

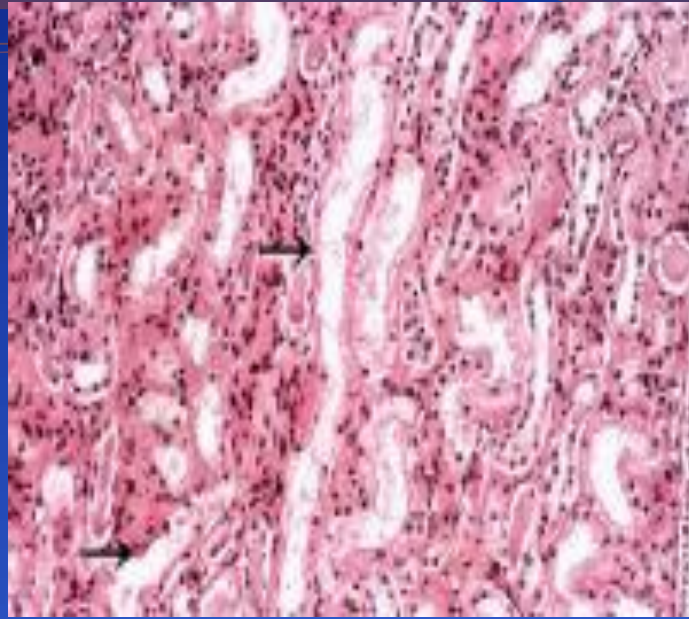
Acute renal failure (ARF) or  
acute kidney injury (AKI),

# Background

- Acute renal failure (ARF) or acute kidney injury (AKI), as it is now referred to in the literature, is defined as an abrupt or rapid decline in renal filtration function. This condition is usually marked by a rise in serum creatinine concentration or azotemia (a rise in blood urea nitrogen [BUN] concentration).

# Background

- However, immediately after a kidney injury, BUN or creatinine levels may be normal, and the only sign of a kidney injury may be decreased urine production.
- A rise in the creatinine level can result from medications (eg, cimetidine, trimethoprim) that inhibit the kidney's tubular secretion.
- A rise in the BUN level can occur without renal injury, resulting instead from such sources as GI or mucosal bleeding, steroid use, or protein loading, so a careful inventory must be taken before determining if a kidney injury is present



- Photomicrograph of a renal biopsy specimen shows renal medulla, which is composed mainly of renal tubules. Patchy or diffuse denudation of the renal tubular cells is observed, suggesting acute tubular necrosis as the cause of acute renal failure.

# The RIFLE system

- In 2004, the Acute Dialysis Quality Initiative work group set forth a definition and classification system for acute renal failure, described by the acronym RIFLE (Risk of renal dysfunction, Injury to the kidney, Failure or Loss of kidney function, and End-stage kidney disease)

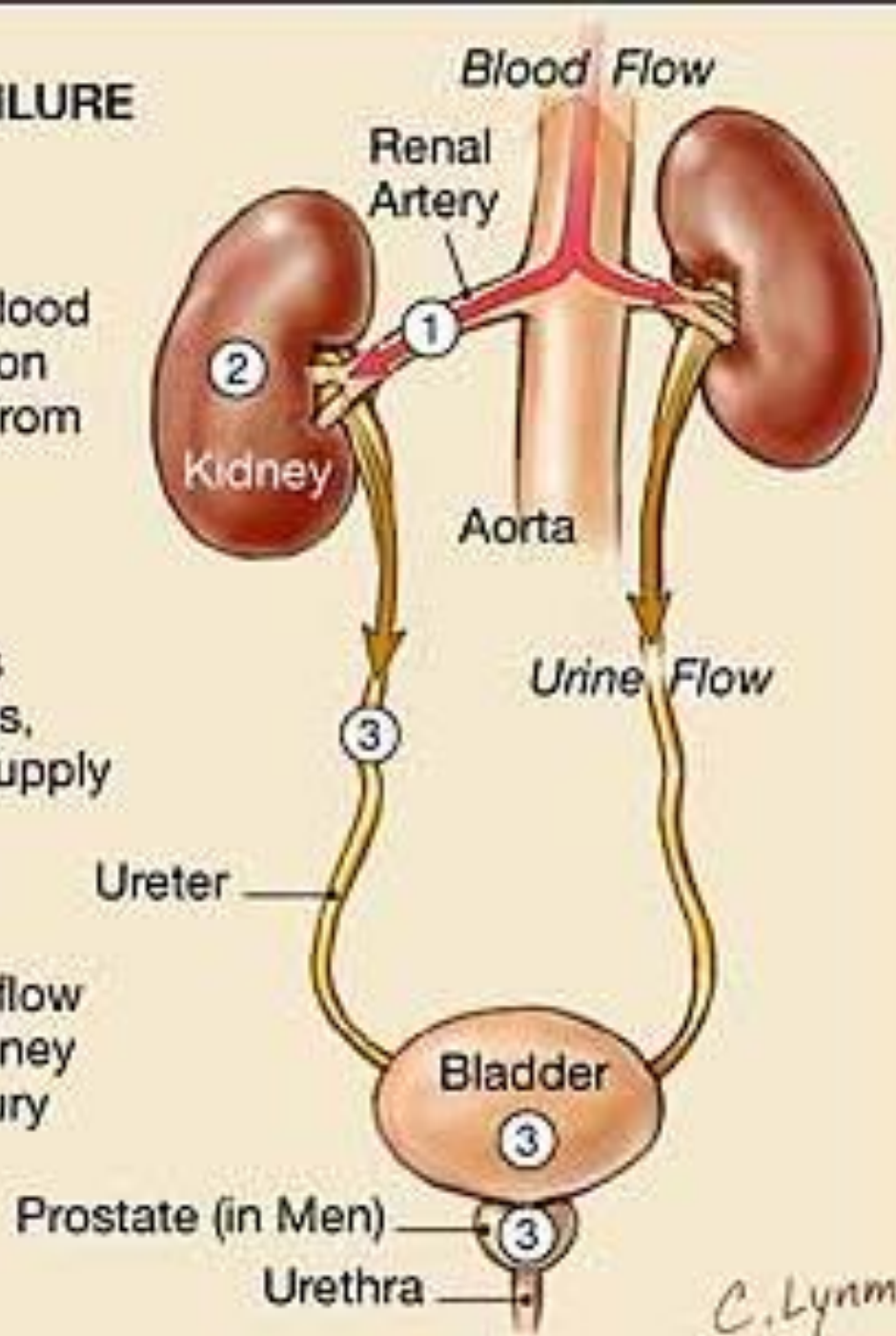
# Table: RIFLE Classification System for Acute Kidney Injury

# Causes

- The causes of AKI traditionally are divided into 3 main categories: prerenal, intrinsic, and postrenal.

## CAUSES OF ACUTE RENAL FAILURE

- ① Prerenal**  
Sudden and severe drop in blood pressure (shock) or interruption of blood flow to the kidneys from severe injury or illness
- ② Intrarenal**  
Direct damage to the kidneys by inflammation, toxins, drugs, infection, or reduced blood supply
- ③ Postrenal**  
Sudden obstruction of urine flow due to enlarged prostate, kidney stones, bladder tumor, or injury





# Prerenal AKI :

- *Volume depletion:*
- Renal losses (diuretics, polyuria)
- GI losses (vomiting, diarrhea)
- Cutaneous losses (burns, Stevens-Johnson syndrome)
- Hemorrhage
- Pancreatitis

# Prerenal AKI :

- *Decreased cardiac output :*
- Heart failure
- Pulmonary embolus
- Acute myocardial infarction
- Severe valvular disease
- Abdominal compartment syndrome (tense ascites)

# Prerenal AKI

- *Systemic vasodilation* :
- Sepsis
- Anaphylaxis
- Anesthetics
- Drug overdose

# Prerenal AKI

- *Afferent arteriolar vasoconstriction :*
- Hypercalcemia
- Drugs (NSAIDs, amphotericin B, calcineurin inhibitors, norepinephrine, radiocontrast agents)
- Hepatorenal syndrome

# Prerenal AKI

- *Efferent arteriolar vasodilation – ACEIs or ARBs*
- *Renal artery occlusion*

# Intrinsic AKI

- *Vascular (large and small vessel):*
- Renal artery obstruction (thrombosis, emboli, dissection, vasculitis)
- Renal vein obstruction (thrombosis)
- Microangiopathy (TTP, hemolytic uremic syndrome [HUS], DIC, preeclampsia)
- Malignant hypertension
- Scleroderma renal crisis
- Transplant rejection
- Atheroembolic disease

# Intrinsic AKI

- *Glomerular:*
- Anti-glomerular basement membrane (GBM) disease (Goodpasture syndrome)
- Anti-neutrophil cytoplasmic antibody-associated glomerulonephritis (ANCA-associated GN) (Wegener granulomatosis, Churg-Strauss syndrome, microscopic polyangiitis)
- Immune complex GN (lupus, postinfectious, cryoglobulinemia, primary membranoproliferative glomerulonephritis)

# Intrinsic AKI

- *Tubular*



# Intrinsic AKI

- **Ischemic:**
- Cytotoxic:
- *Heme pigment (rhabdomyolysis, intravascular hemolysis)*
- *Crystals (tumor lysis syndrome, seizures, ethylene glycol poisoning, megadose vitamin C, acyclovir, indinavir, methotrexate)*
- *Drugs (aminoglycosides, lithium, amphotericin B, pentamidine, cisplatin, ifosfamide, radiocontrast agents)*

# Intrinsic AKI

- **Ischemic:**
- **Interstitial :**
- *Drugs (penicillins, cephalosporins, NSAIDs, proton-pump inhibitors, allopurinol, rifampin, indinavir, mesalamine, sulfonamides)*
- *Infection (pyelonephritis, viral nephritides)*
- *Systemic disease (Sjögren syndrome, sarcoid, lupus, lymphoma, leukemia, tubulonephritis, uveitis)*

# Postrenal AKI

- Ureteric obstruction (stone disease, tumor, fibrosis, ligation during pelvic surgery)
- Bladder neck obstruction (benign prostatic hypertrophy [BPH], cancer of the prostate [CA prostate or prostatic CA], neurogenic bladder, tricyclic antidepressants, ganglion blockers, bladder tumor, stone disease, hemorrhage/clot)
- Urethral obstruction (strictures, tumor, phimosis)
- Intra-abdominal hypertension (tense ascites)
- Renal vein thrombosis

# Pathophysiology

- AKI may be classified into 3 general categories, as follows:
- Prerenal — as an adaptive response to severe volume depletion and hypotension, with structurally intact nephrons
- Intrinsic — in response to cytotoxic, ischemic, or inflammatory insults to the kidney, with structural and functional damage
- Postrenal — from obstruction to the passage of urine.
- While this classification is useful in establishing a differential diagnosis, many pathophysiologic features are shared among the different categories.

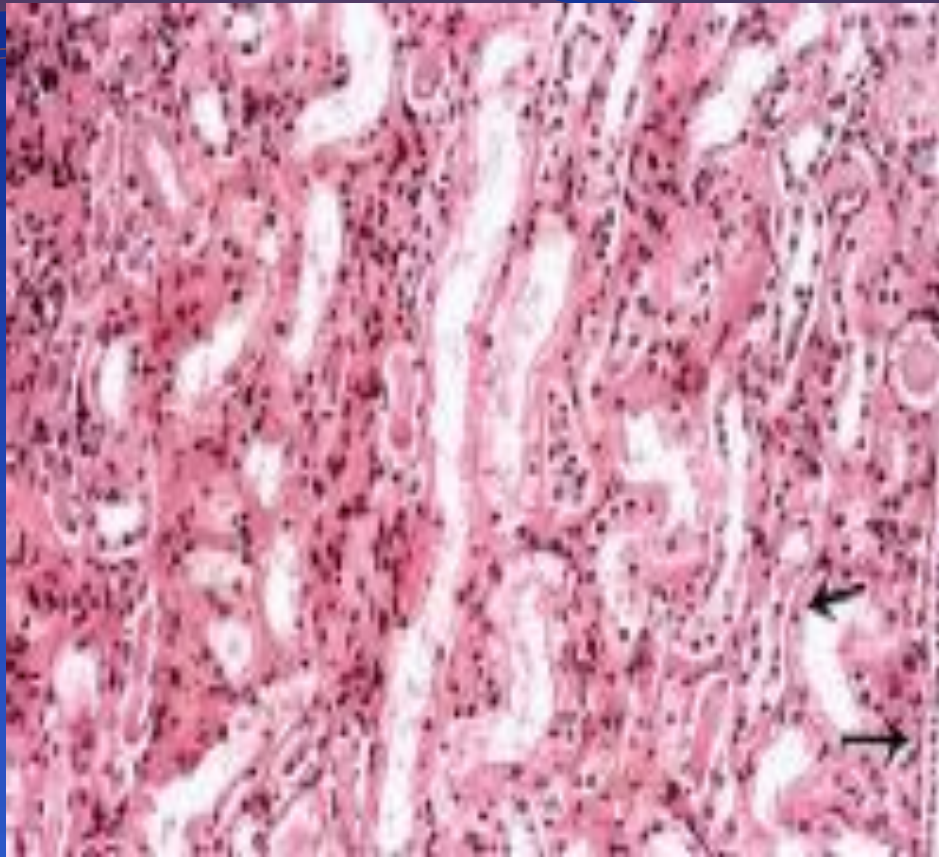
- Patients who develop AKI can be oliguric or nonoliguric, have a rapid or slow rise in creatinine levels, and may have qualitative differences in urine solute concentrations and cellular content. This lack of a uniform clinical presentation reflects the variable nature of the injury.
- Classifying AKI as oliguric or nonoliguric based on daily urine excretion has prognostic value.
- **Oliguria** is defined as a daily urine volume of less than 400 mL/d and has a worse prognosis, except in prerenal failure.
- **Anuria** is defined as a urine output of less than 100 mL/d and, if abrupt in onset, suggests bilateral obstruction or catastrophic injury to both kidneys.
- Stratification of renal failure along these lines helps in decision-making (eg, timing of dialysis) and can be an important criterion for patient response to therapy.

# Pre renal AKI

- Prerenal AKI represents the most common form of kidney injury and often leads to intrinsic AKI if it is not promptly corrected. Volume loss from GI, renal, cutaneous (eg, burns), and internal or external hemorrhage can result in this syndrome. Prerenal AKI can also result from decreased renal perfusion in patients with heart failure or shock (eg, sepsis, anaphylaxis).
- Special classes of medications that can induce prerenal AKI in volume-depleted states are angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs), which are otherwise safely tolerated and beneficial in most patients with chronic kidney disease. Arteriolar vasoconstriction leading to prerenal AKI can occur in hypercalcemic states, with the use of radiocontrast agents, nonsteroidal anti-inflammatory drugs (NSAIDs), amphotericin, calcineurin inhibitors, norepinephrine, and other pressor agents.
- The hepatorenal syndrome can also be considered a form of prerenal AKI, because functional renal failure develops from diffuse vasoconstriction in vessels supplying the kidney.

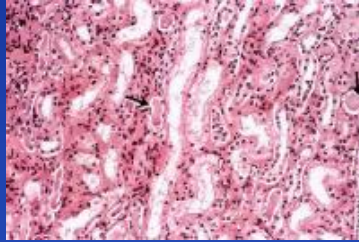
# Intrinsic AKI

- Structural injury in the kidney is the hallmark of intrinsic AKI, and the most common form is acute tubular injury (ATN), either ischemic or cytotoxic.
- Frank necrosis is not prominent in most human cases of ATN and tends to be patchy.
- Less obvious injury includes loss of brush borders, flattening of the epithelium, detachment of cells, formation of intratubular casts, and dilatation of the lumen.
- Although these changes are observed predominantly in proximal tubules, injury to the distal nephron can also be demonstrated. In addition, the distal nephron may become obstructed by desquamated cells and cellular debris.

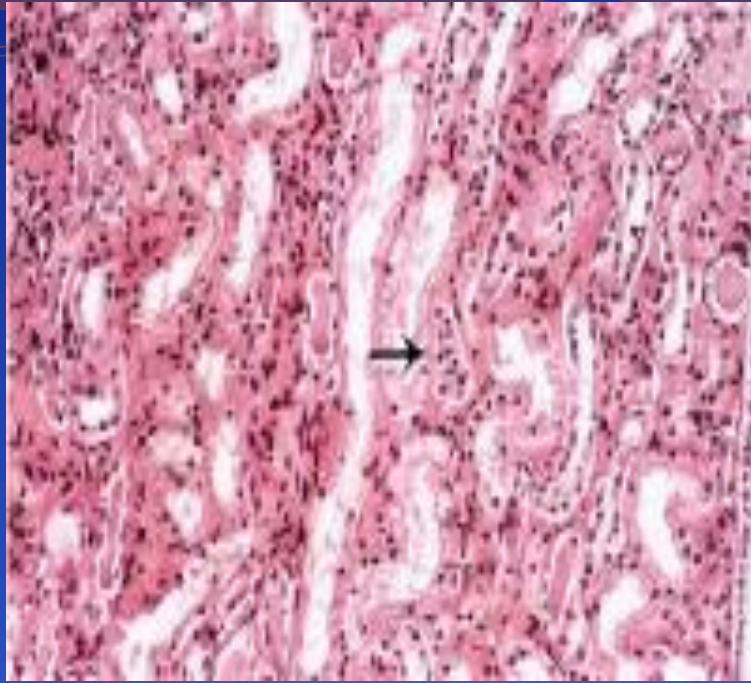


- Flattening of the renal tubular cells due to tubular dilation





- Intratubular cast formation.



- Intratubular obstruction due to the denuded epithelium and cellular debris. Note that the denuded tubular epithelial cells clump together because of rearrangement of intercellular adhesion molecules.

- Many endogenous growth factors that participate in the process of regeneration have not been identified; however, administration of growth factors exogenously has been shown to ameliorate and hasten recovery from AKI. Depletion of neutrophils and blockage of neutrophil adhesion reduce renal injury following ischemia, indicating that the inflammatory response is responsible, in part, for some features of ATN, especially in postischemic injury after transplant.

- Intrarenal vasoconstriction is the dominant mechanism for the reduced glomerular filtration rate (GFR) in patients with ATN. The mediators of this vasoconstriction are unknown, but tubular injury seems to be an important concomitant finding. Urine backflow and intratubular obstruction (from sloughed cells and debris) are causes of reduced net ultrafiltration. The importance of this mechanism is highlighted by the improvement in renal function that follows relief of such intratubular obstruction. In addition, when obstruction is prolonged, intrarenal vasoconstriction is prominent in part due to the tubuloglomerular feedback mechanism, which is thought to be mediated by adenosine and activated when there is proximal tubular damage and the macula densa is presented with increased chloride load.

- Apart from the increase in basal renal vascular tone, the stressed renal microvasculature is more sensitive to potentially vasoconstrictive drugs and otherwise-tolerated changes in systemic blood pressure. The vasculature of the injured kidney has an impaired vasodilatory response and loses its autoregulatory behavior. This latter phenomenon has important clinical relevance because the frequent reduction in systemic pressure during intermittent hemodialysis may provoke additional damage that can delay recovery from ATN. Often, injury results in atubular glomeruli, where the glomerular function is preserved, but the lack of tubular outflow precludes its function.

- A physiologic hallmark of ATN is a failure to maximally dilute or concentrate urine (isosthenuria). This defect is not responsive to pharmacologic doses of vasopressin. The injured kidney fails to generate and maintain a high medullary solute gradient, because the accumulation of solute in the medulla depends on normal distal nephron function. Failure to excrete concentrated urine even in the presence of oliguria is a helpful diagnostic clue in distinguishing prerenal from intrinsic renal disease; in prerenal azotemia, urine osmolality is typically more than 500 mOsm/kg, whereas in intrinsic renal disease, urine osmolality is less than 300 mOsm/kg.

- Glomerulonephritis can be a cause of AKI and usually falls into a class referred to as rapidly progressive glomerulonephritis (RPGN). Glomerular crescents (glomerular injury) are found in RPGN on biopsy; if more than 50% of glomeruli contain crescents, this usually results in a significant decline in renal function. Although comparatively rare, acute glomerulonephritides should be part of the diagnostic consideration in cases of AKI.

# Postrenal AKI

- Mechanical obstruction of the urinary collecting system, including the renal pelvis, ureters, bladder, or urethra, results in obstructive uropathy or postrenal AKI.
- If the site of obstruction is unilateral, then a rise in the serum creatinine level may not be apparent due to contralateral renal function. Although the serum creatinine level may remain low with unilateral obstruction, a significant loss of GFR occurs, and patients with partial obstruction may develop progressive loss of GFR if the obstruction is not relieved. Causes of obstruction include stone disease; stricture; and intraluminal, extraluminal, or intramural tumors.
- Bilateral obstruction is usually a result of prostate enlargement or tumors in men and urologic or gynecologic tumors in women.
- Patients who develop anuria typically have obstruction at the level of the bladder or downstream to it.



# Epidemiology

- Approximately 1% of patients admitted to hospitals have AKI at the time of admission, and the estimated incidence rate of AKI is 2-5% during hospitalization. AKI develops within 30 days postoperatively in approximately 1% of general surgery cases; it develops in up to 67% of intensive care unit patients. Approximately 95% of consultations with nephrologists are related to AKI.

# Mortality/Morbidity

- The mortality rate estimates for AKI vary from 25-90%. The in-hospital mortality rate is 40-50%; in intensive care settings, the rate is 70-80%. Increments of 0.3 mg/dL in serum creatinine have important prognostic significance.
- On long-term followup (1-10 years), approximately 12.5% of AKI survivors are dialysis-dependent (rates range widely, from 1-64%, depending on the patient population) and 19-31% of them have chronic kidney disease.

# Race

- No racial predilection is recognized

# History

- A detailed and accurate history is crucial to aid in diagnosing the type of AKI and in determining its subsequent treatment. A detailed history and a physical examination in combination with routine laboratory tests are useful in making a correct diagnosis.
- Distinguishing AKI from chronic renal failure is important, yet making the distinction can be difficult. A history of chronic symptoms — fatigue, weight loss, anorexia, nocturia, and pruritus — suggests chronic renal failure.

# Take note of the following findings during the physical examination:

- Hypotension
- Volume contraction
- Congestive heart failure
- Nephrotoxic drug ingestion
- History of trauma or unaccustomed exertion
- Blood loss or transfusions
- Evidence of connective tissue disorders or autoimmune diseases
- Exposure to toxic substances, such as ethyl alcohol or ethylene glycol
- Exposure to mercury vapors, lead, cadmium, or other heavy metals, which can be encountered in welders and miners

# Take note of the following findings during the physical examination:

- People with the following comorbid conditions are at a higher risk for developing AKI:
  - Hypertension
  - Congestive cardiac failure
  - Diabetes
  - Multiple myeloma
  - Chronic infection
  - Myeloproliferative disorder
- Urine output history can be useful. Oliguria generally favors AKI. Abrupt anuria suggests acute urinary obstruction, acute and severe glomerulonephritis, or embolic renal artery occlusion. A gradually diminishing urine output may indicate a urethral stricture or bladder outlet obstruction due to prostate enlargement.
- Because of a decrease in functioning nephrons, even a trivial nephrotoxic insult may cause AKI to be superimposed on chronic renal insufficiency.

# Physical

- Skin:
- Petechiae, purpura, ecchymosis, and livedo reticularis provide clues to inflammatory and vascular causes of AK
- Infectious diseases, thrombotic thrombocytopenic purpura (TTP), disseminated intravascular coagulation (DIC), and embolic phenomena can produce typical cutaneous changes.

# Physical

- Eyes
- Evidence of uveitis may indicate interstitial nephritis and necrotizing vasculitis.
- Ocular palsy may indicate ethylene glycol poisoning or necrotizing vasculitis.
- Findings suggestive of severe hypertension, atheroembolic disease, and endocarditis may be observed on careful examination of the eyes.



# Physical

- Cardiovascular system:
- The most important part of the physical examination is the assessment of cardiovascular and volume status.
- The physical examination must include pulse rate and blood pressure recordings measured in both the supine position and the standing position; close inspection of the jugular venous pulse; careful examination of the heart, lungs, skin turgor, and mucous membranes; and assessment for the presence of peripheral edema.
- In hospitalized patients, accurate daily records of fluid intake and urine output and daily measurements of patient weight are important.

# Physical

- Blood pressure recordings can be important diagnostic tools.
- Hypovolemia leads to hypotension; however, hypotension may not necessarily indicate hypovolemia.
- Severe congestive cardiac failure (CHF) may also cause hypotension. Although patients with CHF may have low blood pressure, volume expansion is present and effective renal perfusion is poor, which can result in AKI.
- Severe hypertension with renal failure suggests renovascular disease, glomerulonephritis, vasculitis, or atheroembolic disease.

# Physical

- Abdomen:
- Abdominal examination findings can be useful to help detect obstruction at the bladder outlet as the cause of renal failure, which may be due to cancer or an enlarged prostate.
- The presence of tense ascites can indicate elevated intra-abdominal pressure that can retard renal venous return and result in AKI.
- The presence of an epigastric bruit suggests renal vascular hypertension, which may predispose to AKI.

Several laboratory tests are useful for assessing the etiology of AKI, and the findings can aid in proper management. These tests include complete blood cell (CBC) count, serum biochemistry, urine analysis with microscopy, and urine electrolytes.

- **Blood urea nitrogen (BUN) and serum creatinine:**
  - Although increased levels of BUN and creatinine are the hallmarks of renal failure, the rate of rise is dependent on the degree of renal insult as well as protein intake with respect to BUN.
  - The ratio of BUN to creatinine is an important finding, because the ratio can exceed 20:1 in conditions in which enhanced reabsorption of urea is favored (eg, in volume contraction); this suggests prerenal AKI.
  - BUN may be elevated in patients with GI or mucosal bleeding, steroid treatment, or protein loading.
  - Assuming no renal function, the rise in BUN over 24 hours can be roughly predicted using the following formula: 24-hour protein intake in milligrams X 0.16 divided by total body water in mg/dL added to the BUN value.

- Assuming no renal function, the rise in creatinine can be predicted using the following formulas:
  - For males: weight in kilograms X  $[28 - 0.2(\text{age})]$  divided by total body water in mg/dL added to the creatinine value
  - For females: weight in kilograms X  $[23.8 - 0.17(\text{age})]$  divided by total body water added to the creatinine value
- As a general rule, if serum creatinine increases to more than 1.5 mg/dL/d, rhabdomyolysis must be ruled out

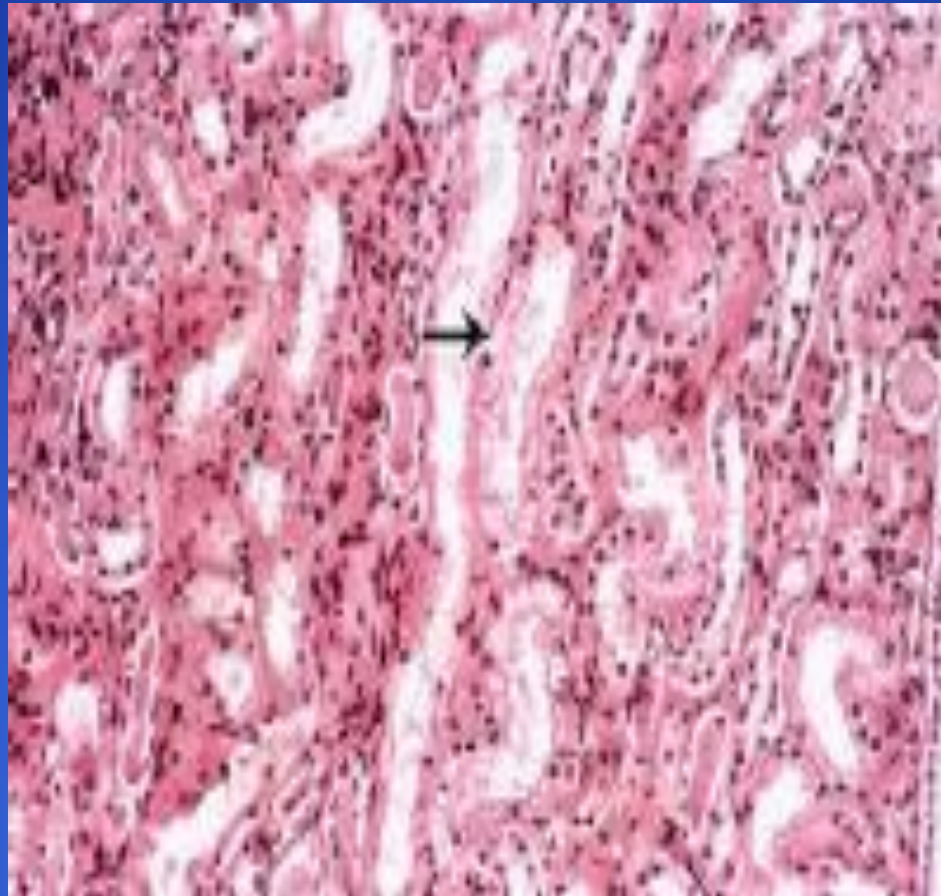
# CBC count, peripheral smear, and serology:

- The peripheral smear may show schistocytes in conditions such as HUS or TTP.
- A finding of increased rouleaux formation suggests multiple myeloma, and the workup should be directed toward immunoelectrophoresis of serum and urine.
- The presence of myoglobin or free hemoglobin, increased serum uric acid level, and other related findings may help further define the etiology of AKI.
- Serologic tests for antinuclear antibody (ANA), ANCA, anti-GBM antibody, hepatitis, and antistreptolysin (ASO) and complement levels may help include and exclude glomerular disease. Although serologic tests can be informative, the costs can be prohibitive if these tests are not ordered judiciously.

# Urinalysis:

- Findings of granular, muddy-brown casts are suggestive of tubular necrosis, as shown below. The presence of tubular cells or tubular cell casts also supports the diagnosis of ATN. Often, oxalate crystals are observed in cases of ATN.

Sloughing of cells, which is responsible for the formation of granular casts, is a feature of acute tubular necrosis.





- Reddish brown or cola-colored urine suggests the presence of myoglobin or hemoglobin, especially in the setting of a positive dipstick for heme and no RBCs on the microscopic examination.
- The dipstick assay may reveal significant proteinuria as a result of tubular injury.
- The presence of RBCs in the urine is always pathologic. Eumorphic RBCs suggest bleeding along the collecting system. Dysmorphic RBCs or RBC casts indicate glomerular inflammation, suggesting glomerulonephritis is present.
- The presence of WBCs or WBC casts suggests pyelonephritis or acute interstitial nephritis. The presence of urine eosinophils is helpful in establishing a diagnosis but is not necessary for allergic interstitial nephritis to be present.
- The presence of eosinophils, as visualized with Wright stain or Hansel stain, suggests interstitial nephritis but can also be seen in urinary tract infections, glomerulonephritis, and atheroembolic disease.
- The presence of uric acid crystals may represent ATN associated with uric acid nephropathy.
- Calcium oxalate crystals are usually present in cases of ethylene glycol poisoning.

# Urine electrolyte findings also can serve as valuable indicators of functioning renal tubules

## Urine electrolytes

- The fractional excretion of sodium (FENa) is the commonly used indicator. However, the interpretation of results from patients in nonoliguric states, those with glomerulonephritis, and those receiving or ingesting diuretics can lead to an erroneous diagnosis. FENa can be a valuable test for helping to detect extreme renal avidity for sodium in conditions such as hepatorenal syndrome. The formula for calculating the FENa is as follows:
  - $FENa = (UNa/PNa) / (UCr/PCr) \times 100$
  - Calculating the FENa is useful in AKI only in the presence of oliguria.
  - In patients with prerenal azotemia, the FENa is usually less than 1%. In ATN, the FENa is greater than 1%. Exceptions to this rule are ATN caused by radiocontrast nephropathy, severe burns, acute glomerulonephritis, and rhabdomyolysis.
  - In the presence of liver disease, FENa can be less than 1% in the presence of ATN. On the other hand, because administration of diuretics may cause the FENa to be greater than 1%, these findings cannot be used as the sole indicators in AKI.
  - In patients who are receiving diuretics, a fractional excretion of urea (FEUrea) can be obtained, since urea transport is not affected by diuretics. The formula for calculating the FEUrea is as follows:  $FEUrea = (Uurea/Purea) / (UCr/PCr) \times 100$
  - FEUrea of less than 35% is suggestive of a prerenal state.

- Bladder pressure: Intra-abdominal pressure of  $< 10$  mm Hg is considered normal and suggests abdominal compartment syndrome is not the cause of AKI. Patients with an intra-abdominal pressure below 15-25 mm Hg are at risk for abdominal compartment syndrome, and those with bladder pressures above 25 mm Hg should be suspected of having AKI as a result of abdominal compartment syndrome.

- Emerging biomarkers: A number of biomarkers are being investigated to risk stratify and predict AKI in those at risk for the disease. The reason for this is because creatinine is a late marker for renal dysfunction and, once elevated, reflects a severe reduction in GFR. The most promising biomarker to date is urinary neutrophil gelatinase-associated lipocalin (NGAL), which has been shown to predict AKI in children undergoing cardiopulmonary bypass surgery.

# Ultrasonography:

- Renal ultrasonography is useful for evaluating existing renal disease and obstruction of the urinary collecting system. The degree of hydronephrosis does not necessarily correlate with the degree of obstruction. Mild hydronephrosis may be observed with complete obstruction if found early.
- Obtaining images of the kidneys can be technically difficult in patients who are obese or in those with abdominal distension due to ascites, gas, or retroperitoneal fluid collection.
- Ultrasonographic scans or other imaging studies showing small kidneys suggest chronic renal failure.

# Doppler ultrasonography:

- Doppler scans are useful for detecting the presence and nature of renal blood flow.
- Because renal blood flow is reduced in prerenal or intrarenal AKI, test findings are of little use in the diagnosis of AKI.
- Doppler scans can be quite useful in the diagnosis of thromboembolic or renovascular disease.
- Increased resistive indices can be observed in patients with hepatorenal syndrome.

# Nuclear scans:

- Radionuclide imaging with technetium-99m-mercaptoacetyltriglycine ( $^{99m}\text{Tc-MAG}_3$ ),  $^{99m}\text{Tc}$ -diethylenetriamine pentaacetic acid ( $^{99m}\text{Tc-DTPA}$ ), or iodine-131 ( $^{131}\text{I}$ )-hippurate can be used to assess renal blood flow and tubular functions.
- Because of a marked delay in tubular excretion of radionuclide in prerenal disease and intrarenal disease, the value of these scans is limited.

- Aortorenal angiography can be helpful in establishing the diagnosis of renal vascular diseases, including renal artery stenosis, renal atheroembolic disease, atherosclerosis with aortorenal occlusion, and in certain cases of necrotizing vasculitis (eg, polyarteritis nodosa).



# Procedures

- Procedures
- Renal biopsy:
- A renal biopsy can be useful in establishing the diagnosis of intrarenal causes of AKI and can be justified if it will change management (eg, initiation of immunosuppressive medications). A renal biopsy may also be indicated when renal function does not return for a prolonged period and a prognosis is required to develop long-term management.
- In as many as 40% of cases, renal biopsy results reveal an unexpected diagnosis.
- Acute cellular or humoral rejection in a transplanted kidney can be definitively diagnosed only by performing a renal biopsy.

# Chronic kidney disease (CKD)

# Background

- Chronic kidney disease (CKD) is a worldwide public health problem and is now recognized as a common condition that is associated with an increased risk of cardiovascular disease and chronic renal failure (CRF).

- The Kidney Disease Outcomes Quality Initiative (K/DOQI) of the National Kidney Foundation (NKF) defines chronic kidney disease as either kidney damage or a decreased kidney glomerular filtration rate (GFR) of less than 60 mL/min/1.73 m<sup>2</sup> for 3 or more months.

- Whatever the underlying etiology, the destruction of renal mass with irreversible sclerosis and loss of nephrons leads to a progressive decline in GFR. The different stages of chronic kidney disease form a continuum in time; prior to February 2002, no uniform classification of the stages of chronic kidney disease existed. At that time, K/DOQI published a classification of the stages of chronic kidney disease, as follows:

- Stage 1: Kidney damage with normal or increased GFR ( $>90$  mL/min/1.73 m<sup>2</sup>)
- Stage 2: Mild reduction in GFR (60-89 mL/min/1.73 m<sup>2</sup>)
- Stage 3: Moderate reduction in GFR (30-59 mL/min/1.73 m<sup>2</sup>)
- Stage 4: Severe reduction in GFR (15-29 mL/min/1.73 m<sup>2</sup>)
- Stage 5: Kidney failure (GFR  $< 15$  mL/min/1.73 m<sup>2</sup> or dialysis)

- In stage 1 and stage 2 chronic kidney disease, GFR alone does not clinch the diagnosis. Other markers of kidney damage, including abnormalities in the composition of blood or urine or abnormalities in imaging tests, should also be present in establishing a diagnosis of stage 1 and stage 2 chronic kidney disease.

- Approximately 1 million nephrons are present in each kidney, each contributing to the total GFR.
- Regardless of the etiology of renal injury, with progressive destruction of nephrons, the kidney has an innate ability to maintain GFR by hyperfiltration and compensatory hypertrophy of the remaining healthy nephrons. This nephron adaptability allows for continued normal clearance of plasma solutes so that substances such as urea and creatinine start to show significant increases in plasma levels only after total GFR has decreased to 50%, when the renal reserve has been exhausted. The plasma creatinine value will approximately double with a 50% reduction in GFR. A rise in plasma creatinine from a baseline value of 0.6 mg/dL to 1.2 mg/dL in a patient, although still within the reference range, actually represents a loss of 50% of functioning nephron mass.
- The residual nephron hyperfiltration and hypertrophy, although beneficial for the reasons noted, has been hypothesized to represent a major cause of progressive renal dysfunction. This is believed to occur because of increased glomerular capillary pressure, which damages the capillaries and leads initially to focal and segmental glomerulosclerosis and eventually to global glomerulosclerosis. This hypothesis has been based on studies of five-sixths nephrectomized rats, which develop lesions that are identical to those observed in humans with chronic kidney disease.



Factors other than the underlying disease process and glomerular hypertension that may cause progressive renal injury include the following:

- Systemic hypertension
- Acute insults from nephrotoxins or decreased perfusion
- Proteinuria
- Increased renal ammoniogenesis with interstitial injury
- Hyperlipidemia
- Hyperphosphatemia with calcium phosphate deposition
- Decreased levels of nitrous oxide
- Smoking

# Causes

- Causes include the following:
- Vascular disease - Renal artery stenosis, cytoplasmic pattern antineutrophil cytoplasmic antibody (C-ANCA)-positive and perinuclear pattern antineutrophil cytoplasmic antibody (P-ANCA)-positive vasculitides, antineutrophil cytoplasmic antibody (ANCA)-negative vasculitides, atheroemboli, hypertensive nephrosclerosis, renal vein thrombosis
- Primary glomerular disease - Membranous nephropathy, immunoglobulin A (IgA) nephropathy, focal and segmental glomerulosclerosis (FSGS), minimal change disease, membranoproliferative glomerulonephritis, rapidly progressive (crescentic) glomerulonephritis

# Causes

- Secondary glomerular disease - Diabetes mellitus, systemic lupus erythematosus, rheumatoid arthritis, mixed connective tissue disease, scleroderma, Goodpasture syndrome, Wegener granulomatosis, mixed cryoglobulinemia, postinfectious glomerulonephritis, endocarditis, hepatitis B and C, syphilis, human immunodeficiency virus (HIV), parasitic infection, heroin use, gold, penicillamine, amyloidosis, light chain deposition disease, neoplasia, thrombotic thrombocytopenic purpura (TTP), hemolytic-uremic syndrome (HUS), Henoch-Schönlein purpura, Alport syndrome, reflux nephropathy
- Tubulointerstitial disease - Drugs (eg, sulfa, allopurinol), infection (viral, bacterial, parasitic), Sjögren syndrome, chronic hypokalemia, chronic hypercalcemia, sarcoidosis, multiple myeloma cast nephropathy, heavy metals, radiation nephritis, polycystic kidneys, cystinosis
- Urinary tract obstruction - Urolithiasis, benign prostatic hypertrophy, tumors, retroperitoneal fibrosis, urethral stricture, neurogenic bladder

# History

- Patients with chronic kidney disease stages 1-3 (GFR  $>30$  mL/min) are generally asymptomatic and do not experience clinically evident disturbances in water or electrolyte balance or endocrine/metabolic derangements. Generally, these disturbances clinically manifest with chronic kidney disease stages 4-5 (GFR  $< 30$  mL/min). Uremic manifestations in patients with chronic kidney disease stage 5 are believed to be primarily secondary to an accumulation of toxins, the identity of which is generally not known.

- The ability to maintain potassium (K) excretion at near normal levels is generally maintained in chronic kidney disease patients as long as both aldosterone secretion and distal flow are maintained. Another defense against potassium retention in patients with chronic kidney disease is increased potassium excretion in the GI tract, which also is under control of aldosterone.

- Therefore, hyperkalemia usually develops when the GFR falls to less than 20-25 mL/min because of the decreased ability of the kidneys to excrete potassium. It can be observed sooner in patients who ingest a potassium-rich diet or if serum aldosterone levels are low, such as in type IV renal tubular acidosis commonly observed in people with diabetes or with use of angiotensin-converting enzyme (ACE) inhibitors or nonsteroidal anti-inflammatory drugs (NSAIDs).
- Hyperkalemia in chronic kidney disease can be aggravated by an extracellular shift of potassium, such as that occurs in the setting of acidemia or from lack of insulin. Hypokalemia is uncommon but can develop among patients with very poor intake of potassium, gastrointestinal or urinary loss of potassium, diarrhea, or diuretic use.

- Metabolic acidosis often is mixed, normal anion gap and increased anion gap, the latter observed generally with chronic kidney disease stage 5 but with the anion gap generally not higher than 20 mEq/L. In chronic kidney disease, the kidneys are unable to produce enough ammonia in the proximal tubules to excrete the endogenous acid into the urine in the form of ammonium.
- In chronic kidney disease stage 5, accumulation of phosphates, sulphates, and other organic anions are the cause of the increase in anion gap. Metabolic acidosis has been shown to have deleterious effects on protein balance, leading to a negative nitrogen balance, increased protein degradation, increased essential amino acid oxidation, reduced albumin synthesis, and a lack of adaptation to a low protein diet. Hence, this is associated with protein-energy malnutrition, loss of lean body mass, and muscle weakness. The mechanism for reducing protein may include effects on ATP-dependent ubiquitin proteasomes and increased activity of branched chain keto acid dehydrogenases.

- The evidence for the benefits and risks of correcting metabolic acidosis is very limited, with no randomized controlled trials in pre-ESRD patients, none in children, and only 3 small trials in dialysis patients. These trials suggest that there may be some beneficial effects on both protein metabolism and bone metabolism, but the trials were underpowered to provide robust evidence. Experts recommend alkali therapy to maintain the serum bicarbonate concentration above 22 mEq/L.
- Inflammation and hemostasis may increase the risk of kidney function decline, but prospective studies are lacking. The Atherosclerosis Risk in Communities (ARIC) Study, a prospective observational cohort, observed markers of inflammation and hemostasis in 14,854 middle-aged adults.[2] The risk for decreased kidney function associated with the inflammatory and hemostasis markers was examined, using data from 1787 cases of chronic kidney disease (CKD) that developed between 1987 and 2004.



- After adjustments for various factors, such as demographics smoking, blood pressure, diabetes, lipid levels, prior myocardial infarction (MI), antihypertensive use, and alcohol use, the above study revealed that the risk for chronic kidney disease rose with increasing quartiles of white blood cell (WBC) count, fibrinogen, von Willebrand factor, and factor VIIIc. The investigators found a strong inverse association between serum albumin level and chronic kidney disease risk. The study's findings suggested that inflammation and hemostasis are antecedent pathways for chronic kidney disease.
- Salt and water handling by the kidney is altered in patients with chronic kidney disease. Extracellular volume expansion and total-body volume overload results from failure of sodium and free water excretion. This generally becomes clinically manifested when the GFR falls to less than 10-15 mL/min, when compensatory mechanisms have become exhausted. As kidney function declines further, sodium retention and extracellular volume expansion lead to peripheral and, not uncommonly, pulmonary edema and hypertension. At a higher GFR, excess sodium and water intake could result in a similar picture if the ingested amounts of sodium and water exceed the available potential for compensatory excretion.

- Normochromic normocytic anemia principally develops from decreased renal synthesis of erythropoietin, the hormone responsible for bone marrow stimulation for red blood cell (RBC) production. It starts early in the course of disease and becomes more severe as the GFR progressively decreases with the availability of less viable renal mass. No reticulocyte response occurs. RBC survival is decreased, and tendency of bleeding is increased from the uremia-induced platelet dysfunction. Other causes of anemia in chronic kidney disease patients include chronic blood loss, secondary hyperparathyroidism, inflammation, nutritional deficiency, and accumulation of inhibitors of erythropoiesis.
- Anemia is associated with fatigue, reduced exercise capacity, impaired cognitive and immune function, and reduced quality of life. Anemia is also associated with the development of cardiovascular disease, the new onset of heart failure, or the development of more severe heart failure. Anemia is associated with increased cardiovascular mortality.

- Renal bone disease is a common complication of chronic kidney disease and results in both skeletal complications (eg, abnormality of bone turnover, mineralization, linear growth) and extraskeletal complications (eg, vascular or soft tissue calcification). Different types of bone disease occur with chronic kidney disease, as follows: (1) high turnover bone disease due to high parathyroid hormone (PTH) levels; (2a) low turnover bone disease (adynamic bone disease); (2b) defective mineralization (osteomalacia); (3) mixed disease; and (4) beta-2-microglobulin associated bone disease.
- Secondary hyperparathyroidism develops because of hyperphosphatemia, hypocalcemia, decreased renal synthesis of 1,25-dihydroxycholecalciferol (1,25-dihydroxyvitamin D, or calcitriol), intrinsic alteration in the parathyroid gland that give rises to increased PTH secretion as well as increased parathyroid growth, and skeletal resistance to PTH.
- Calcium and calcitriol are primary feedback inhibitors; hyperphosphatemia is a stimulus to PTH synthesis and secretion.

- Phosphate retention begins in early chronic kidney disease; when the GFR falls, less phosphate is filtered and excreted, but serum levels do not rise initially because of increased PTH secretion, which increases renal excretion. As the GFR falls toward chronic kidney disease stages 4-5, hyperphosphatemia develops from the inability of the kidneys to excrete the excess dietary intake. Hyperphosphatemia suppresses the renal hydroxylation of inactive 25-hydroxyvitamin D to calcitriol, so serum calcitriol levels are low when the GFR is less than 30 mL/min. Increased phosphate concentration also effects PTH concentration by its direct effect on parathyroid gland (posttranscriptional effect).
- Hypocalcemia develops primarily from decreased intestinal calcium absorption because of low plasma calcitriol levels and possibly from calcium binding to elevated serum levels of phosphate.

- Low serum calcitriol levels, hypocalcemia, and hyperphosphatemia have all been demonstrated to independently trigger PTH synthesis and secretion. As these stimuli persist in chronic kidney disease, particularly in the more advanced stages, PTH secretion becomes maladaptive and the parathyroid glands, which initially hypertrophy, become hyperplastic. The persistently elevated PTH levels exacerbate hyperphosphatemia from bone resorption of phosphate.
- If serum levels of PTH remain elevated, a high bone turnover lesion, known as osteitis fibrosa, develops. This is one of several bone lesions, which as a group are commonly known as renal osteodystrophy. These lesions develop in patients with severe chronic kidney disease and are common in those with ESRD.
- The prevalence of adynamic bone disease in the United States has increased, and it has been described before the initiation of dialysis in some cases. The pathogenesis of adynamic bone disease is not well defined, but several factors may contribute, including high calcium load, use of vitamin D sterols, increasing age, previous corticosteroid therapy, peritoneal dialysis, and increased level of N-terminally truncated PTH fragments. Low turnover osteomalacia in the setting of chronic kidney disease is associated with aluminum accumulation and is markedly less common. Dialysis-related amyloidosis from beta-2-microglobulin accumulation in patients who have required chronic dialysis for at least 8-10 years is another form of bone disease that manifests with cysts at the ends of long bones.

- Other manifestations of uremia in ESRD, many of which are more likely in patients who are inadequately dialyzed, include the following:
- Pericarditis - Can be complicated by cardiac tamponade, possibly resulting in death.
- Encephalopathy - Can progress to coma and death
- Peripheral neuropathy
- Restless leg syndrome
- GI symptoms - Anorexia, nausea, vomiting, diarrhea
- Skin manifestations - Dry skin, pruritus, ecchymosis
- Fatigue, increased somnolence, failure to thrive
- Malnutrition
- Erectile dysfunction, decreased libido, amenorrhea
- Platelet dysfunction with tendency to bleeding

# Physical

- The physical examination often is not very helpful but may reveal findings characteristic of the condition underlying chronic kidney disease (eg, lupus, severe arteriosclerosis, hypertension) or complications of chronic kidney disease (eg, anemia, bleeding diathesis, pericarditis).

# Laboratory Studies



# The following tests may be indicated:

- Serum electrolytes, BUN, and creatinine - The BUN and creatinine levels will be elevated in patients with chronic kidney disease. Hyperkalemia or low bicarbonate levels may be present in patients with chronic kidney disease.
- Serum calcium, phosphate, vitamin D, and intact parathyroid hormone (PTH) levels are obtained to look for evidence of renal bone disease.
- CBC count - Normochromic normocytic anemia is commonly seen in chronic kidney disease. Other underlying causes of anemia should be ruled out.
- Serum albumin - Patients may have hypoalbuminemia due to urinary protein loss or malnutrition.
- Lipid profile - A lipid profile should be performed in all patients with chronic kidney disease because of their increased risk of cardiovascular disease.

# The following tests may be indicated:

- Urinalysis - Dipstick proteinuria may suggest a glomerular or tubulointerstitial problem. The urine sediment finding of RBCs, RBC casts, suggests proliferative glomerulonephritis. Pyuria and/or WBC casts are suggestive of interstitial nephritis (particularly if eosinophiluria is present) or urinary tract infection.
- Spot urine collection for total protein-to-creatinine ratio allows reliable approximation (extrapolation) of total 24-hour urinary protein excretion. A value of greater than 2 g is considered to be within the glomerular range, and a value of greater than 3-3.5 g is within the nephrotic range; less than 2 is characteristic of tubulointerstitial problems.
- Twenty-four-hour urine collection for total protein and CrCl

## **In certain cases, the following tests may be ordered as part of the evaluation of patients with chronic kidney disease:**

- Serum and urine protein electrophoresis to screen for a monoclonal protein possibly representing multiple myeloma
- Antinuclear antibodies (ANA), double-stranded DNA antibody levels to screen for systemic lupus erythematosus
- Serum complement levels - May be depressed with some glomerulonephritides
- C-ANCA and P-ANCA levels - Helpful if positive in diagnosis of Wegener granulomatosis and polyarteritis nodosa or microscopic polyangiitis, respectively
- Anti-glomerular basement membrane (anti-GBM) antibodies - Highly suggestive of underlying Goodpasture syndrome
- Hepatitis B and C, HIV, Venereal Disease Research Laboratory (VDRL) serology - Conditions associated with some glomerulonephritides

# The following imaging studies may be indicated:

- Plain abdominal x-ray - Particularly useful to look for radio-opaque stones or nephrocalcinosis
- Intravenous pyelogram - Not commonly used because of potential for intravenous contrast renal toxicity; often used to diagnose renal stones

# The following imaging studies may be indicated:

- Renal ultrasound - Small echogenic kidneys are observed in advanced renal failure. Kidneys usually are normal in size in advanced diabetic nephropathy, where affected kidneys initially are enlarged from hyperfiltration. Structural abnormalities, such as polycystic kidneys, also may be observed. This is a useful test to screen for hydronephrosis, which may not be observed in early obstruction, or involvement of the retroperitoneum with fibrosis, tumor, or diffuse adenopathy. Retrograde pyelogram may be indicated if a high index of clinical suspicion for obstruction exists despite a negative study finding.
- Renal radionuclide scan - Useful to screen for renal artery stenosis when performed with captopril administration but is unreliable for GFR of less than 30 cc/min; also quantitates differential renal contribution to total GFR

# The following imaging studies may be indicated:

- CT scan - CT scan is useful to better define renal masses and cysts usually noted on ultrasound. Also, it is the most sensitive test for identifying renal stones. IV contrast-enhanced CT scans should be avoided in patients with renal impairment to avoid acute renal failure; this risk significantly increases in patients with moderate-to-severe chronic kidney disease. Dehydration also markedly increases this risk.
- MRI is very useful in patients who require a CT scan but who cannot receive intravenous contrast. It is reliable in the diagnosis of renal vein thrombosis, as are CT scan and renal venography. Magnetic resonance angiography also is becoming more useful for diagnosis of renal artery stenosis, although renal arteriography remains the criterion standard.
- Voiding cystourethrogram (VCUG) - Criterion standard for diagnosis of vesicoureteral reflux

- The Cockcroft-Gault formula for estimating CrCl should be used routinely as a simple means to provide a reliable approximation of residual renal function in all patients with chronic kidney disease. The formulas are as follows:
- $\text{CrCl (male)} = ([140 - \text{age}] \times \text{weight in kg}) / (\text{serum creatinine} \times 72)$
- $\text{CrCl (female)} = \text{CrCl (male)} \times 0.85$

# Procedures

- Percutaneous renal biopsy is performed most often with ultrasound guidance and the use of a mechanical gun. It generally is indicated when renal impairment and/or proteinuria approaching the nephrotic range are present and the diagnosis is unclear after appropriate other workup. It is not indicated in the setting of small echogenic kidneys on ultrasound because these are severely scarred and represent chronic irreversible injury. The most common complication of this procedure is bleeding, which can be life threatening in a minority of occurrences.
- Surgical open renal biopsy can be considered when the risk of renal bleeding is felt to be great, occasionally with solitary kidneys, or when percutaneous biopsy is technically difficult to perform.



# Histologic Findings

- Renal histology in chronic kidney disease reveals findings compatible with the underlying primary renal diagnosis and, generally, findings of segmental and globally sclerosed glomeruli and tubulointerstitial atrophy, often with tubulointerstitial mononuclear infiltrates.