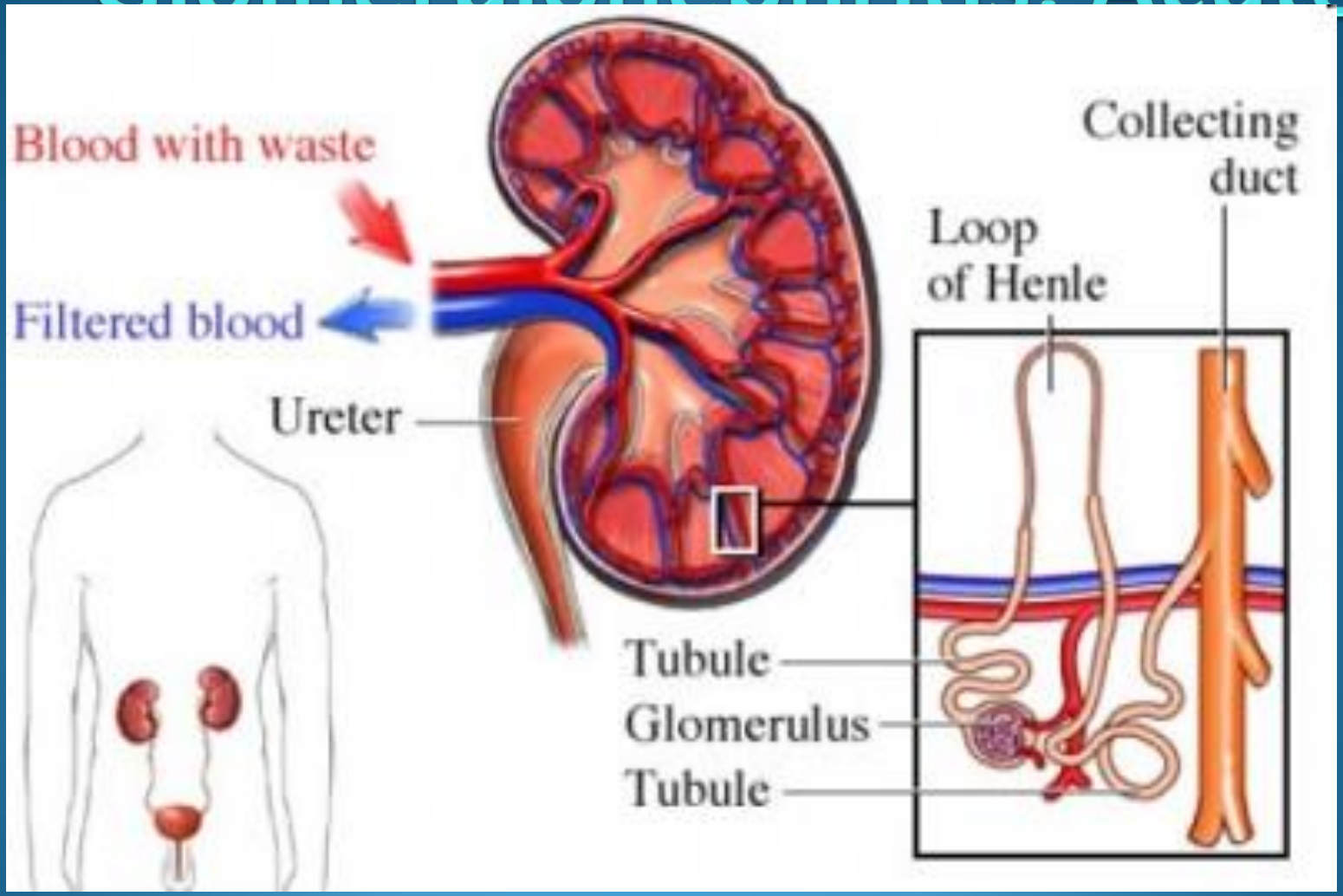
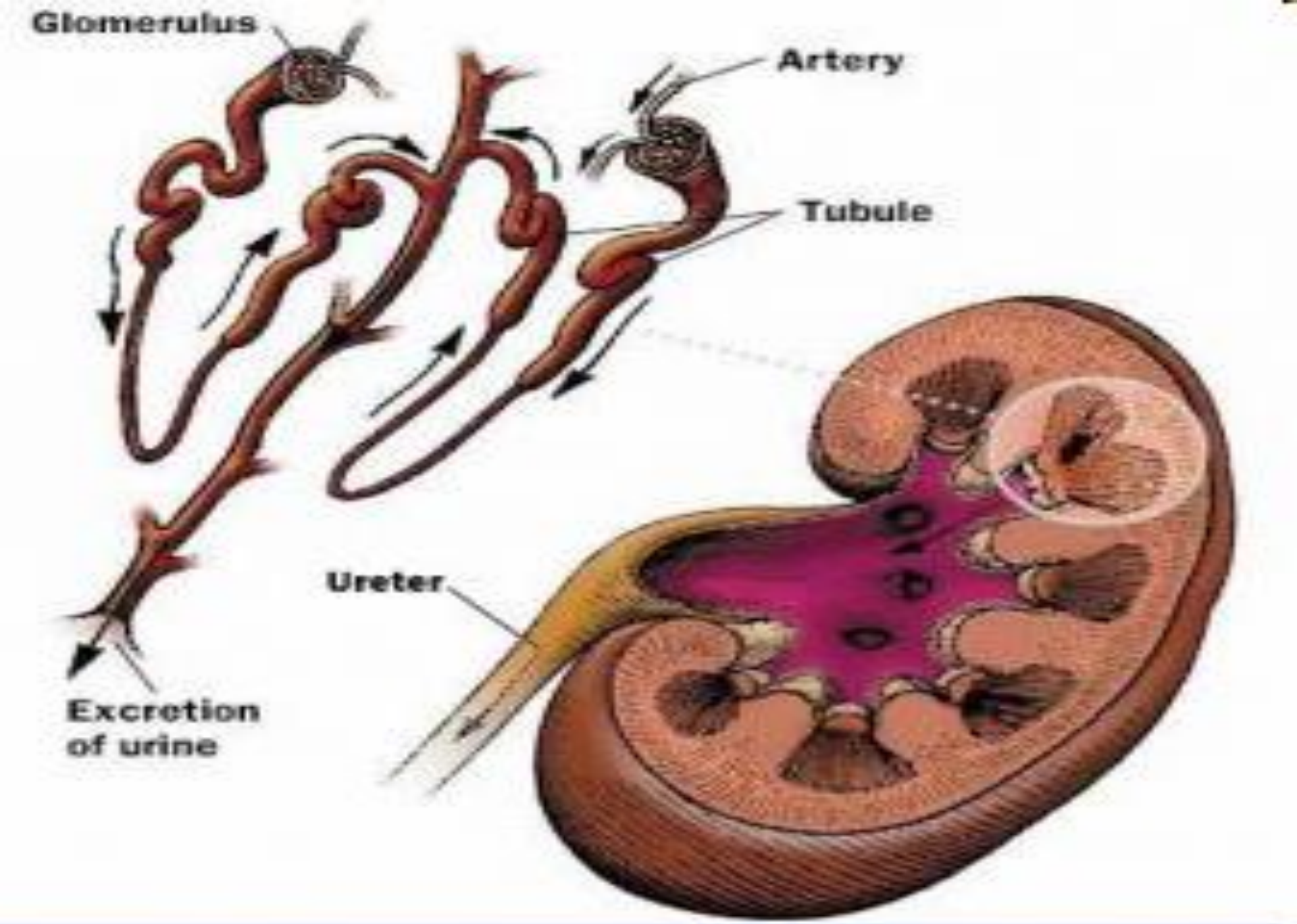
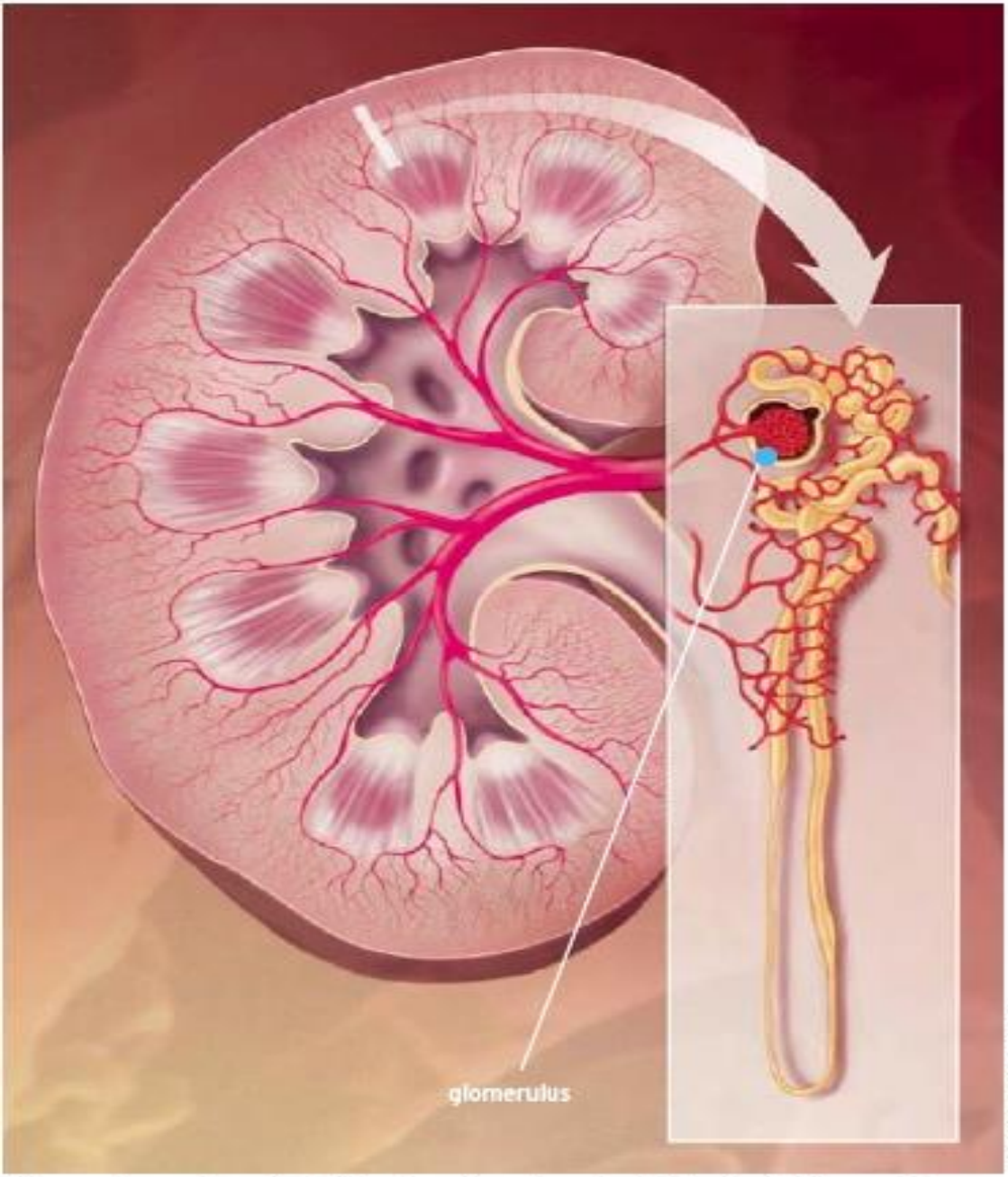
Glomerulonephritis, Acute



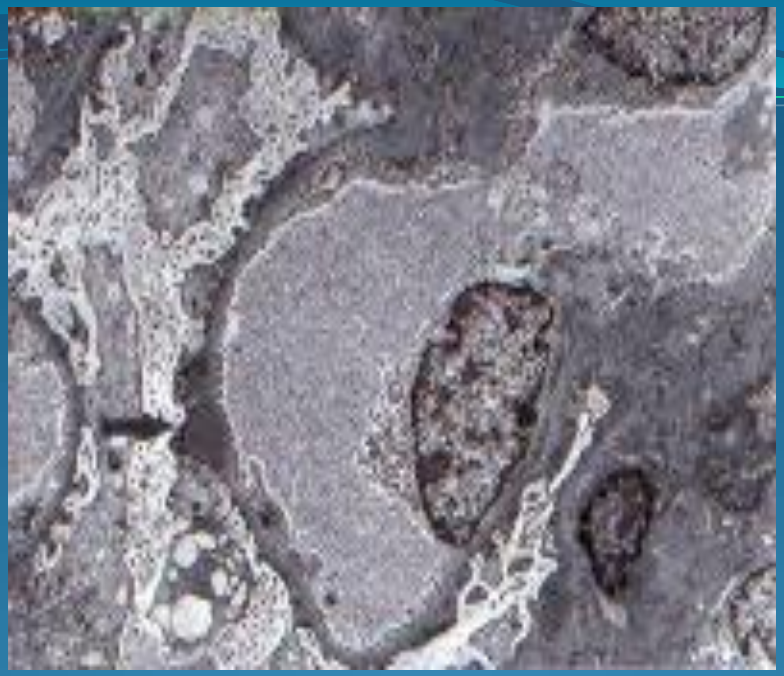




The nephron (inset) is the functional unit within the kidney, where the glomerulus filters the blood.

Background

- Bright initially described acute glomerulonephritis (GN) in 1927.
- Acute poststreptococcal glomerulonephritis (PSGN) is the archetype of acute GN.
- Acute nephritic syndrome is the most serious and potentially devastating form of various renal syndromes.
- Acute GN is characterized by the abrupt onset of hematuria and proteinuria, often accompanied by azotemia (ie, decreased glomerular filtration rate [GFR]) and renal salt and water retention



- Ultrastructure (electron microscopy): Photograph showing proliferation of endothelial cells and mesangial cells and leukocyte infiltrate associated with presence of large, subepithelial, electron-dense deposits (ie, "hump") (see arrow).

Causes

- The causal factors that underlie this syndrome can be broadly divided into infectious and noninfectious groups.

Infectious

- Streptococcal: Poststreptococcal GN usually develops 1-3 weeks following acute infection with specific nephritogenic strains of group A beta-hemolytic streptococcus. The incidence of GN is approximately 5-10% in persons with pharyngitis and 25% in those with skin infections.

Nonstreptococcal postinfectious glomerulonephritis

- Bacterial - Infective endocarditis, shunt nephritis, sepsis, pneumococcal pneumonia, typhoid, secondary syphilis, meningococcemia, and infection with methicillin-resistant Staphylococcus aureus (MRSA)
- Viral - Hepatitis B, infectious mononucleosis, mumps, measles, varicella, vaccinia, echovirus, parvovirus, and coxsackievirus
- Parasitic - Malaria, toxoplasmosis

Noninfectious

- Multisystem systemic diseases - Systemic lupus erythematosus, vasculitis, Henoch-Schönlein purpura, Goodpasture syndrome, Wegener granulomatosis
- Primary glomerular diseases - Membranoproliferative GN (MPGN), Berger disease (ie, immunoglobulin A [IgA] nephropathy), "pure" mesangial proliferative GN
- Miscellaneous - Guillain-Barré syndrome, radiation of Wilms tumor, diphtheria-pertussis-tetanus vaccine, serum sickness

Pathophysiology

- Acute GN has 2 components: structural changes and functional changes.

Structural changes

- Cellular proliferation: This leads to an increase in the number of cells in the glomerular tuft because of the proliferation of endothelial, mesangial,[3] and epithelial cells. The proliferation could be endocapillary (ie, within the confines of the glomerular capillary tufts) or extracapillary (ie, in the Bowman space involving the epithelial cells). In extracapillary proliferation, proliferation of parietal epithelial cells leads to the formation of crescents, a feature characteristic of certain forms of rapidly progressive GN.
- Leukocyte proliferation: This is indicated by the presence of neutrophils and monocytes within the glomerular capillary lumen and often accompanies cellular proliferation.
- Glomerular basement membrane thickening: This development appears as thickening of capillary walls using light microscopy. Using electron microscopy, this may appear as the result of thickening of basement membrane proper (eg, diabetes) or deposition of electron-dense material, either on the endothelial or epithelial side of the basement membrane.
- Hyalinization or sclerosis: These conditions indicate irreversible injury.
- Electron-dense deposits: Such deposits could be subendothelial, subepithelial, intramembranous, or mesangial, and they correspond to an area of immune complex deposition.
- These structural changes could be focal, diffuse or segmental, and global.

Functional changes

- Functional changes include proteinuria, hematuria, reduction in GFR (ie, oligoanuria), and active urine sediment with RBCs and RBC casts. The decreased GFR and avid distal nephron salt and water retention result in expansion of intravascular volume, edema, and, frequently, systemic hypertension.

Poststreptococcal glomerulonephritis

- M-protein of the organism was previously believed to be responsible for PSGN, but these studies have been discounted.
- Nephritis-associated streptococcal cationic protease and its zymogen precursor (NAPR) have been identified as a glyceraldehyde-3-phosphate dehydrogenase that functions as a plasmin(ogen) receptor.
- This binds to plasmin and activates complement via alternate pathway.
- Antibody levels to NAPR are elevated in streptococcal infections (of group A, C, and G) associated with glomerulonephritis but are not elevated in streptococcal infections without glomerulonephritis, whereas anti-streptolysin-O titers are elevated in both circumstances.
- These antibodies to NAPR persist for years and perhaps are protective against further episodes of PSGN. In a study in adults, the 2 most frequently identified infectious agents were streptococcus (27.9%) and staphylococcus (24.4%)

Epidemiology

- United States:
- GN comprises 25-30% of all cases of end-stage renal disease (ESRD). About one fourth of patients present with acute nephritic syndrome. Most cases that progress do so relatively quickly, and end-stage renal failure may occur within weeks or months of acute nephritic syndrome onset. Asymptomatic episodes of PSGN exceed symptomatic episodes by a ratio of 3-4:1.

Epidemiology

- International
- Geographic and seasonal variations in the prevalence of PSGN are more marked for pharyngeally associated GN than for cutaneously associated disease

Race

- Postinfectious GN has no predilection for any racial or ethnic group. A higher incidence (related to poor hygiene) may be observed in some socioeconomic groups.

Sex

- Acute GN predominantly affects males (ie, 2:1 male-to-female ratio).

Age

- Postinfectious GN can occur at any age but usually develops in children. Outbreaks of PSGN are common in children aged 6-10 years.

History

- Taking a proper history is important and helpful.
- Determine onset of disease: Ask the patient about onset and duration of illness.
- Identify a possible etiologic agent (eg, streptococcal throat infection [pharyngitis], skin infection [pyoderma]): Recent fever, sore throat, joint pains, hepatitis, travel, valve replacement, and/or intravenous drug use may be causative factors. Rheumatic fever rarely coexists with acute PSGN.
- Identify systemic disease (eg, arthralgia, diabetes).
- Assess the consequences of the disease process (eg, uremic symptoms): Inquire about loss of appetite, generalized itching, tiredness, listlessness, nausea, easy bruising, nose bleeds, facial swelling, leg edema, and shortness of breath.
- Identify clinical features: Inquire about edema, decreased volume and frequency of urination, systemic hypertension, uremic symptoms, costovertebral tenderness (ie, enlarged kidneys [rare]), and gross hematuria. Gross hematuria is the most common abnormality observed in patients with acute PSGN and often manifests as smoky-, coffee-, or cola-colored urine.

Physical

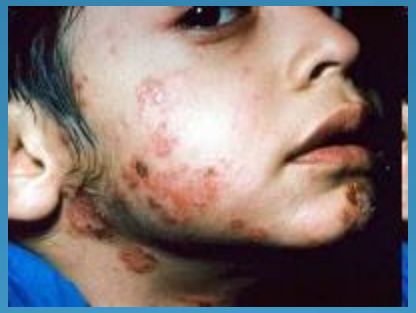
Signs of fluid overload:

- *Periorbital and/or pedal edema*
- *Edema and hypertension due to fluid overload (in 75% of patients)*
- *Crackles (ie, if pulmonary edema)*
- *Elevated jugular venous pressure*
- *Ascites and pleural effusion (possible)*

Physical

- Rash (ie, vasculitis, Henoch-Schönlein purpura)
- Pallor
- Renal angle (ie, costovertebral) fullness or tenderness, joint swelling, or tenderness

Post streptococcal glomerulonephritis



Laboratory Studies

1. Urinalysis and sediment examination:

- These tests are crucial in the evaluation of patients with acute nephritic syndrome.
- Look for protein, blood, RBCs and WBCs, dysmorphic red cells, acanthocytes, cellular (ie, RBC, WBC) casts, granular casts, and oval fat bodies. In some instances, marked sterile pyuria is present.
- Finding RBC casts is an almost pathognomonic sign of GN.
- Urine electrolytes, urine sodium, and fractional excretion of sodium (FENa) assays are needed to assess salt avidity.

Laboratory Studies

- Blood, urea, and nitrogen (BUN); serum creatinine; and serum electrolytes (especially serum potassium level)
- Complete blood cell count
- Erythrocyte sedimentation rate

- Complement levels (C3, C4, CH50)
  - Low C3 levels are found in almost all patients with acute poststreptococcal nephritis; C4 levels may be slightly low. Hypocomplementemia is noted in 73.9% of adult patients.
  - Type III cryoglobulinemia may be present.

- Twenty-four–hour urine test for total protein and creatinine clearance: Remember that creatinine clearance is a "steady-state" measurement. The creatinine clearance may not reveal the true picture because of rapidly changing renal function; therefore, it is better to wait until renal function has stabilized before performing creatinine clearance.

- Antistreptolysin-O titer (ASOT) or streptozyme titer: Increasing titer levels confirm recent infection. In patients with skin infection, anti-DNase B titers are more sensitive than ASOT for infection with Streptococcus.
- Antibody to NAPR: Levels are elevated in streptococcal infections with GN but not in streptococcal infections without GN.
- If MRSA is the inciting agent, then hypocomplementemia is usually not present, but plasma immunoglobulins, especially IgA, are markedly elevated.

- Qualitative estimation of proteinuria: Determination of high-molecular weight (HMW) protein, like fractional excretion of IgG (FEIgG), and low-molecular weight (LMW) protein, like alpha-1-microglobulin, may help predict the clinical outcome and may help in guiding steroid and immunosuppressive therapy, especially in patients with primary glomerular diseases with nephrotic syndrome.

Imaging Studies

- Abdominal ultrasound:

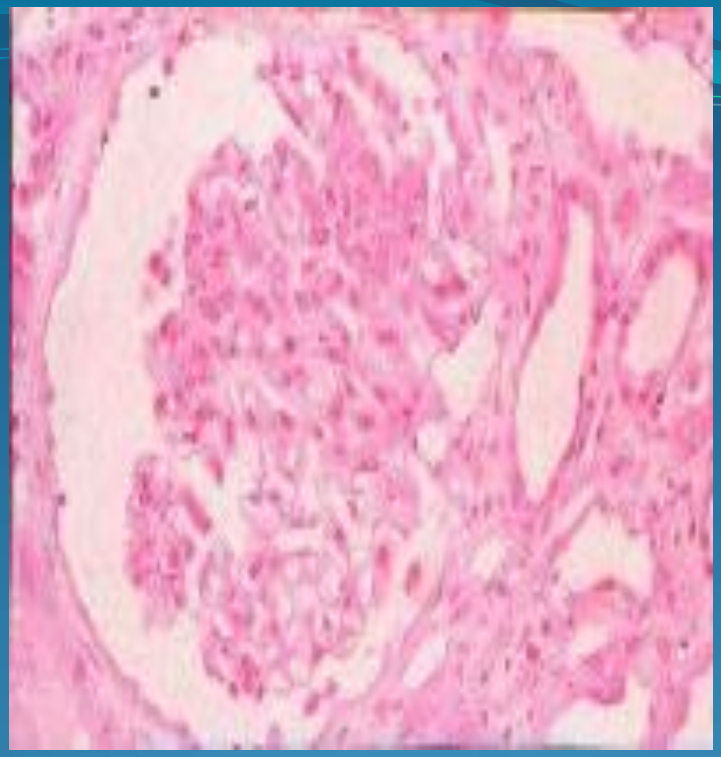
- Assesses renal size
- Assesses echogenicity of renal cortex
- Excludes obstruction

Procedures

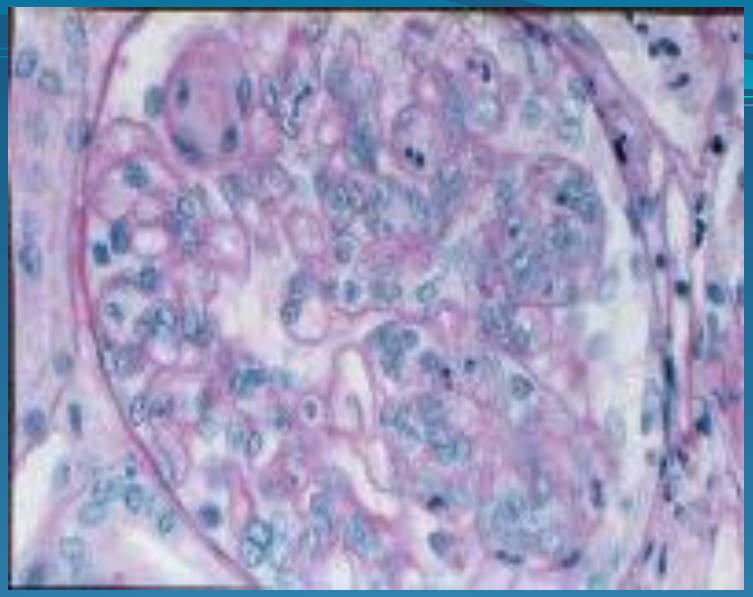
- Generally, a renal biopsy is not necessary for a diagnosis of acute PSGN; however, in most cases, it is important because histology guides both prognosis and therapy.

Histologic Findings

- Diffuse endocapillary proliferative changes are found. The most common histologic patterns are diffuse (72.1%), focal (12.8%), and mesangial (8.1%) proliferative GN in adults.
- In postinfectious GN, the glomerulus is hypercellular with marked cellular infiltration (ie, polymorphonuclear neutrophils, monocytes).
- Immunofluorescence may show fine, granular deposits of immunoglobulin G in a "starry sky" appearance.
- Large subepithelial deposits may be observed on electron microscopy. Crescents may be observed

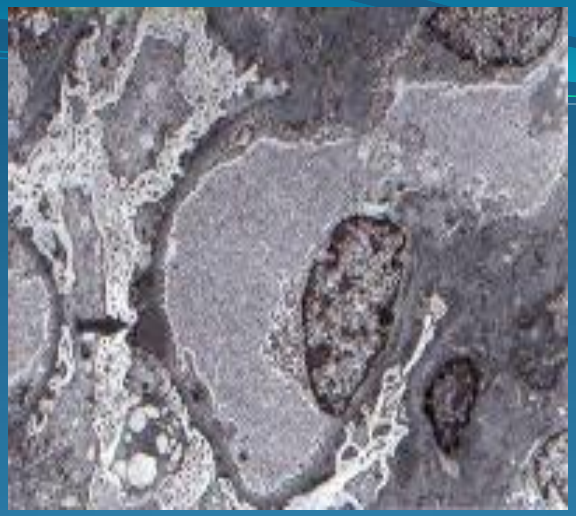


- Photograph showing enlargement of glomerular tuft with marked decrease of urinary space and hypercellularity. The hypercellularity is due to proliferation of endogenous cells and polymorphonuclear leukocyte infiltrate.



- Photograph showing enlargement of glomerular tuft with marked decrease of urinary space and hypercellularity. The hypercellularity is due to proliferation of endogenous cells and polymorphonuclear leukocyte infiltrate

- Fine granular deposits of immunoglobulin G (IgG) along the basement membrane and mesangium, with "starry sky" appearance

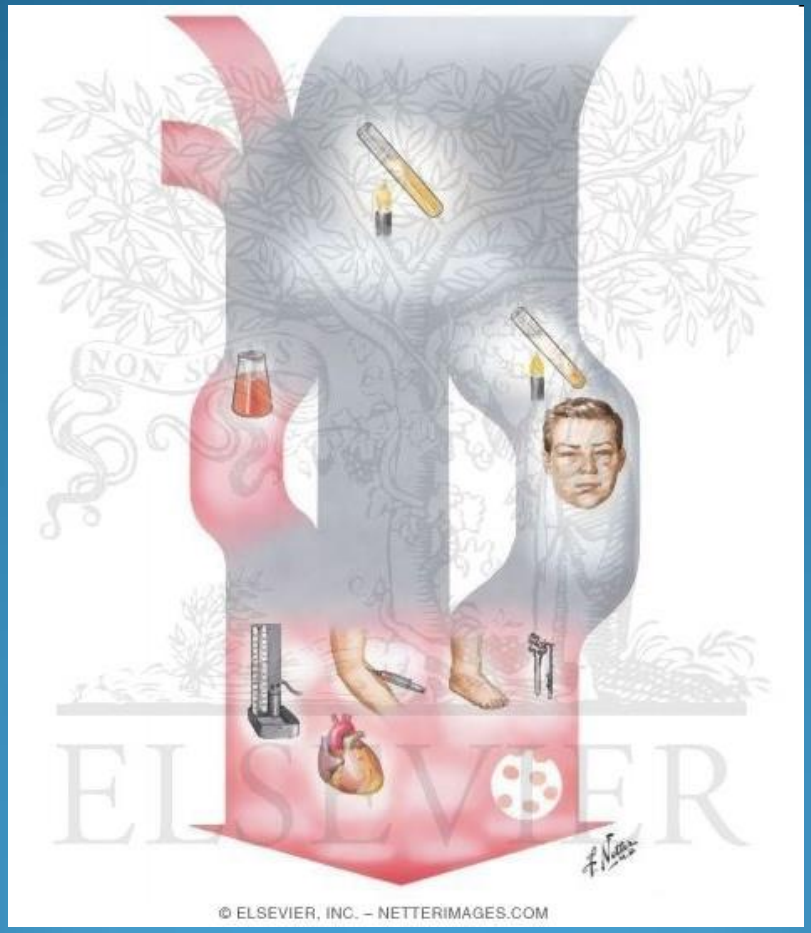


- Photograph showing proliferation of endothelial cells and mesangial cells and leukocyte infiltrate associated with presence of large, subepithelial, electron-dense deposits (ie, "hump")

Glomerulonephritis, Chronic

- Nearly all forms of acute glomerulonephritis have a tendency to progress to chronic glomerulonephritis.
- The condition is characterized by irreversible and progressive glomerular and tubulointerstitial fibrosis, ultimately leading to a reduction in the glomerular filtration rate (GFR) and retention of uremic toxins. If disease progression is not halted with therapy, the net result is chronic kidney disease (CKD), end-stage renal disease (ESRD), and cardiovascular disease.
- The diagnosis of CKD can be made without knowledge of the specific cause.

Clinical Course of Chronic Glomerulonephritis



- The National Kidney Foundation defines CKD as;
- (1) evidence of kidney damage based on abnormal urinalysis results (eg, proteinuria, hematuria) or structural abnormalities observed on ultrasound images or
- (2) a GFR of less than 60 mL/min for 3 or more months. Based on this definition, the National Kidney Foundation developed guidelines that classify the progression of renal disease into 5 stages, from kidney disease with a preserved GFR to end-stage kidney failure.

This classification includes treatment strategies for each progressive level, as follows:

- Stage 1: This stage is characterized by kidney damage with a normal GFR (≥ 90 mL/min). The action plan is diagnosis and treatment, treatment of comorbid conditions, slowing of the progressing of kidney disease, and reduction of cardiovascular disease risks.
- Stage 2: This stage is characterized by kidney damage with a mild decrease in the GFR (60-90 mL/min). The action plan is estimation of the progression of kidney disease.
- Stage 3: This stage is characterized by a moderately decreased GFR (30-59 mL/min). The action plan is evaluation and treatment of complications.
- Stage 4: This stage is characterized by a severe decrease in the GFR (15-29 mL/min). The action plan is preparation for renal replacement therapy.
- Stage 5: This stage is characterized by kidney failure. The action plan is kidney replacement if the patient is uremic.

- At the later stages of glomerular injury, biopsy results cannot help distinguish the primary disease. Histology and clues to the etiology are often derived from other systemic diseases, if present. Considerable cause-specific variability is observed in the rate at which acute glomerulonephritis progresses to chronic glomerulonephritis.

Causes

- The progression from acute glomerulonephritis to chronic glomerulonephritis is variable. Whereas complete recovery of renal function is the rule for patients with poststreptococcal glomerulonephritis, several other glomerulonephritides, such as immunoglobulin A (IgA) nephropathy, often have a relatively benign course and many do not progress to ESRD.

- **Rapidly progressive glomerulonephritis or crescentic glomerulonephritis**: Approximately 90% of patients progress to ESRD within weeks or months.
- **Focal segmental glomerulosclerosis**: Approximately 80% of patients progress to ESRD in 10 years. Patients with the collapsing variant, which is termed malignant focal segmental glomerulosclerosis, have a more rapid progression. This form may be idiopathic or related to HIV infection.

- **Membranous nephropathy**: Approximately 20-30% of patients with membranous nephropathy progress to chronic renal failure (CRF) and ESRD in 10 years.
- Membranoproliferative glomerulonephritis: Approximately 40% of patients with membranoproliferative glomerulonephritis progress to CRF and ESRD in 10 years.
- **IgA nephropathy**: Approximately 10% of patients with IgA nephropathy progress to CRF and ESRD in 10 years

- **Poststreptococcal glomerulonephritis**: Approximately 1-2% of patients with poststreptococcal glomerulonephritis progress to CRF and ESRD. Older children who present with crescentic glomerulonephritis are at greatest risk.
- **Lupus nephritis**: Overall, approximately 20% of patients with lupus nephritis progress to CRF and ESRD in 10 years; however, patients with certain histologic variants (eg, class IV) may have a more rapid decline

Pathophysiology

- Reduction in nephron mass from the initial injury reduces the GFR.
- This reduction leads to hypertrophy and hyperfiltration of the remaining nephrons and to the initiation of intraglomerular hypertension.
- These changes occur in order to increase the GFR of the remaining nephrons, thus minimizing the functional consequences of nephron loss.
- The changes, however, are ultimately detrimental because they lead to glomerulosclerosis and further nephron loss.

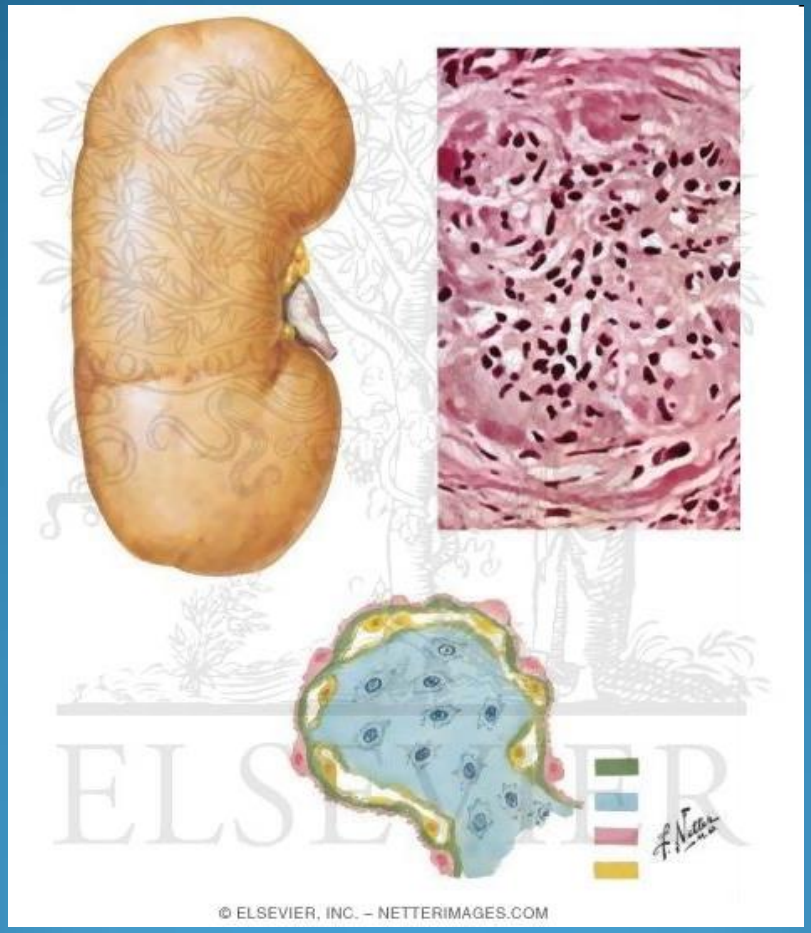
Pathophysiology

- In early renal disease (stages 1-3), a substantial decline in the GFR may lead to only slight increases in serum creatinine levels. Azotemia (ie, a rise in BUN and serum creatinine levels) is apparent when the GFR decreases to less than 60-70 mL/min. In addition to a rise in BUN and creatinine levels, the substantial reduction in the GFR results in decreased production of
- (1) erythropoietin, thus resulting in anemia;
- (2) decreased production of vitamin D, resulting in hypocalcemia, secondary hyperparathyroidism, hyperphosphatemia, and renal osteodystrophy;
- (3) reduction in acid, potassium, salt, and water excretion, resulting in acidosis, hyperkalemia, hypertension, and edema; and
- (4) platelet dysfunction, leading to increased bleeding tendencies.

Pathophysiology

- Accumulation of toxic waste products (uremic toxins) affects virtually all organ systems. Azotemia occurring with the signs and symptoms listed above is known as uremia. Uremia occurs at a GFR of approximately 10 mL/min. Some of these toxins (eg, BUN, creatinine, phenols, guanidines) have been identified, but none has been found to be responsible for all the symptoms.

Chronic Glomerulonephritis



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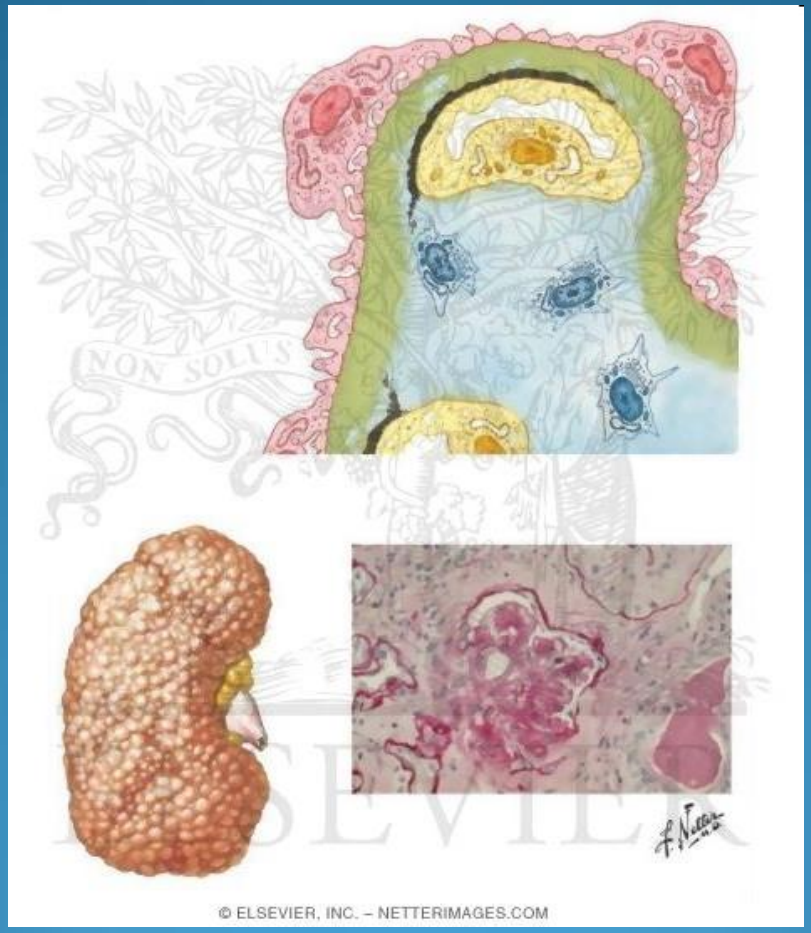

Epidemiology
Frequency

- **United States**
- Chronic glomerulonephritis is the third leading cause of ESRD and accounts for 10% of patients on dialysis in the United States.
- **International**
- Chronic glomerulonephritis accounted for up to 40% of patients on dialysis in Japan and some Asian countries. However, more recent data suggest that, in Japan for instance, the rate of chronic glomerulonephritis in patients on dialysis is 28%. The cause of this declining rate is not known. Concurrent with the decline in chronic glomerulonephritis in these countries is an increase in diabetic nephropathy in up to 40% of patients on dialysis.

Mortality/Morbidity

- ESRD and death are common outcomes unless renal replacement therapy is instituted.

History

- The history should focus on cause-specific symptoms to determine the causes of CKD (if unknown) and on symptoms related to uremia to determine if renal replacement therapy is needed.

Cause-specific history: Obtain a cause-specific history so that further workup and management of the disease (if systemic) can be planned.

- *Uremia-specific history*
- *The following symptoms suggest uremia:*
- *Weakness and fatigue*
- *Loss of energy, appetite, and weight*
- *Pruritus*
- *Early morning nausea and vomiting*
- *Change in taste sensation*
- *Reversal in sleep pattern (ie, sleepiness in daytime, wakefulness at night)*
- *Peripheral neuropathy*
- *Seizures*
- *Tremors*
- *The presence of edema and hypertension suggests volume retention.*
- *Dyspnea or chest pain that varies with position suggests fluid overload and pericarditis, respectively.*
- *Leg cramps may suggest hypocalcemia or other electrolyte abnormalities.*
- *Weakness, lethargy, and fatigue may be due to anemia.*

Physical

- *Cause-specific physical examination findings are discussed in articles on the specific causes. See Causes for links to such articles.*
- *Uremia-specific findings*
- *Hypertension*
- *Jugular venous distension (if severe volume overload is present)*
- *Pulmonary rales (if pulmonary edema is present)*
- *Pericardial friction rub in pericarditis*
- *Tenderness in the epigastric region or blood in the stool (possible indicators for uremic gastritis or enteropathy)*
- *Decreased sensation and asterixis (indicators for advanced uremia)*

Laboratory Studies

- **Urinalysis**
- The presence of dysmorphic RBCs, albumin, or RBC casts suggests glomerulonephritis as the cause of renal failure.
- Waxy or broad casts are observed in all forms of CKD, including chronic glomerulonephritis.
- Low urine-specific gravity indicates loss of tubular concentrating ability, an early finding in persons with CDK.

Urinary protein excretion

- This can be estimated by calculating the protein-to-creatinine ratio on a spot morning urine sample. The ratio of urinary protein concentration (in mg/dL) to urinary creatinine (in mg/dL) reflects 24-hour protein excretion in grams. For instance, if the spot urine protein value is 300 mg/dL and the creatinine value is 150 mg/dL, then the ratio is 300 divided by 150, which equals 2. Thus, in this example, the 24-hour urine protein excretion is 2 g.

- The estimated creatinine clearance rate is used to assess and monitor the GFR. The 2 formulas available to calculate the value are the Cockroft-Gault formula, which estimates creatinine clearance, and the Modification of Diet in Renal Disease Study (MDRD) formula, which is used to calculate the GFR. The Cockroft-Gault formula is simple to use but overestimates the GFR by 10-15% because creatinine is both filtered and secreted. The MDRD formula is much more complex but is available as a PDA through the National Kidney Foundation or can be calculated online through the Hypertension, Dialysis, and Clinical Nephrology Web site.

- The estimated creatinine clearance rate is also used to monitor response to therapy and to initiate an early transition to renal replacement therapy (eg, dialysis access placement, transplantation evaluation). The degree of proteinuria, especially albuminuria, helps predict renal prognosis in patients with chronic glomerulonephritis. Patients with greater than 1 g/d have an increased risk of progression to ESRD.

CBC count

- Anemia is a significant finding in patients with some decline in the GFR.
- Physicians must be aware that anemia can occur even in patients with serum creatinine levels of less than 2 mg/dL. Even severe anemia can occur at low serum creatinine levels. Anemia is the result of marked impairment of erythropoietin production

Serum chemistry

- Serum creatinine and urea nitrogen levels are elevated.
- Impaired excretion of potassium, free water, and acid results in hyperkalemia, hyponatremia, and low serum bicarbonate levels, respectively.
- Impaired vitamin D-3 production results in hypocalcemia, hyperphosphatemia, and high levels of parathyroid hormone.
- Low serum albumin levels may be present if uremia interferes with nutrition or if the patient is nephrotic.

Renal ultrasonogram

- Obtain a renal ultrasonogram to determine renal size, to assess for the presence of both kidneys, and to exclude structural lesions that may be responsible for azotemia.
- Small kidneys often indicate an irreversible process.

Procedures

- **Kidney biopsy**
- If the kidney is small, kidney biopsy is usually unnecessary; no specific pattern of disease can be discerned at this point.
- A kidney biopsy may be considered in the minority of patients who exhibit an acute exacerbation of their chronic disease. This may be particularly pertinent to patients with preserved kidney size and in those with lupus nephrite

Histologic Findings

- In early stages, the glomeruli may still show some evidence of the primary disease.
- In advanced stages, the glomeruli are hyalinized and obsolescent. The tubules are disrupted and atrophic, and marked interstitial fibrosis and arterial and arteriolar sclerosis occur.