- Oral prednisone (1 mg/kg/day several months) and then tapering

Antineutrophil Cytoplasmic Autoantibody-Associated Glomerulonephritis (Type III)

- Combined use of high-dose corticosteroids and cyclophosphamide induces remission in >90% of pts.
- Maintenance therapy, using azathioprine or mycophenolate mofetil for at least 18 months

Post streptococcal Glomerulonephritis (PSGN)

- Mostly seen in children aged between 5 and 15 years and is uncommon in children younger than 2 years of age and in adults older than 50 years.
- It follows pharyngeal or skin infection caused by the nephritogenic strains of group A streptococci.
- The latent period is commonly **7 to 14 days for pharyngitis and 14 to 28 days for skin infection**
- Hematuria and edema
- Hypertension
- Signs & symptoms of volume overload (dyspnea, orthopnea, cough)
- RBC casts in urine
- Proteinuria is common but often not in the nephrotic range
- Antistreptolysin O (ASO) titer: is a blood test to measure antibodies against streptolysin O, a substance produced by group A Streptococcus bacteria

Treatment of PSGN

- Early antibiotic therapy does not prevent subsequent PSGN, but it may reduce the severity of the disease.
- It can prevent the spread of the streptococcal infection to other family members.
- Supportive measures to control fluid volume and blood pressure.
- Because the hypertension is of the low-renin type, ACEIs and β-blockers are not expected to be useful.
- If the pt has crescentic disease, use of pulse steroids and/or immunosuppressive agents can be considered
- The acute manifestations of PSGN are self-limited, and for more than 95% of pts renal function has returned to baseline within 3 to 6 weeks.
- Hypertension and azotemia resolve in 1 to 2 weeks.
- Gross hematuria lasts for 1 to 2 weeks, and proteinuria usually resolves within 6 months in more than 90% of children.
- However, microscopic hematuria may persist for up to 2 years.
- Children have more rapid recovery than adults.