ACUTE RENAL FAILURE

- ✓ Acute renal failure (ARF) is a syndrome characterized by rapid decline in glomerular filtration rate (hours to days), retention of nitrogenous waste products, and perturbation of extracellular fluid volume and electrolyte and acid-base homeostasis.
- ✓ ARF complicates approximately 5% of hospital admissions and up to 30% of admissions to intensive care units.
- ✓ **Oliguria** (urine output < 400 mL/d) is a frequent but not invariable clinical feature (~50%).
- ✓ ARF is usually asymptomatic and diagnosed when biochemical monitoring of hospitalized patients reveals a recent increase in blood urea and creatinine concentrations.
- ✓ It may complicate a wide range of diseases, which for purposes of diagnosis and management are conveniently divided into three categories:
    - Diseases that cause renal hypoperfusion without compromising the integrity of renal parenchyma (**Prerenal ARF**, prerenal azotemia) (~55%);
    - Diseases that directly involve renal parenchyma (**Intrinsic renal ARF**, renal azotemia) (~40%); and
    - Diseases associated with urinary tract obstruction (**Postrenal ARF**, postrenal azotemia) (~5%).
- ✓ Most ARF is reversible, the kidney being relatively unique among major organs in its ability to recover from almost complete loss of function.
- ✓ Nevertheless, ARF is associated with major in-hospital morbidity and mortality, in large part due to the serious nature of the illnesses that precipitate the ARF.
- ✓ **Anuria** is defined as a urine output of <50 mL/d, **oliguria** is when the daily urine output is 50 to 450 mL/d, and **nonoliguria** occurs when the patient can make >450 mL of urine per day.

EPIDEMIOLOGY

- ✓ Acute renal failure occurs almost exclusively in hospitalized patients; hallmark studies conducted in the United States and abroad indicate the incidence of community-acquired ARF (development of ARF before hospitalization) is just 1%; approximately 75% of these admissions result from decreased kidney blood flow, termed prerenal azotemia.
- ✓ Other less-common causes include obstructive uropathy (17%) and intrinsic renal disease (11%).
- ✓ Community-acquired ARF can usually be reversed by correcting the underlying problems of volume status or obstruction.
- ✓ Hospital-acquired ARF is much more common, and the incidence and severity vary based on intensive care unit (ICU) or non-ICU setting.
- ✓ The incidence of ARF in general medicine patients is approximately 2% to 5%, with the most common causes being prerenal azotemia, postoperative complications, or nephrotoxin exposure.
- ✓ These patients can experience one or more of these renal insults throughout their hospitalization.
- ✓ Conversely, ICU-acquired ARF is more prevalent and severe.
- ✓ Data suggest the incidence of ARF in patients in the ICU approaches 25%, stemming from multiple risk factors, including older age, infection, nephrotoxin exposure, male gender, multiorgan dysfunction, and the need for mechanical ventilation.

- ✓ Although many patients with ARF will initially require dialysis, a small percentage wills devlop end-stage renal disease requiring long-term dialysis.

CLASSIFICATION

- ✓ ARF is classified into **Three** categories based on precipitating and etiologic factors: **Prerenal** or hypoperfusion states, **Intrarenal** or intrinsic renal parenchymal injury, and **Postrenal ARF** or urinary obstructive disorders.
- ✓ These standard classifications facilitate diagnosis and disease management.
- ✓ ARF can be further described according to the **amount of urine** produced per day as **Anuric ARF** (<50 mL/day), **Oliguric ARF** (50 to 400 mL/day), and **Nonoliguric** (>400 mL/day).
- ✓ Although ARF is often thought of as a decrease in urine output, nonoliguric ARF accounts for up to 60% of cases of ARF.
- ✓ Patients with nonoliguric ARF do not concentrate the urine that is produced and continue to retain urea, creatinine, and other waste products of metabolism.

ETIOLOGY

- ➢ **PRERENAL AZOTEMIA**
  - ✓ Renal blood flow (RBF) is maintained at about 20% of cardiac output based on glomerular filtration needs.
  - ✓ Prerenal azotemia occurs when RBF decreases to a level adequate to sustain cells but inadequate to maintain normal GFR.
  - ✓ Therefore, cellular injury does not occur and the GFR can be normalized rapidly once the pathologic state is corrected.
  - ✓ Reduced RBF may be secondary to any event that results in decreased renal perfusion or intense compensatory afferent arteriolar vasoconstriction.
  - ✓ **Common causes** of prerenal azotemia in the outpatient setting include conditions that result in a decline in effective blood volume, such as congestive heart failure, or a decline in intravascular volume, such as vomiting, diarrhea, poor fluid intake, fever, or the use of diuretics.
  - ✓ Use of drugs that induce renal vasoconstriction, such as cyclosporine or tacrolimus, can also lead to prerenal azotemia.
  - ✓ Elderly patients are susceptible to the development of prerenal azotemia because of decreased cardiac output due to myocardial dysfunction or pericardial disease, dehydration with insufficient fluid intake, and chronic use of drugs that alter intrarenal hemodynamics, such as nonsteroidal anti-inflammatory drugs (NSAIDs) and angiotensin-converting enzyme (ACE) inhibitors.
  - ✓ Heart failure, liver dysfunction, and sepsis are common causes of prerenal azotemia in hospitalized patients.
  - ✓ Anesthesia decreases effective blood volume, and when accompanied by a reduction in mean arterial pressure, can lead to a decrease in RBF, leading to prerenal azotemia in surgical patients.
  - ✓ Vascular diseases (e.g., renal artery emboli, atheroembolic renal disease) may reduce RBF and cause prerenal ARF.
  - ✓ Thrombocytopenic purpura and hemolytic uremic syndrome may also lead to prerenal ARF, but more commonly they also cause significant glomerular injury.
  - ✓ **Mild hypoperfusion**, caused by volume depletion, leads to prerenal azotemia with a mild decrease in GFR.

- ✓ The kidneys attempt to increase intravascular volume by conserving salt and water through increased proximal and distal reabsorption as well as increased antidiuretic hormone (ADH) release.
- ✓ GFR is maintained initially, but only small amounts of concentrated urine are produced.
- ✓ Due to avid sodium reabsorption, urine sodium and the fractional excretion of sodium (FE_{Na}) are low (<1Φpc).
- ✓ Urine is concentrated due to water conservation; thus, urine osmolality and the urine creatinine:plasma creatinine ratio are high.
- ✓ Because urea reabsorption is also increased, a disproportionate increase in blood urea nitrogen (BUN) relative to SCr occurs; therefore, the BUN:SCr ratio often is greater than 20:1.
- ✓ Prerenal azotemia is rapidly reversible if the underlying cause is corrected.
- ✓ Restoration of renal perfusion should reverse prerenal azotemia, but in some cases, prerenal ARF can lead to intrarenal, ischemic ATN.
- ✓ About 20% of cardiac output perfuses the kidneys, resulting in high oxygen delivery compared with total renal oxygen consumption.
- ✓ A high oxygen supply is required to support active ion and solute transport.
- ✓ The outer medulla of the kidney is the site of the lowest partial pressure of intrarenal oxygen (pO_2), existing on the brink of hypoxia.
- ✓ It is also the location of very active tubular segments, such as the thick ascending limb of the loop of Henle and the pars recta of the proximal tubule.
- ✓ The outer medulla is at great risk for ischemia because of its low pO_2 and high metabolic activity, even in the setting of normal RBF.
- ✓ The kidneys are vulnerable to changes in oxygen balance.
- ✓ A reduction in RBF, as in a prerenal state, compromises oxygen reserve and if prolonged can lead to the development of ischemic ATN.
- ✓ Clinically, this occurs when an insult such as hypotension and oliguria due to medications, sepsis, surgery, or bleeding occurs in the setting of a prerenal state.
- ✓ Rapid detection and correction of prerenal azotemia can prevent ischemic injury and the associated morbidity and mortality.

- **FUNCTIONAL ACUTE RENAL FAILURE**
  - ✓ Functional ARF refers to those entities that result in a decline in glomerular ultrafiltrate production secondary to a reduced glomerular hydrostatic pressure without damage to the kidney itself.
  - ✓ The decline in glomerular hydrostatic pressure is a direct consequence of changes in glomerular afferent (vasoconstriction) and efferent (vasodilation) arteriolar circumference.
  - ✓ These clinical conditions most commonly occur in individuals who have reduced effective blood volume (e.g., CHF, cirrhosis, severe pulmonary disease, or hypoalbuminemia) or renovascular disease (e.g., renal artery stenosis), and cannot compensate for changes in afferent or efferent arteriolar tone.
  - ✓ Examples of disorders that result in afferent arteriolar vasoconstriction (and an increase in afferent arteriolar resistance) include hypercalcemia and the administration of certain medications (e.g., Cyclosporine and NSAIDs).

- ✓ A decrease in efferent arteriolar resistance usually results from the administration of an angiotensin-converting enzyme inhibitor (ACEI) or angiotensin II receptor antagonist.
- ✓ With correction of the underlying pathologic process or discontinuation of the responsible medication, renal function rapidly returns to baseline.
- ✓ The hepatorenal syndrome is included in this classification scheme since the kidney itself is not damaged and there is intense afferent arteriolar vasoconstriction leading to a decline in glomerular filtration.
- ✓ In all the above conditions, the urinalysis is no different from its baseline state and the urinary indices suggest prerenal azotemia.
- ✓ This syndrome of functional ARF is very common in individuals with CHF who receive an ACEI in an attempt to improve left ventricular function.
- ✓ The decline in efferent arteriolar resistance resulting from the inhibition of angiotensin II occurs rapidly.
- ✓ Therefore, if the dose of the ACEI is increased too rapidly, there will be a decline in glomerular ultrafiltrate production with a concomitant rise in the serum creatinine, leading to functional ARF.
- ✓ If the increase in the serum creatinine is not too severe (usually <1 mg/dL) the medication can be continued.
- ✓ Renal function should gradually improve as renal parenchymal perfusion pressure increases with improvement in left ventricular function.

➢ **INTRINSIC ACUTE RENAL FAILURE**

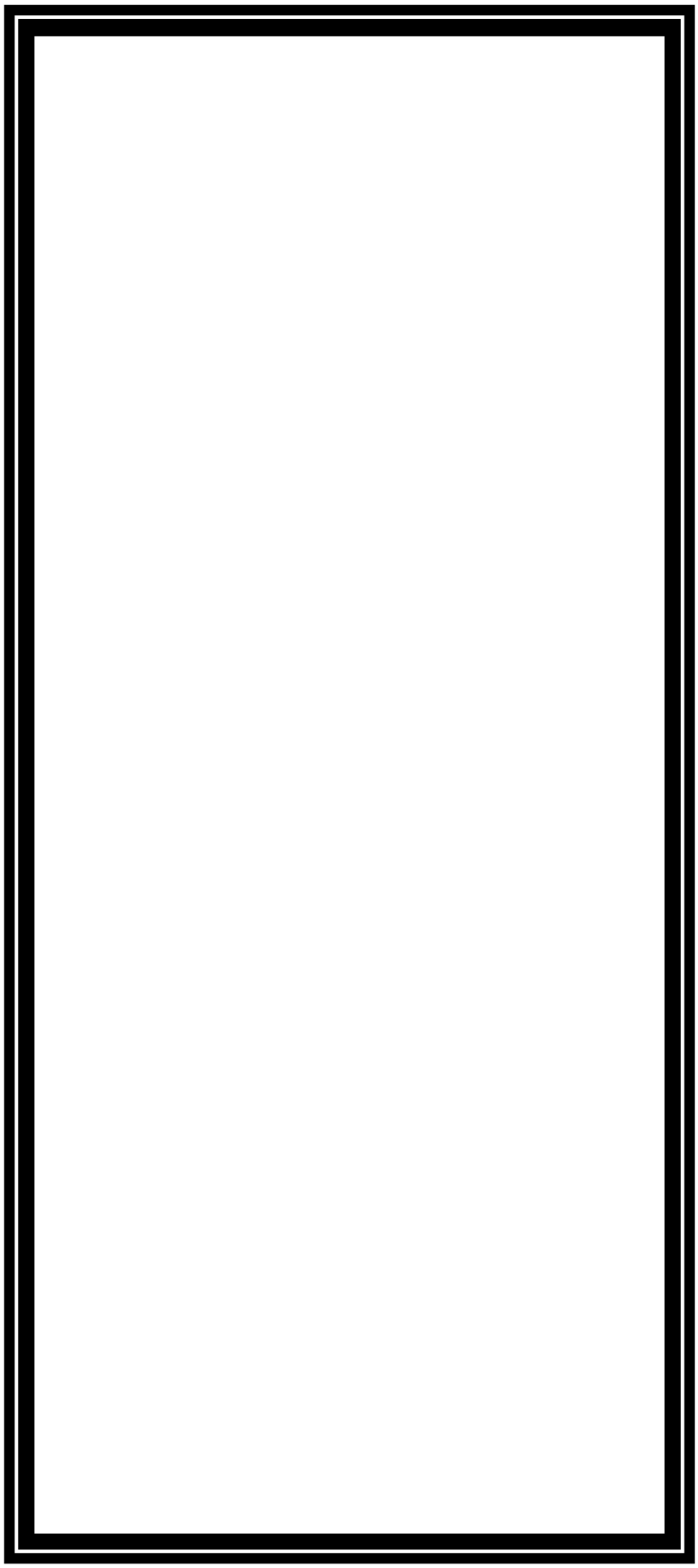
- ✓ Intrinsic ARF is a decrease in renal function resulting from more severe or prolonged ischemic, toxic, or immunologic mechanisms and is associated with structural damage to glomeruli, tubules, vascular supply, or interstitial tissue.
- ✓ Such damage to the renal parenchyma often follows prerenal or postrenal azotemia, and if the degree of insult or the duration of hypoperfusion or obstruction is sufficient, it is not immediately reversible.
- ✓ Tubular dysfunction leads to impaired reabsorption of solutes and water; thus, an increase in urinary sodium concentration and fractional excretion of sodium and a defect in urinary concentrating ability with a decrease in urine osmolality are observed.
- ✓ Recovery from intrarenal disease commonly takes 10 to 14 days, but it may take 6 weeks to more than a year.
- ✓ Ischemic or toxic ATN is a leading cause of ARF in hospitalized patients.
- ✓ ATN is a histologic finding signifying necrotic damage to the renal tubules.

➢ **POSTRENAL ACUTE RENAL FAILURE**

- ✓ Obstruction of the collecting system generally must involve both kidneys (and a solitary kidney) to cause significant renal failure.
- ✓ Obstruction of the urinary tract may result from bladder outlet obstruction caused by prostate enlargement, tumor, or urethral stricture; urethral obstruction from tumor, stone, or fibrosis; or even crystal (uric acid, calcium oxalate) deposition in the tubules.
- ✓ Several medications can lead to crystal-induced postrenal ARF, including acyclovir, sulfonamides, methotrexate, indinavir, and triamterene.

- ✓ Obstruction should be considered in patients with acute anuria, particularly in those with a recent history of alternating polyuria and oliguria.
- ✓ Postrenal azotemia is simply an accumulation of nitrogenous wastes secondary to obstruction of urine flow.
- ✓ This disorder accounts for approximately 15% of cases of ARF.

CAUSES OF ACUTE RENAL FAILURE	
CLASSIFICATION	**COMMON CLINICAL DEPLETION**
Prerenal Azotemia	**Intravascular Volume Depletion** ✓ Hemorrhage (surgery, trauma) ✓ Dehydration (gastrointestinal losses, aggressive diuretic administration) ✓ Severe burns ✓ Hypovolemic shock ✓ Sequestration (peritonitis, pancreatitis)
	Decreased Effective Circulating Volume ✓ Cirrhosis with ascites ✓ Congestive heart failure
	Hypotension, Shock Syndromes ✓ Antihypertensive vasodilating medications ✓ Septic shock ✓ Cardiomyopathy
	Increased Renal Vascular Occlusion or Constriction ✓ Bilateral renal artery stenosis ✓ Unilateral renal stenosis in solitary kidney ✓ Renal artery or vein thrombosis (embolism, atherosclerosis) ✓ Vasopressor medications (phenylephrine, norepinephrine)
Functional Acute Renal Failure	**Afferent Arteriole Vasoconstrictors** ✓ Cyclosporine ✓ Nonsteroidal anti-inflammatory drugs
	Efferent Arteriole Vasodilators ✓ Angiotensin-converting enzyme inhibitors ✓ Angiotensin II–receptor antagonists
Intrinsic Acute Renal Failure	Glomerular Disorders ✓ Glomerulonephritis ✓ Systemic lupus erythematosus ✓ Malignant hypertension ✓ Vasculitic disorders (Wegener's granulomatosis)
	Acute Tubular Necrosis ✓ Prolonged prerenal states ✓ Drug induced (contrast media, aminoglycosides, amphotericin B)
	Acute Interstitial Nephritis ✓ Drug induced (quinolones, penicillins, sulfa drugs)
Postrenal Acute Renal Failure	**Ureter Obstruction (Bilateral or Unilateral in Solitary Kidney)** ✓ Malignancy (prostate or cervical cancer) ✓ Prostate hypertrophy Anticholinergic drugs (affect bladder outlet muscles) ✓ Renal calculi



OTHER CAUSES

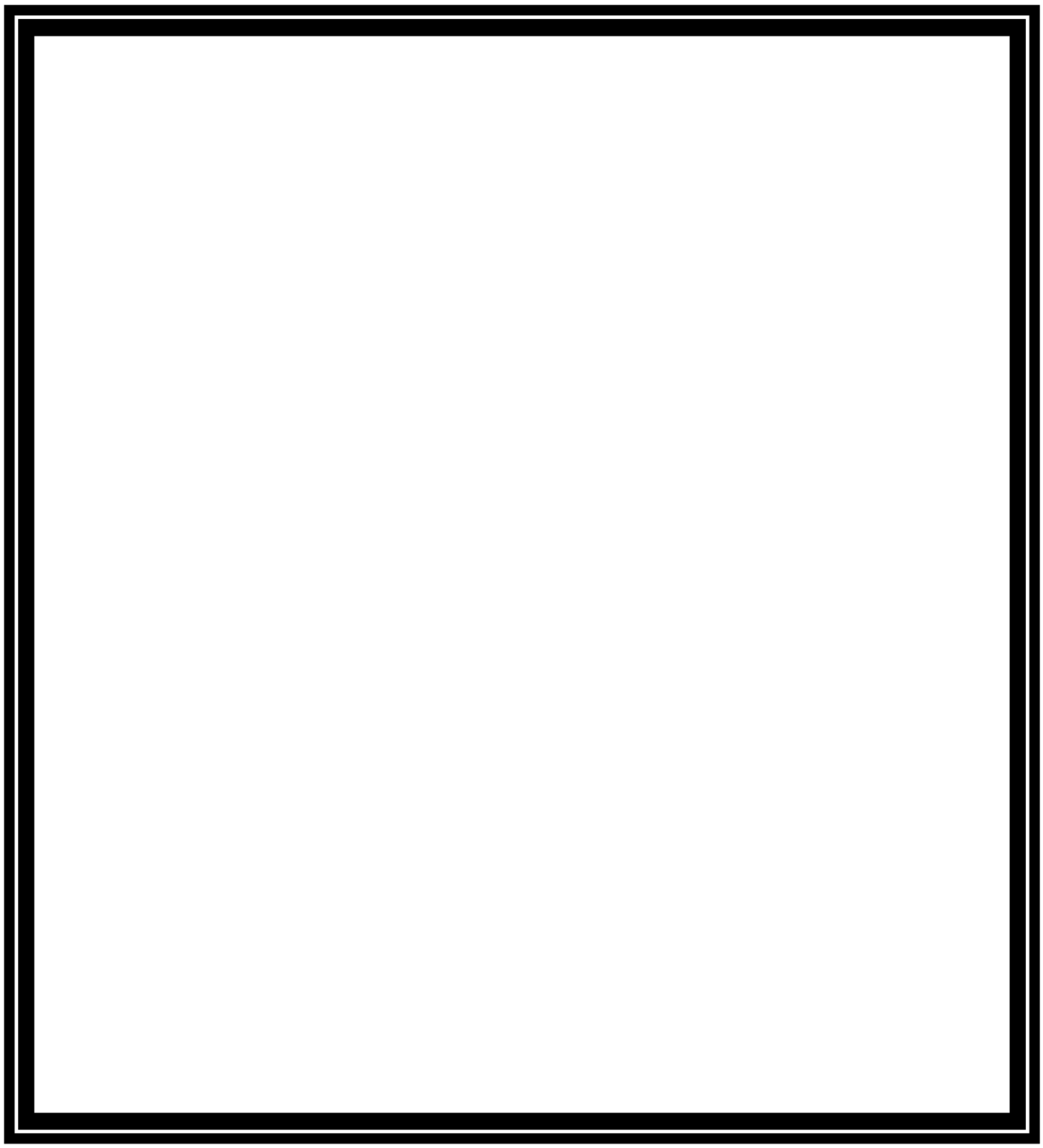
- **MEDICAL CAUSES**
  - ✓ The common medical causes of ARF are fluid and electrolyte depletion, infectious diarrhoea, non-diarrhoeal infections, glomerulonephritis, poisoning with heavy metals, G6-PD deficiency, snake bite and nephrotoxic drugs.
  - **Fluid and electrolyte depletion**
    - It is a major cause in the tropics.
    - Diseases of the gastrointestinal tract, particularly acute diarrhoea, dysentery, cholera and gastroenteritis, lead to loss of large amounts of fluid, varying from 5 L to 10 L per day.
    - The resultant hypovolaemia causes acute oliguric renal failure.
    - Excessive heat exposure is another cause of significant fluid loss in the tropics.
  - **Infectious diarrhoea**
    - It is a common cause in small children in India and Bangladesh.
    - A number of such patients present with features of haemolytic uraemic syndrome (HUS); the chief underlying mechanism is microangiopathy.
  - **Glomerulonephritis**
    - Acute glomerulonephritis and rapidly progressive glomerulonephritis (RPGN) together account for a very high proportion of ARF in children; they are less frequent in adults.
    - The majority of patients with acute glomerulonephritis recover, whereas those with RPGN may develop irreversible rapidly progressive renal failure.
  - **Poisoning** with heavy metals such as copper sulphate and mercuric chloride.
  - **Glucose 6-phosphate dehydrogenase deficiency** :
    - The syndrome of haemolysis with ARF is common in patients with G6-PD deficiency.
    - It is observed following the administration of antimalarials (primaquine, quinine), or analgesics like acetylsalicylic acid, phenacetin, acetanilid, or drugs such as sulphonamides, nitrofurantoin and chloramphenicol.
    - The disease also occurs after acute infections, especially falciparum malaria.
    - The onset is abrupt and is characterised by haemoglobulinuria, anaemia, jaundice, oliguria and renal failure.
  - **Snake venom:**
    - Snakebite accounted for about 2% of all medical admissions in some medical college hospitals in India; 12% of these cases had ARF.
- **Obstetric causes**
  - ✓ Septic abortion is the most common cause of obstetric ARF in the tropics.
  - ✓ The most common presenting symptoms are lower abdominal pain, vaginal bleeding, nausea, vomiting, and oliguria or anuria.
  - ✓ Sepsis and anaemia are observed in the majority of cases.
  - ✓ Abruptio placentae, placenta previa, pre-eclampsia, and postpartum ARF are other important causes of obstetric ARF.
- **Obstructive uropathy and other surgical causes**
  - ✓ Obstructive uropathy is an important cause of ARF.
  - ✓ Calculus disease is endemic in many tropical countries and is a major cause of obstructive uropathy in northern India.

- ✓ Surgical causes of ARF are seen less frequently in the tropics.
- ✓ Sepsis and hypotension are responsible for the high mortality seen in this group.

PATHOPHYSIOLOGY

- ✓ The course of ischemic ARF is typically characterized by three phases:
  1. The initiation,
  2. Maintenance, and
  3. Recovery phases.
- ✓ The initiation phase (hours to days) is the initial period of renal hypoperfusion during which ischemic injury is evolving.
- ✓ GFR declines because
  - Glomerular ultrafiltration pressure is reduced as a consequence of the fall in renal blood flow,
  - The flow of glomerular filtrate within tubules is obstructed by casts comprised of epithelial cells and necrotic debris derived from ischemic tubule epithelium, and
  - There is backleak of glomerular filtrate through injured tubular epithelium
- ✓ Ischemic injury is most prominent in the terminal medullary portion of the proximal tubule (S3 segment, pars recta) and the medullary portion of the thick ascending limb of the loop of Henle.
- ✓ Both segments have high rates of active (ATP-dependent) solute transport and oxygen consumption and are located in a zone of the kidney (the outer medulla) that is relatively ischemic, even under basal conditions, by virtue of the unique countercurrent arrangement of the medullary vasculature.
- ✓ Cellular ischemia results in a series of alterations in energetics, ion transport, and membrane integrity that ultimately lead to cell injury and, if severe, cell apoptosis or necrosis.
- ✓ These alterations include depletion of ATP, inhibition of active sodium transport and transport of other solutes, impairment of cell volume regulation and cell swelling, cytoskeletal disruption and loss of cell polarity, cell-cell and cellmatrix attachment, accumulation of intracellular calcium, altered phospholipid metabolism, oxygen free radical formation, and peroxidation of membrane lipids.
- ✓ Importantly, renal injury can be limited by restoration of renal blood flow during this period.
- ✓ The initiation phase is followed by a maintenance phase (typically 1 to 2 weeks) during which renal cell injury is established, GFR stabilizes at its nadir (typically 5 to 10 mL/min), urine output is lowest, and uremic complications arise.
- ✓ The reasons why the GFR remains low during this phase, despite correction of systemic hemodynamics, are still being defined.
- ✓ Putative mechanisms include persistent intrarenal vasoconstriction and medullary ischemia triggered by dysregulated release of vasoactive mediators from injured endothelial cells (e.g., decreased nitric oxide, increased endothelin-1, adenosine, and platelet-activating factor), congestion of medullary blood vessels, and reperfusion injury induced by reactive oxygen species and other mediators derived from leukocytes or renal parenchymal cells.
- ✓ In addition, epithelial cell injury per se may contribute to persistent intrarenal vasoconstriction by a process termed tubuloglomerular feedback.

- ✓ Specialized epithelial cells in the macula densa region of distal tubules detect increases in distal salt (probably chloride) delivery that occur as a consequence of impaired reabsorption by more proximal nephron segments.
- ✓ Macula densa cells in turn stimulate constriction of adjacent afferent arterioles by a poorly defined mechanism and further compromise glomerular perfusion and filtration, thereby contributing to a vicious cycle.
- ✓ A recovery phase is characterized by renal parenchymal cell, particularly tubule epithelial cell, repair and regeneration and a gradual return of GFR to or towards premorbid levels.
- ✓ The recovery phase may be complicated by a marked diuretic phase due to excretion of retained salt and water and other solutes, continued use of diuretics, and/or delayed recovery of epithelial cell function (solute and water reabsorption) relative to glomerular filtration.



CLINICAL PRESENTATION OF ACUTE RENAL FAILURE

- **GENERAL**
  - ✓ Outpatients often are not in acute distress; hospitalized patients may develop ARF after a catastrophic event
- **SYMPTOMS**
  - ✓ Outpatient: Change in urinary habits, weight gain, or flank pain
  - ✓ Inpatient: Typically ARF is noticed by clinicians before it is noticed by the patient
- **SIGNS**
  - ✓ Patient may have edema; urine may be colored or foamy.
  - ✓ Vital signs may indicate orthostatic hypotension in volume depleted patients
- **LABORATORY TESTS**
  - ✓ Urine and blood chemistries may determine prerenal cause complete blood cell count (CBC) and differential rules out
  - ✓ Infectious causes
  - ✓ Urine microscopy may reveal casts, WBCs, RBCs, and eosinophils
- **OTHER DIAGNOSTIC TESTS**
  - ✓ Renal ultrasound or cystoscopy may be needed to rule out obstruction; renal biopsy reserved for difficult diagnoses

CLINICAL FEATURES AND DIFFERENTIAL DIAGNOSIS

- ✓ Patients presenting with renal failure should be assessed initially to determine if the decline in GFR is acute or chronic.
- ✓ An acute process is easily established if a review of laboratory records reveals a recent rise in blood urea and creatinine levels, but previous measurements are not always available.
- ✓ Findings that suggest chronic renal failure include anemia, neuropathy, and radiologic evidence of renal osteodystrophy or small scarred kidneys.
- ✓ However, it should be noted that anemia may also complicate ARF, and renal size may be normal or increased in several chronic renal diseases (e.g., diabetic nephropathy, amyloidosis, polycystic kidney disease).
- ✓ Once a diagnosis of ARF has been established, several issues should be addressed promptly:
  - The identification of the cause of ARF,
  - The elimination of the triggering insult (e.g., nephrotoxin) and/or institution of disease-specific therapies, and
  - The prevention and management of uremic complications.

CLINICAL ASSESSMENT

- ✓ Clinical clues to **Prerenal ARF** are symptoms of thirst and orthostatic dizziness and physical evidence of orthostatic hypotension and tachycardia, reduced jugular venous pressure, decreased skin turgor, dry mucous membranes, and reduced axillary sweating.
- ✓ Case records should be reviewed for documentation of a progressive fall in urine output and body weight and recent initiation of treatment with NSAIDs, ACE inhibitors, or angiotensin II receptor blockers.
- ✓ Careful clinical examination may reveal stigmata of chronic liver disease and portal hypertension, advanced cardiac failure, sepsis, or other causes of reduced “effective” arterial blood volume.

- ✓ **Intrinsic renal ARF** due to ischemia is likely following severe renal hypoperfusion complicating hypovolemic or septic shock or following major surgery.
- ✓ The likelihood of ischemic ARF is increased further if ARF persists despite normalization of systemic hemodynamics.
- ✓ Diagnosis of nephrotoxic ARF requires careful review of the clinical data and pharmacy, nursing, and radiology records for evidence of recent exposure to nephrotoxic medications or radiocontrast agents or to endogenous toxins (e.g., myoglobin, hemoglobin, uric acid, myeloma protein, or elevated levels of serum calcium).
- ✓ Although ischemic and nephrotoxic ARF account for more than 90% of cases of intrinsic renal ARF, other renal parenchymal diseases must be considered.
- ✓ Flank pain may be a prominent symptom following occlusion of a renal artery or vein and with other parenchymal diseases distending the renal capsule (e.g., severe glomerulonephritis or pyelonephritis).
- ✓ Subcutaneous nodules, livedo reticularis, bright orange retinal arteriolar plaques, and digital ischemia, despite palpable pedal pulses, are clues to atheroembolization.
- ✓ ARF in association with oliguria, edema, hypertension, and an "active" urine sediment (nephritic syndrome) suggests acute glomerulonephritis or vasculitis.
- ✓ Malignant hypertension is a likely cause of ARF in patients with severe hypertension and evidence of hypertensive injury to other organs (e.g., left ventricular hypertrophy and failure, hypertensive retinopathy and papilledema, neurologic dysfunction).
- ✓ Fever, arthralgias, and a pruritic erythematous rash following exposure to a new drug suggest allergic interstitial nephritis, although systemic features of hypersensitivity are frequently absent.
- ✓ **Postrenal ARF** presents with suprapubic and flank pain due to distention of the bladder and of the renal collecting system and capsule, respectively.
- ✓ Colicky flank pain radiating to the groin suggests acute ureteric obstruction.
- ✓ Prostatic disease is likely if there is a history of nocturia, frequency, and hesitancy and enlargement or induration of the prostate on rectal examination.
- ✓ Neurogenic bladder should be suspected in patients receiving anticholinergic medications or with physical evidence of autonomic dysfunction.
- ✓ Definitive diagnosis of postrenal ARF hinges on judicious use of radiologic investigations and rapid improvement in renal function following relief of obstruction.

URINALYSIS

- ✓ Anuria suggests complete urinary tract obstruction but may complicate severe cases of prerenal or intrinsic renal ARF.
- ✓ Wide fluctuations in urine output raise the possibility of intermittent obstruction, whereas patients with partial urinary tract obstruction can present with polyuria due to impairment of urine concentrating mechanisms.
- ✓ In **prerenal ARF**, the sediment is characteristically acellular and contains transparent hyaline casts ("bland," "benign," "inactive" urine sediment).
- ✓ Hyaline casts are formed in concentrated urine from normal constitutents of urine—principally Tamm-Horsfall protein, which is secreted by epithelial cells of the loop of Henle.
- ✓ **Postrenal ARF** may also present with an inactive sediment, although hematuria and pyuria are common in patients with intraluminal obstruction or prostatic disease.

- ✓ Pigmented "muddy brown" granular casts and casts containing tubule epithelial cells are characteristic of ATN and suggest ischemic or nephrotoxic ARF.
- ✓ They are usually found in association with microscopic hematuria and mild "tubular" proteinuria (<1 g/d); the latter reflects impaired reabsorption and processing of filtered proteins by injured proximal tubules.
- ✓ Casts are absent, however, in 20 to 30% of patients with ischemic or nephrotoxic ARF and are not a requisite for diagnosis.
- ✓ In general, red blood cell casts indicate glomerular injury or, less often, acute tubulointerstitial nephritis.
- ✓ White cell casts and nonpigmented granular casts suggest interstitial nephritis, whereas broad granular casts are characteristic of chronic renal disease and probably reflect interstitial fibrosis and dilatation of tubules.
- ✓ Eosinophiluria (>5% of urine leukocytes) is a common finding (~90%) in antibiotic-induced allergic interstitial nephritis when studied using Hansel's stain; however, lymphocytes may predominate in allergic interstitial nephritis induced by NSAIDs.
- ✓ Eosinophiluria is also a feature of atheroembolic ARF.
- ✓ Occasional uric acid crystals (pleomorphic in shape) are common in the concentrated urine of prerenal ARF but suggest acute urate nephropathy if seen in abundance.
- ✓ Oxalate (envelope-shaped) and hippurate (needle-shaped) crystals raise the possibility of ethylene glycol ingestion and toxicity.
- ✓ Proteinuria of >1 g/d suggests injury to the glomerular ultrafiltration barrier ("glomerular proteinuria") or excretion of myeloma light chains.
- ✓ Heavy proteinuria is also a frequent finding (~80%) in patients who develop combined allergic interstitial nephritis and minimal change glomerulopathy when treated with NSAIDs.
- ✓ A similar syndrome can be triggered by ampicillin, rifampicin, or interferon α.
- ✓ Hemoglobinuria or myoglobinuria should be suspected if urine is strongly positive for heme by dipstick, but contains few red cells, and if the supernatant of centrifuged urine is positive for free heme.
- ✓ Bilirubinuria may provide a clue to the presence of hepatorenal syndrome.

RENAL FAILURE INDICES

- ✓ Analysis of urine and blood biochemistry is particularly useful for distinguishing prerenal ARF from ischemic or nephrotoxic intrinsic renal ARF.
- ✓ The fractional excretion of sodium (FE_{Na}) is most useful in this regard.
- ✓ The FE_{Na} relates sodium clearance to creatinine clearance.
- ✓ Sodium is reabsorbed avidly from glomerular filtrate in patients with prerenal ARF, in an attempt to restore intravascular volume, but not in patients with ischemic or nephrotoxic intrinsic ARF, as a result of tubular epithelial cell injury.
- ✓ In contrast, creatinine is not reabsorbed in either setting.
- ✓ Consequently, patients with prerenal ARF typically have a FE_{Na} of <1.0% (frequently <0.1%), whereas the FE_{Na} in patients with ischemic or nephrotoxic ARF is usually >1.0%.
- ✓ The **renal failure index** provides comparable information, since clinical variations in serum sodium concentration are relatively small.
- ✓ **Urine sodium concentration** is a less sensitive index for distinguishing prerenal ARF from ischemic and nephrotoxic ARF as values overlap between groups.

- ✓ Similarly, indices of urinary concentrating ability such as urine specific gravity, urine osmolality, urine-to-plasma urea ratio, and blood urea-to-creatinine ratio are of limited value in differential diagnosis.
- ✓ Many caveats apply when interpreting biochemical renal failure indices.
- ✓ FE_{Na} may be >1.0% in prerenal ARF if patients are receiving diuretics or have bicarbonaturia (accompanied by sodium to maintain electroneutrality), preexisting chronic renal failure complicated by salt wasting, or adrenal insufficiency.
- ✓ In contrast, the FENa is <1.0% in approximately 15% of patients with nonoliguric ischemic or nephrotoxic ARF, probably reflecting patchy injury to tubular epithelium with preservation of reabsorptive function in some areas.
- ✓ The FE_{Na} is also often <1.0% in ARF due to urinary tract obstruction, glomerulonephritis, and vascular diseases.

LABORATORY FINDINGS

- ✓ Serial measurements of serum creatinine can provide useful pointers to the cause of ARF.
- ✓ Prerenal ARF is typified by fluctuating levels that parallel changes in hemodynamic function.
- ✓ Creatinine rises rapidly (within 24 to 48 h) in patients with ARF following renal ischemia, atheroembolization, and radiocontrast exposure.
- ✓ Peak creatinine levels are observed after 3 to 5 days with contrast nephropathy and return to baseline after 5 to 7 days.
- ✓ In contrast, creatinine levels typically peak later (7 to 10 days) in ischemic ARF and atheroembolic disease.
- ✓ The initial rise in serum creatinine is characteristically delayed until the second week of therapy with many tubule epithelial cell toxins (e.g., aminoglycosides, cisplatin) and probably reflects the need for accumulation of these agents within cells before GFR falls.
- ✓ Hyperkalemia, hyperphosphatemia, hypocalcemia, and elevations in serum uric acid and creatine kinase (MM isoenzyme) levels at presentation suggest a diagnosis of rhabdomyolysis.
- ✓ Hyperuricemia [>890μmol/L(>15mg/dL)] in association with hyperkalemia, hyperphosphatemia, and increased circulating levels of intracellular enzymes such as lactate dehydrogenase may indicate acute urate nephropathy and tumor lysis syndrome following cancer chemotherapy.
- ✓ A wide serum anion and osmolal gap (measured serum osmolality minus the serum osmolality calculated from serum sodium, glucose, and urea concentrations) indicate the presence of an unusual anion or osmole in the circulation and are clues to diagnosis of ethylene glycol or methanol ingestion. Severe anemia in the absence of hemorrhage raises the possibility of hemolysis, multiple myeloma, or thrombotic microangiopathy.
- ✓ Systemic eosinophilia suggests allergic interstitial nephritis but is also a feature of atheroembolic disease and polyangiitis nodosa.

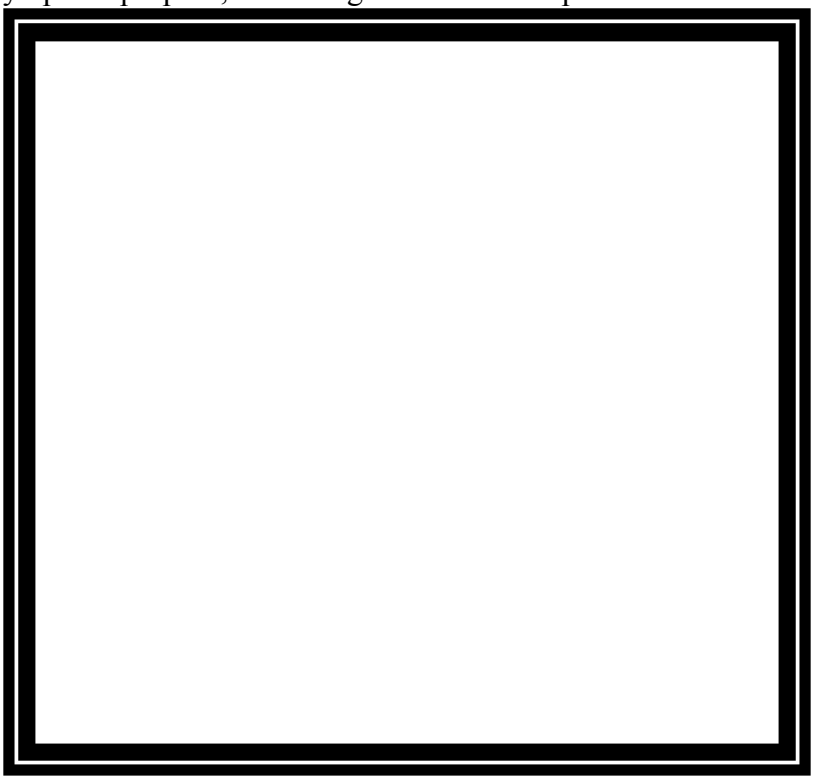
RADIOLOGIC FINDINGS

- ✓ Imaging of the urinary tract by ultrasonography is useful to exclude postrenal ARF.
- ✓ Computed tomography and magnetic resonance imaging are alternative imaging modalities.
- ✓ Whereas pelvicalyceal dilatation is usual with urinary tract obstruction (98% sensitivity), dilatation may be absent immediately following obstructtion or in patients with ureteric encasement (e.g., retroperitoneal fibrosis, neoplasia).

- ✓ Retrograde or anterograde pyelography are more definitive investigations in complex cases and provide precise localization of the site of obstruction.
- ✓ A plain film of the abdomen, with tomography if necessary, is a valuable initial screening technique in patients with suspected nephrolithiasis.
- ✓ Doppler ultrasonography and magnetic resonance angiography are useful for assessment of patency of renal arteries and veins in patients with suspected vascular obstruction; however, contrast angiography is usually required for definitive diagnosis.

RENAL BIOPSY

- ✓ Biopsy is reserved for patients in whom prerenal and postrenal ARF have been excluded and the cause of intrinsic renal ARF is unclear.
- ✓ Renal biopsy is particularly useful when clinical assessment and laboratory investigations suggest diagnoses other than ischemic or nephrotoxic injury that may respond to disease-specific therapy.
- ✓ Examples include glomerulonephritis, vasculitis, hemolyticuremic syndrome, thrombotic thrombocytopenic purpura, and allergic interstitial nephritis.



THERAPEUTIC PLAN

PREVENTION

- ✓ In the patient who suddenly develops oliguria with rising BUN and SCr concentrations, it is important to distinguish whether the underlying disease process is prerenal or postrenal, because rapid correction of these conditions can prevent progression to ischemic injury and development of ARF.
- ✓ Correction of volume deficits can lead to prompt restoration of renal perfusion.
- ✓ Therapeutic agents known to further reduce blood flow must be withdrawn and potential nephrotoxins, such as aminoglycosides, radiocontrast dye, NSAIDs, and ACE inhibitors, should be administered cautiously, if at all.

- ✓ Initial efforts should also be directed at ruling out urinary tract obstruction.
- ✓ Factors suggesting obstruction include a normal urinalysis, rapid changes in urine output, and residual urine on postvoiding catheterization.
- ✓ If renal calculi are present, a radiograph of the abdomen will detect the 90% that are radiopaque.
- ✓ In the absence of obstruction, urinary indices provide the most reliable method of distinguishing prerenal azotemia from ATN.
- ✓ It is important to differentiate between prerenal and intrinsic ARF on the basis of these clinical laboratory measurements.
- ✓ If prerenal azotemia is suspected, aggressive fluid resuscitation should result in an increased urine output.
- ✓ If urine flow does not increase, additional fluids should be given cautiously, if at all, because fluid overload is likely to ensue if ARF is already established.
- ✓ Also, a fluid challenge can be detrimental to the patient with intrinsic renal damage (ATN). Thus, the patient who presents with a high urinary sodium (in the absence of diuretic use) and FE_{Na} >2% probably has ATN and should not receive fluid resuscitation.
- ✓ Preventing associated complications, such as infection and gastrointestinal bleeding, is very important.
- ✓ Careful maintenance of intravenous access, minimal use of indwelling urinary bladder catheters, and early recognition and treatment of wound and other infections are necessary.
- ✓ Monitoring for signs of blood loss (e.g., testing stools for occult blood, monitoring the hematocrit, and controlling gastric pH with H_2 antagonists or antacids) minimizes the morbidity associated with bleeding.
- ✓ If potential nephrotoxic insults are likely to occur, specific preventive measures, such as hydration and volume repletion before and during nephrotoxin exposure, are recommended.
- ✓ For example, when using amphotericin B or aminoglycosides, ensuring that patients are well hydrated may eliminate or reduce the severity of renal damage.
- ✓ Other preventive measures to consider are therapeutic drug monitoring of aminoglycoside concentrations, fluid hydration before cisplatin therapy, and the use of allopurinol and urine alkalinization during high-dose chemotherapy to avoid uric acid nephropathy.
- ✓ Combination therapy with more than one nephrotoxic agent carries additional risk and should be avoided if possible.
- ✓ Substitution of less nephrotoxic agents should be considered in older adults and others at risk for renal dysfunction.
- ✓ For example, in high-risk patients, it may be possible to avoid radiocontrast agents and use less invasive diagnostic techniques such as ultrasonography.
- ✓ Nephrotoxins should be avoided or discontinued, and doses of medications whose pharmacokinetics or pharmacodynamics are affected by renal dysfunction should be adjusted.

PREVENTING ACUTE RENAL FAILURE
Identify patients at risk ✓ Older adults ✓ Patients with abnormal renal function or diabetes ✓ Voilume-depleted patient
Avoid nephrotoxic agents ✓ Nonsteroidal anti-inflammatory drugs ✓ Aminoglycosides ✓ Amphotericin B ✓ ACE inhibitors in volume depleted patients
Use prevention strategies ✓ Contrast media (Extracellular fluid volume expansion) ✓ Rhabdomyolysis (Correct intravascular volume, Urinary alkalinization, Mannitol infusion) ✓ Tumorlysis syndrome (Allopurinol, Diuresis, Urinary alkalinization) ✓ Surgical procedures (Optimize volume status, avoid multiple insults and hypotension)

SUPPORTIVE CARE

- ✓ ARF often persists for several days or weeks, necessitating prolonged supportive care.
- ✓ The minimum daily fluid needs include replacement of measurable losses (i.e., urine output, nasogastric suction, vomiting, chest tube drainage, and fistula output) and insensible losses through the skin and lungs (approximately 600 to 900 mL/day).
- ✓ The choice of fluid intake should be determined by the need for colloid or crystalloid, electrolytes, and calories.

FLUID MANAGEMENT

- ✓ The normal kidney is critical to the maintenance of volume homeostasis, which permits constant circulatory and extracellular fluid volumes despite varying water and salt consumption and varying loss.
- ✓ The presence of pedal or sacral edema or pulmonary edema in the setting of ARF implies that water or salt intake has exceeded the injured kidney's ability to excrete the water and salt load.
- ✓ This situation can be anticipated in the oliguric or anuric patient but often complicates nonoliguric ARF as well.
- ✓ Most patients with ARF lose the ability to concentrate or dilute the urine and as a consequence excrete a constant volume of urine regardless of fluid intake.
- ✓ For example, a patient with ATN whose urine output is fixed at 500 mL per day but receives 1,000 mL per day of parenteral nutrition, along with various intravenous antibiotics, will gradually develop volume overload and edema unless the volume administered is adjusted.
- ✓ Volume status management is based on careful physical examination, and the patient must be examined daily to measure supine and standing blood pressure and pulse, skin turgor, and mucous membrane hydration; auscultate the lungs for evidence of pulmonary congestion; perform a general examination for sacral or pedal edema; review daily intake and output; and measure daily (serial) weight changes accurately.
- ✓ A bolus of normal saline (250 to 500 mL) may be used initially in most cases.
- ✓ The rate of fluid replacement is determined by the extent of hemodynamic compromise.
- ✓ The prescription for fluid and sodium intake should be specified.

- ✓ In general, a patient who is euvolemic should be given an additional 300 to 500 mL per day of electrolyte-free water to replace insensible water losses.
- ✓ A sodium intake of less than 2 g per day should be prescribed.
- ✓ Patients with increased insensible fluid loss, such as those with burns or severe diarrhea, have much larger fluid needs.
- ✓ The patient with clinical evidence of fluid overload should be restricted to a fluid intake less than the daily urine output.
- ✓ Patients with clinical evidence of volume depletion should be given additional volume to achieve a euvolemic state.
- ✓ Sustained hypovolemia may worsen renal injury or delay recovery from renal failure.
- ✓ Increased fluid needs should be anticipated during the polyuric recovery phase of ARF.
- ✓ In the ICU, clinical assessment of volume status can be confounded by surgical wound loss, severe pneumonia, or edema caused by altered capillary permeability.
- ✓ Here, measurements of central venous pressure and capillary wedge pressure are important adjuncts to volume status monitoring.
- ✓ These patients often are receiving multiple parenteral medications that constitute a large obligatory volume load.
- ✓ Often these medications can be given slowly in a concentrated solution to minimize the volume administered.
- ✓ Likewise, the volume of parenteral nutrition should be adjusted to optimize calories and protein in a minimum volume.
- ✓ The clinician must keep in mind the solutions in which various medications are delivered.

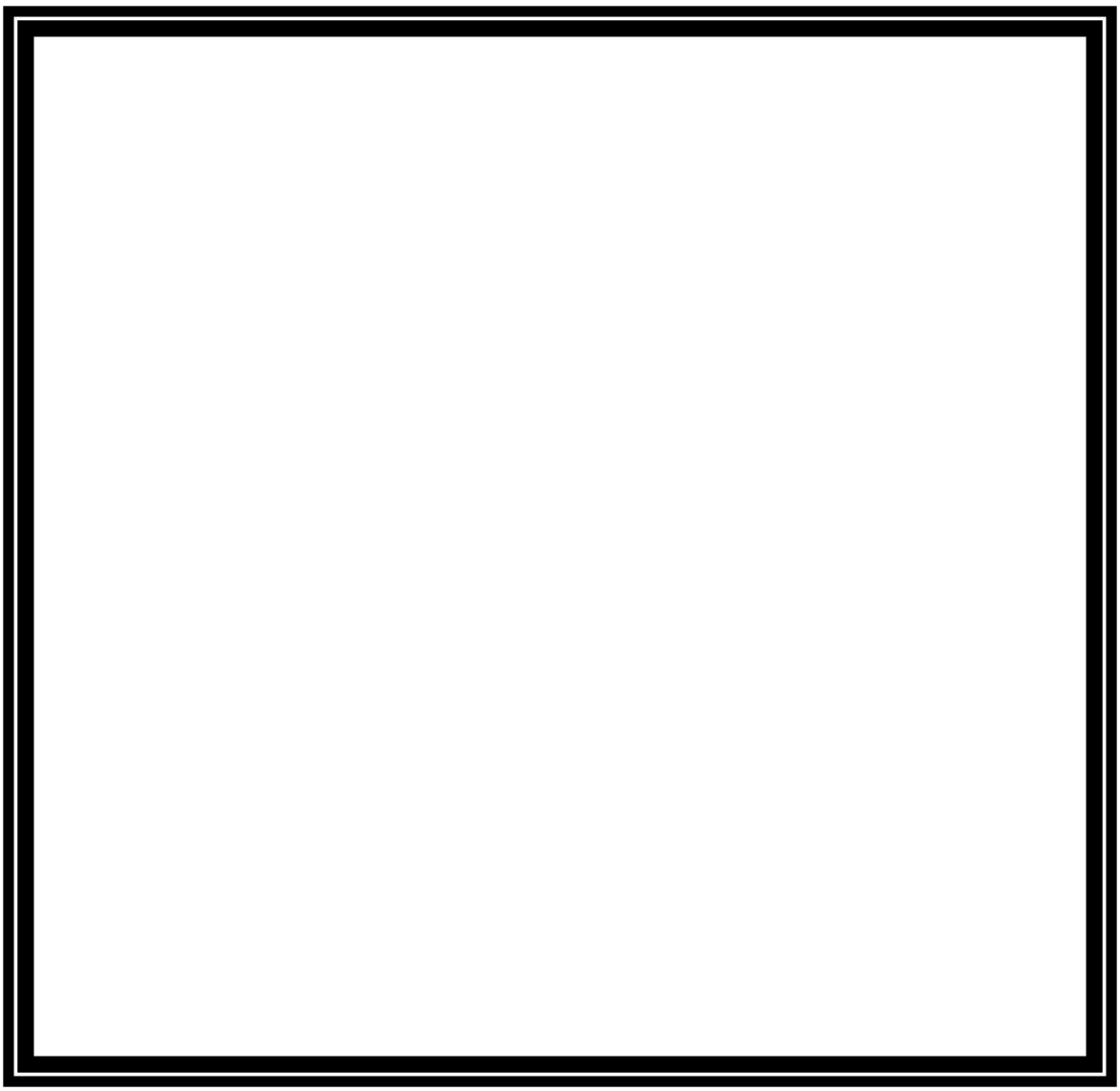
ELECTROLYTE HOMEOSTASIS

- ✓ Electrolyte abnormalities that occur in ARF include disorders of sodium, potassium, phosphate, magnesium, and calcium homeostasis.
- ✓ Hypernatremia and hyponatremia often are observed in patients with ARF.
- ✓ Because abnormal serum sodium concentrations are caused by disorders of water metabolism, sodium homeostasis is linked to volume management.
- ✓ **Hyponatremia** usually results from an excess of free water relative to solute, whereas **hypernatremia** results when free water intake is inadequate.
- ✓ It is important to keep track of the amount of free water delivered in intravenous solutions and to limit this free water whenever necessary.
- ✓ For example, administering 500 mL of 0.45% saline is equivalent to giving 250 mL of 0.9% (normal) saline and 250 mL of electrolyte-free water.
- ✓ Other sources of free water excess include parenteral and enteral feedings.
- ✓ **Hyperkalemia** can be a serious consequence of ARF; potassium intake can exceed the injured kidney's reduced potassium excretory capacity.
- ✓ In addition, there can be shifts between intracellular and extracellular compartments secondary to acid–base balance.
- ✓ Hyperkalemia usually is prevented by restricting daily potassium intake to less than 50 mEq.
- ✓ Certain food types, such as fruits, chocolates, and nuts, must be eliminated from the diet.
- ✓ Often, potassium is omitted from parenteral fluids, and it is important not to overlook nondietary exogenous sources of potassium; these include drugs such as potassium penicillin G and salt substitutes.

- ✓ Finally, drugs that impair renal potassium excretion, such as potassium-sparing diuretics, NSAIDs, and ACE inhibitors, should be avoided if possible.
- ✓ If potassium restriction is inadequate to prevent hyperkalemia, sodium polystyrene sulfonate can be used to exchange sodium for potassium in the bowel and increase intestinal excretion of potassium.
- ✓ Although usually administered orally (15 to 30 gm in 20% sorbitol), in the presence of an ileus, potassium exchange resins are effective when given as an enema.
- ✓ Because these compounds exchange sodium for potassium, large sodium loads can worsen volume overload or cause hypernatremia.
- ✓ Repeated administration can lead to diarrhea as a result of sorbitol intake, which may complicate acidosis by increasing intestinal bicarbonate loss.
- ✓ Persistent hyperkalemia despite potassium intake restriction and sodium polystyrene administration is an indication for dialysis.
- ✓ However, other endogenous causes of hyperkalemia (e.g., severe acidosis, insulinopenia, hemolysis, rhabdomyolysis, and ischemic tissue injury) should also be investigated.
- ✓ **Hypocalcemia** may occur secondary to the hypomagnesemia associated with cisplatin, amphotericin B, or aminoglycoside administration.
- ✓ **Hypomagnesemia** also inhibits synthesis and release of parathyroid hormone, which may cause hypocalcemia.
- ✓ Decreased synthesis of 1,25-dihydroxyvitamin D by the injured kidney reduces intestinal calcium absorption and can contribute to hypocalcemia.
- ✓ In addition, hypocalcemia can result from frequently administered blood products preserved in citrate.
- ✓ Hypocalcemia is prevented and treated with generous calcium supplementation either orally (3 to 4 g/day in divided doses) or, for symptomatic hypocalcemia, as calcium acetate, calcium gluconate, or calcium chloride.
- ✓ Magnesium should be repleted (cautiously) orally or parenterally.
- ✓ Avoiding magnesium-containing antacids decreases the potential for hypermagnesemia.
- ✓ **Phosphorus** accumulates during renal failure and may result in **hyperphosphatemia**.
- ✓ Although hyperphosphatemia is much more problematic in patients with chronic renal failure, high serum phosphorus levels can contribute to hypocalcemia.
- ✓ Restricting dietary phosphate and administering phosphate-binding antacids (e.g., calcium-containing antacids) usually maintains serum phosphate within the normal range.

TREATMENT

- ✓ Three basic therapeutic interventions are currently used in ARF: **Pharmacologic, Dialytic,** and **Nutritional therapies.**
- ✓ Despite considerable recent research, none of these has been found to improve mortality rates or hasten renal function recovery significantly.
- ✓ Thus, the initial care of a patient with ARF should focus on reversing the underlying cause, correcting fluid and electrolyte imbalances, and preventing further renal injury by providing supportive measures.



PHARMACOTHERAPY

- ✓ Therapeutic modalities for treating ARF are designed to increase RBF, increase urine output, maintain fluid and electrolyte balance, remove metabolic wastes, and slow or reverse kidney damage.

DIURETICS

- ✓ Although diuretic therapy (e.g., mannitol and furosemide) helps to protect the kidney from injury in experimental ischemia, most clinical trials have failed to show effectiveness of these agents in treating or preventing ischemic ARF.
- ✓ If administered early in the course of ARF, both furosemide and mannitol can convert oliguric ARF to a nonoliguric state.
- ✓ However, most clinicians would agree that nonoliguric patients are easier to manage than oliguric patients and have fewer complications, less need for dialysis, and shorter hospital stays than those with oliguric renal failure.
- ✓ Maintaining a high urine output may prevent volume overload and allow increased nutritional support.

- ✓ At present, loop diuretics or mannitol should be used to optimize fluid management in newly apparent intrinsic ARF.
- ✓ Diuretics should be avoided in the setting of contrast nephropathy and as routine prophylaxis of ARF because resultant hypovolemia could accelerate the progression from prerenal azotemia.

MANNITOL

- ✓ Mannitol was the first pharmacologic substance used in ARF, and many nephrologists continue to use it to treat ARF.
- ✓ Proposed mechanisms of benefit include increased filtration pressure, improved urine flow rates, reduced tubular cell inflammation, and improved RBF caused by a decrease in renal vascular resistance.
- ✓ Mannitol is also a free radical scavenger.
- ✓ Despite these theoretical benefits, there are several reports of mannitol-induced ARF, and consistent benefit in patients with ARF has not been found.
- ✓ As soon as possible after a decrease in urine output is noted, a short course of mannitol might be tried.
- ✓ In adults, a wide range of mannitol doses sufficient to expand intravascular volume and increase renal perfusion pressure have been tried.
- ✓ In general, 20% mannitol solution dosed at 0.5 g per kg can be infused over 30 to 60 minutes, then repeated in an hour if there is no response.
- ✓ If urine output follows, additional doses are titrated to maintain urine output.
- ✓ If diuresis does not occur and additional doses are given, intravascular volume overload and congestive heart failure may occur.
- ✓ Mannitol is recommended for prevention and early treatment of myoglobinuric ARF174 and is used with adequate hydration to prevent cisplatin-associated nephrotoxicity.

LOOP DIURETICS

- ✓ Loop diuretics usually are considered the diuretics of choice in patients with renal insufficiency.
- ✓ The benefits of loop diuretics in early ARF are thought to result from decreased tubule obstruction, reduction of active transport processes and oxygen demand in the tubular cells, or renal vasodilation resulting in increased RBF.
- ✓ All loop diuretics (i.e., furosemide, torsemide, ethacrynic acid, and bumetanide) affect the ascending limb of the loop of Henle to prevent sodium reabsorption.
- ✓ However, ethacrynic acid is not used in patients with renal failure because of accumulation and ototoxicity.
- ✓ Ethacrynic acid is reserved for patients allergic to sulfa medications.
- ✓ Diuretics have similar efficacy when given in equivalent doses.
- ✓ Bumetanide is an effective and potent loop diuretic and can be used in patients with ARF; however, its use in these patients has not been studied extensively.
- ✓ Torsemide and bumetanide have better oral bioavailability than furosemide.
- ✓ Compared to furosemide, torsemide's advantages include a high oral bioavailability (80% to 100%) and a long duration of activity (12 to 24 hours), allowing for less frequent dosing.
- ✓ Although the use of loop diuretics remains controversial, they should be considered after an inadequate response to a fluid challenge.

- ✓ Recent trials have shown an increase in urine output with the use of loop diuretics in ARF patients.
- ✓ Increase in urinary output not only makes fluid management easier in critically ill patients, but can also be used as a prognostic tool to assess the severity of renal insult.
- ✓ Because the window of opportunity may be narrow, an initial intravenous furosemide dose of 1.5 to 3 mg per kg (100 to 200 mg) should be infused over 15 to 30 minutes.
- ✓ If urine output does not increase within an hour, the dose should be doubled and a thiazide added. If there is no response, therapy should be discontinued.
- ✓ Doses >500 mg are unlikely to be of benefit.
- ✓ If urine output increases, additional doses can be given to maintain urine flow.
- ✓ Patients who have a poor response to intermittent doses of a loop diuretic may benefit from a continuous furosemide infusion at a dose of 10 to 40 mg per hour, titrated according to the patient's urine output.
- ✓ Continuous infusion of loop diuretics has been reported to be more effective than intermittent dosing.
- ✓ It is thought that maintaining effective amounts of diuretic within the luminal tubule will enhance the diuretic response.
- ✓ Also, continuous infusion decreases the frequency of adverse reactions, such as myalgias and ototoxicity.
- ✓ Before a continuous infusion of a loop diuretic is started, a loading dose should be given to decrease the time necessary to achieve therapeutic drug concentrations.

VASOACTIVE AGENTS

DOPAMINE

- ✓ Dopamine is an endogenous catecholamine whose actions are mediated by stimulation of various dopaminergic and adrenergic receptors.
- ✓ The mechanisms by which dopamine modulates RBF depend on the rate of infusion.
- ✓ Dopaminergic effects occur at low doses of 0.5 to 1 µg/kg/minute.
- ✓ Activation of dopamine-1 and dopamine-2 receptors leads to intrarenal vasodilation and increased RBF.
- ✓ In addition, dopamine-1 receptor stimulation leads to diuresis via actions on the medullary ascending limb of the loop of Henle and brush border of the proximal tubule.
- ✓ Stimulation of β-1 adrenergic receptors occurs at doses of 1 to 3 µg/kg/minute, resulting in increased cardiac output and increased RBF.
- ✓ Because an increase in RBF with resultant diuresis occurs at lower infusion rates, these doses are referred to as “low-dose” or “renal-dose dopamine.”
- ✓ Alpha-adrenergic effects (i.e., vasoconstriction) predominate at doses of 5 to 20 µg/kg/minute.
- ✓ Dopamine may also decrease renal oxygen demand by inhibiting Na-K ATPase and tubular sodium reabsorption.
- ✓ Dopamine at a dose of 2 µg/kg/min was found to have no protective effect against radiocontrast nephrotoxicity in patients with underlying renal disease compared to those treated with saline.
- ✓ Low-dose dopamine resulted in greater diuresis without a change in creatinine clearance, while low-dose dobutamine exhibited a greater improvement in estimated creatinine clearance without an increase in urine output.

- ✓ It is widely assumed that dobutamine in combination with dopamine could improve cardiac index, cause arterial vasodilation, and maximize RBF and natriuresis in oliguric patients with left ventricular dysfunction. However, although urine output may be enhanced, it has not been established whether dopamine prevents ARF or improves outcome in this setting.
- ✓ Dopamine use is not without risks.
- ✓ Adverse effects include tachycardia and arrhythmias, which can occur even at low doses.
- ✓ Its β-adrenergic effects can increase oxygen demand, leading to tissue hypoxia and ischemia.
- ✓ Dopamine is also associated with poor gastric emptying and gastroduodenal motility, aggravating digestive intolerance to enteral feedings; an impairment of respiratory drive, hindering weaning from mechanical ventilation; and suppression of secretion and function of anterior pituitary hormones.
- ✓ Extravasation can occur if dopamine is administered peripherally.

CALCIUM CHANNEL BLOCKERS

- ✓ After ischemic ARF, calcium channel blockers may protect against ARF by inhibiting vasoconstrictive responses of the afferent arterioles and increasing GFR.
- ✓ In addition, calcium antagonists may prevent damage from elevated intracellular calcium after hypoxic injury.
- ✓ These agents have been examined extensively in experimental ARF models, yet few clinical studies confirm their beneficial effects.

ATRIAL NATRIURETIC PEPTIDE

- ✓ Atrial natriuretic peptide (ANP) is a hormone synthesized by the cardiac atria that increases GFR by dilating afferent arterioles while constricting efferent arterioles.
- ✓ The hormone also inhibits tubular reabsorption of sodium and chloride, redistributes renal medullary blood flow, and disrupts tubuloglomerular feedback.
- ✓ Anaritide is a 25-amino acid synthetic form of ANP.

NUTRITIONAL SUPPORT

- ✓ With renal failure, the kidney can no longer regenerate bicarbonate, and metabolic acidosis ensues.
- ✓ This acidosis accelerates proteolysis and branched-chain amino acid oxidation and can be corrected with sodium bicarbonate.
- ✓ ARF in the setting of multiple organ failure is associated with lean body mass catabolism, malnutrition, and a high rate of mortality.
- ✓ Attempting to enhance patient outcomes through nutritional support remains controversial.
- ✓ An early clinical study showed greater survival rates and enhanced recovery of renal function in patients receiving small doses of essential amino acids plus glucose than in patients receiving glucose alone.
- ✓ Subsequent studies suggested that such supplementation might improve renal function and patient outcomes, but these results are not conclusive.
- ✓ Unfortunately, the dietary restrictions needed to manage ARF may offset efforts to optimize nutritional support, and the possible benefits of avoiding short-term dialysis must be weighed against the potential increase in morbidity and mortality caused by impaired nutrition.

- ✓ The need for nutrition support varies according to the patient's nutritional status, degree of hypercatabolism, GFR, clinical condition, and plans for dialysis or ultrafiltration therapy.
- ✓ In the nonhypercatabolic patient with better residual renal function (i.e., GFR >10 mL/min), a mixture of essential and nonessential amino acids or protein may be provided at 0.6 to 0.8 g/kg/day.
- ✓ Amino acid or protein needs may be considerably higher in very ill or severely wasted hypercatabolic patients with ARF who are expected to need dialysis.
- ✓ Generally about 1.2 g amino acids/kg/day is prescribed for patients receiving intermittent hemodialysis, and protein needs may even be higher in patients receiving continuous renal replacement therapy.
- ✓ Parenteral nutrition often is necessary in patients with ARF, but the composition of the solution must be modified in accordance with the loss of renal function.
- ✓ In general, most clinicians agree that patients who are severely ill do better if they are given sufficient caloric intake (25 to 35 kcal/kg/day) to attenuate gluconeogenesis and minimize negative nitrogen balance.
- ✓ This can be provided with parenteral formulations.
- ✓ The biggest limitation of parenteral nutrition in patients with acute renal failure is fluid volume.
- ✓ Also, parenteral nutrition is more expensive than enteral nutrition.
- ✓ Patients on renal replacement therapy will require both enteral and parenteral nutrition to meet the recommended protein requirements.
- ✓ Again, the method of nutritional support in ARF should be determined by individual patient needs and monitored closely.
- ✓ Use of renal replacement therapy can substantially reduce the nutrient composition of nutrition regimens provided in ARF.
- ✓ In patients on continuous renal replacement, measurable amounts of vitamin C, copper, and chromium can be found in the ultrafiltrate.
- ✓ Therefore, supplementation with water-soluble vitamins and selected trace elements may be necessary in this patient population.

RENAL REPLACEMENT THERAPY

- ✓ The early use of dialysis to treat ARF has been associated with increased survival.
- ✓ For the past several decades, intermittent hemodialysis has been the conventional renal replacement therapy for severe ARF.
- ✓ Continuously administered (e.g., venovenous hemofiltration or hemodiafiltration) renal replacement therapies have emerged.
- ✓ The advantages of continuous renal replacement therapy over intermittent hemodialysis include more precise fluid and metabolic control, less hemodynamic instability, better removal of harmful cytokines, and the ability to deliver unlimited nutritional support.
- ✓ The drawbacks to continuous renal replacement therapy include the need for prolonged anticoagulation, and the procedure entails constant sophisticated surveillance.
- ✓ Continuous renal replacement therapy is reserved for critically ill patients with renal failure.
- ✓ In ARF, the role of renal replacement therapy is to prevent complications of ARF and to provide temporary support until the renal insufficiency resolves.

- ✓ The decision to initiate dialysis and the frequency of dialysis should be based on the patient's clinical condition rather than a particular BUN or SCr.
- ✓ There is no consensus on the timing with dialysis intervention in ARF.
- ✓ Absolute indications for dialysis are pericarditis and uremic symptoms, because these can be resolved only by dialysis.
- ✓ Relative indications include volume overload, hyperkalemia, and acidosis.