CHAPTER 45

Acute Renal Failure

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KEY CONCEPTS

1. Acute renal failure (ARF) is a common complication in the hospitalized patient and is associated with a high mortality rate.
2. ARF is predominantly categorized based on the anatomic area of injury or malfunction: (a) prerenal—decreased renal blood flow, (b) intrinsic—a structure within the kidney is damaged, and (c) postrenal—an obstruction is present within the urine collection system.
3. Risk factors for ARF include advanced age, acute infection, preexisting chronic respiratory or cardiovascular disease, dehydration, and chronic kidney disease.
4. ARF lacks a specific and sensitive sign to herald its onset. Hence, a thorough patient history, including medications, recent procedures and illnesses, physical examination, and laboratory assessment of serum and urine are necessary components of an ARF evaluation after an elevated serum creatinine (S_{cr}) is noted.
5. Prevention is key; there are very few therapeutic options for the therapeutic management of established ARF.
6. Supportive management remains the primary approach to prevent or reduce the complications associated with ARF. Supportive therapies include: renal replacement therapies (RRTs), nutritional support, avoidance of nephrotoxins, and blood pressure and fluid management.
7. For those patients with prolonged or severe ARF, RRTs are the cornerstone of support and facilitate an aggressive approach to fluid, electrolyte and waste management.
8. Diuretic resistance is a common phenomenon in the patient with ARF and can be addressed with aggressive sodium restriction, combination diuretic therapy, or a continuous infusion of a loop diuretic.
9. Drug-dosing regimens for ARF patients receiving intermittent hemodialysis (IHD) are predominantly extrapolated from data derived from patients with chronic kidney disease (CKD); however, important pharmacokinetic differences exist in patients with ARF that should be considered.
10. Drug dosing guidelines for ARF patients receiving continuous renal replacement therapies (CRRTs) are poorly characterized and individualized doses may need to be determined by estimating the clearance of medications associated with a high risk of toxicity by the patient and the CRRT procedure.

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The development of acute renal failure (ARF) presents a difficult challenge to the clinician because there are many possible causes and the onset is often asymptomatic. In the ambulatory setting, patients may not notice ARF symptoms for days to weeks. Changes in clinical and laboratory markers of its presence can be subtle and are often overlooked. Despite its often insidious presentation, the consequences of ARF can be serious, especially in hospitalized patients, among whom mortality rates of up to 60% have been reported.[1,2]

Supportive therapy is the focus of management for those with established ARF, as there is no therapy that directly reverses the injury associated with the numerous causes of ARF. Management goals include maintenance of blood pressure, fluid, and electrolyte homeostasis, all of which may be dramatically altered in the presence of ARF. Additional therapies designed to eliminate or minimize the insult that precipitated ARF include discontinuation of the offending drug (i.e., the nephrotoxin), cardiac support of the failing heart, removal of the obstruction from the urinary collection system, corticosteroids to minimize any intrinsic inflammatory process, antibiotic therapy to treat any infection, or other specific maneuvers to limit or reverse the kidney injury. Because of the poor clinical outcomes and lack of specific therapies, the importance of preventing ARF cannot be overemphasized. Individuals at highest risk, such as those with chronic kidney disease (CKD) and the elderly with chronic medical conditions, need to be identified and their exposure to harmful diagnostic or therapeutic procedures or medications minimized.

Renal replacement therapies (RRTs) such as hemodialysis and peritoneal dialysis have been available for decades, but have not resulted in dramatic improvements in the outcomes of patients with ARF. However, newer RRT modalities including an array of continuous renal replacement therapies (CRRTs) appear to offer some benefits, although available resources may limit their use and drug dosing is handicapped by a paucity of data. Careful patient monitoring for response to these therapies and attention to pharmacokinetic alterations make it possible to develop rational drug-dosing regimens for these complex patients. Despite the supportive care that CRRTs offer, development of ARF is frequently a catastrophic event. In this chapter, the epidemiology and multiple etiologies of ARF, as well as the clinical features associated with the most common types of ARF, are presented. Methods to recognize and identify the extent of functional loss are also discussed. Finally preventative strategies and management approaches for those with established ARF are reviewed.

DEFINITION OF ACUTE RENAL FAILURE

ARF is broadly defined as a decrease in glomerular filtration rate (GFR), generally occurring over hours to days, sometimes over weeks,

that is associated with an accumulation of waste products, including urea and creatinine. This relatively abrupt decline in renal function is in contrast to CKD, which is defined by the presence of proteinuria/albuminuria for at least 3 months, in combination with a GFR of <90 mL/min/1.73 m^2.[3] A decrease in urine output is often observed, but is not required for ARF to be present.[4] Compared to a normal urine output of ≥1,200 mL/day, patients with ARF are often categorized as being anuric (urine output <50 mL/day), oliguric (urine output <500 mL/day), or nonoliguric (urine output >500 mL/day).

Currently, there is no universally accepted definition of ARF in clinical practice: in fact, more than 30 definitions for ARF are reported in the medical literature.[5] Many of these definitions incorporate selective aspects of ARF observed in different patient populations. Comparisons between studies that describe incidences, treatment effects, and patient outcomes can thus be difficult, if not impossible to interpret. Although a serum creatinine (S_{cr}) or calculated creatinine clearance (Cl_{cr}) may not provide a reliable characterization of renal function in all ARF situations, clinicians frequently use some combination of the absolute S_{cr} value, change in S_{cr} value over time, and/or urine output as the primary criteria for diagnosing the presence of ARF.[4,6] The commonly used and highly variable definitions for ARF are nonspecific and open to various interpretations. On a patient-by-patient basis, the semantics of the ARF definition are relatively meaningless. However, to move the prevention and treatment of ARF forward, consistent definitions must be employed. Without them, clinicians will be unable to accurately use any data generated because the nonspecific classification of ARF will be an insurmountable barrier to the identification of who was studied, and hence, to whom the data apply. A means to standardize the various aspects of the clinical presentation is necessary to allow integration of the literature observations to bedside management. A new consensus-derived definition and classification system for ARF was recently proposed, and is currently being validated (Fig. 45–1).[7,8] This three-tiered classification uses both GFR and urine output, plus two clinical outcomes that may occur subsequent to an episode of ARF as components of the paradigm. Definitions of risk of dysfunction (R), injury to the kidney (I), and failure of the kidney (F) are outlined. The clinical outcomes of loss of function (L), and end-stage renal disease (E) complete the RIFLE acronym. Thus far, validation studies have confirmed the value of these criteria in predicting hospital mortality, although further assessment is still necessary.[9,10]

EPIDEMIOLOGY

ARF is an uncommon condition in the community-dwelling, generally healthy population, with an annual incidence of approximately 0.02% (Table 45–1).[11] In individuals with preexisting CKD, however, the incidence may be as high as 13%. In nonhospitalized patients, dehydration, exposure to selected pharmacologic agents such as contrast media, and the presence of heart failure are associated with an increased risk of ARF. Additionally, trauma, rhabdomyolysis, vessel thrombosis, and drugs are common culprits in the development of ARF.[11] The pharmacologic agents commonly associated with ARF, including contrast media, chemotherapeutic agents, nonsteroidal antiinflammatory drugs (NSAIDs), angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and antiviral medications are discussed in detail in Chap. 49. [11,12]

1 The hospitalized individual is at high risk of developing ARF; the reported incidence is 7%.[13] The incidence of ARF is markedly higher in critically ill patients, ranging from 6% to 23%.[6] The high mortality rate related to ARF, which is reported to range from 35% to 80%, is a significant clinical concern that has been relatively unresponsive to therapeutic intervention over the last four decades. Although the relative contribution of ARF to mortality rates of the underlying disease states is unclear given that current illness and ARF cannot be reliably quantified, it is certain that the presence of ARF will independently contribute significantly to overall mortality.[6] For survivors of ARF, subsequent morbidity or development of some degree of CKD is also a consideration. Although 90% of individuals recover enough renal function to live normal lives, approximately half of these are left with subclinical deficits. Five percent will not regain

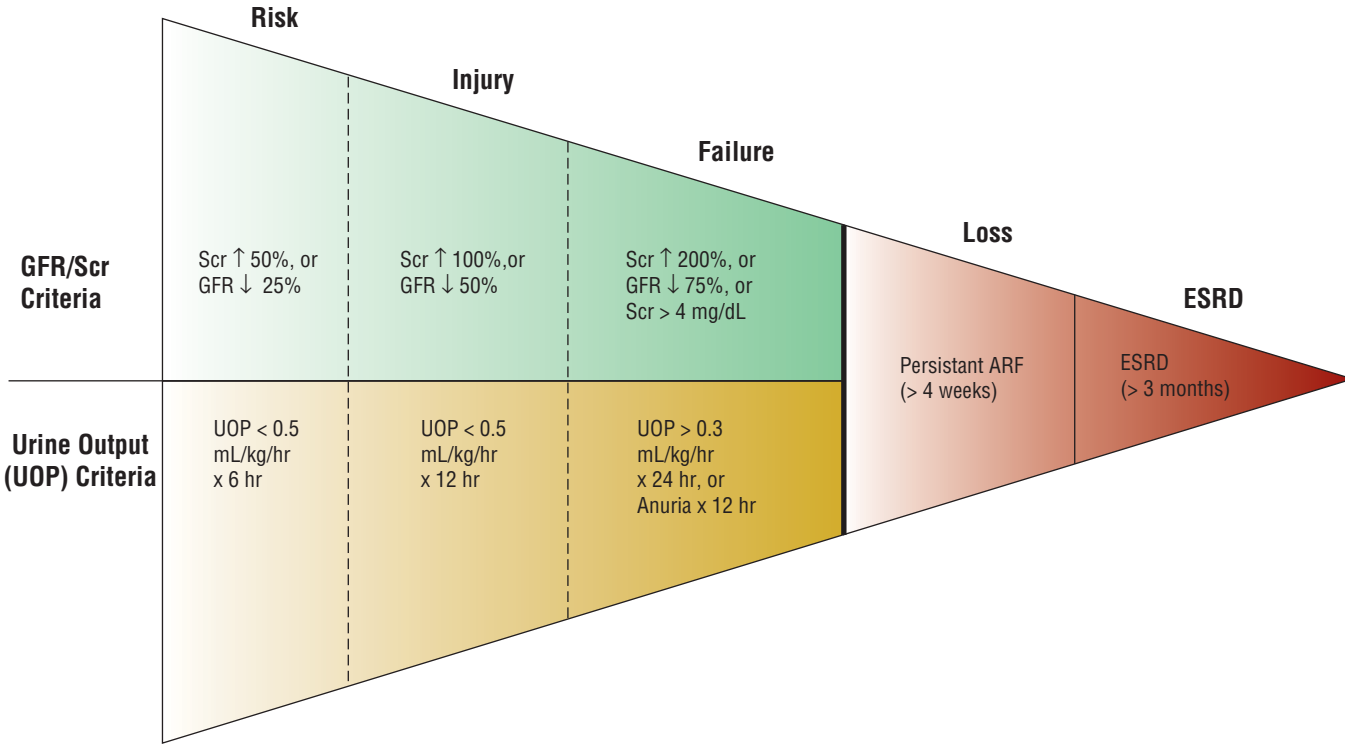

FIGURE 45-1. RIFLE classification for acute renal failure (ARF). (ESRD, end-stage renal disease; GFR, glomerular filtration rate; S_{cr}, serum creatinine). *(Reprinted and adapted from Crit Care Clin, Vol. 21, Bellomo R. Defining, quantifying, and classifying acute renal failure, pages 223-237, Copyright © 2005, with permission from Elsevier.)*

TABLE 45-1 Incidence and Outcomes of Acute Renal Failure Relative to Where It Occurs

	Community-Acquired	Hospital-Acquired	ICU-Acquired
Incidence	Low (<1%)	Moderate (2%–5%)	High (6%–23%)
Cause	Single	Single or multiple	Multifactorial
Overall survival rate	70%–95%	30%–50%	10%–30%
Worsened outcome if:	RRT required Poor preadmission health Other failed organ systems	RRT required Poor preadmission health Ischemic ARF cause Other failed organ systems	Intrinsic renal disease Ischemic ARF cause Septic RRT required Poor preadmission health Other failed organ systems
Better outcome if:	Nonoliguric	Nonoliguric Nephrotoxic cause	Prerenal cause Postrenal cause Nonoliguric Nephrotoxic cause Hyperglycemia prevented

ARF, acute renal failure; RRT, renal replacement therapy.

sufficient renal function to live independently and thus require long-term peritoneal or hemodialysis or transplantation. An additional 5% will suffer from a progressive deterioration in kidney function after initial recovery, likely as a consequence of hyperfiltration and sclerosis of the remaining glomeruli.[14]

ETIOLOGY

2 The etiology of ARF can be divided into broad categories based on the anatomic location of the injury associated with the precipitating factor(s). The management of patients presenting with this disorder is largely predicated on identification of the specific etiology responsible for the patient's current acute kidney injury (Table 45–2). Traditionally, the causes of ARF have been categorized as (a) prerenal, which results from decreased renal perfusion in the setting of undamaged parenchymal tissue, (b) intrinsic, the result of structural damage to the kidney, most commonly the tubule from a ischemic or toxic insult, and (c) postrenal, caused by obstruction of urine flow downstream from the kidney (Fig. 45–2).

3 The most common cause of hospital-acquired ARF is prerenal ischemia as the result of reduced renal perfusion secondary to sepsis, reduced cardiac output, and/or surgery. Drug-induced ARF may account for 18% to 33% of in-hospital occurrences. Other risk factors for developing ARF while hospitalized include advanced age (>60 years of age), male gender, acute infection, and preexisting chronic diseases of the respiratory or cardiovascular systems.[6]

PATHOPHYSIOLOGY

PSEUDORENAL AND FUNCTIONAL ACUTE RENAL FAILURE

In selected situations their can be a rise in either the blood urea nitrogen (BUN) or the S_{cr}, suggesting presence of renal dysfunction when in fact GFR is not diminished. This could be the result of cross-reactivity with the assay used to measure the BUN or S_{cr}, or selective inhibition of the secretion of creatinine into the proximal tubular lumen (see Chap. 44). The initiation or discontinuation of such agents should be considered in the assessment for acute changes in renal function, and should be looked for as part of the work up in any patient who is suspected to have ARF.

In functional ARF, a decline in GFR secondary to a reduced glomerular hydrostatic pressure, which is the driving force for the formation of ultrafiltrate, can occur without damage to the kidney itself. The decline in glomerular hydrostatic pressure may be a direct consequence of changes in glomerular afferent (vasoconstriction) and efferent (vasodilation) arteriolar circumference. These clinical conditions are most commonly seen in individuals who have reduced effective blood volume (e.g., heart failure, cirrhosis, severe pulmonary disease, or hypoalbuminemia) or renovascular disease (e.g., renal artery stenosis) and who cannot compensate for changes in afferent or efferent arteriolar tone. A decrease in efferent arteriolar resistance as the result of initiation of angiotensin-converting enzyme inhibitor or angiotensin receptor blocker therapy is a common cause of this syndrome. The hepatorenal syndrome is also included in this classification because the kidney itself may be damaged, and there is intense afferent arteriolar vasoconstriction leading to a decline in glomerular hydrostatic pressure. In all the above conditions, the urinalysis is no different from its baseline state and the urinary indices suggest prerenal azotemia.

Functional ARF is very common in individuals with heart failure who receive an angiotensin converting enzyme inhibitor or an angiotensin receptor blocker in an attempt to improve their left ventricular function. Because the decline in efferent arteriolar resistance resulting from the inhibition of angiotensin II occurs within days, if the dose of the angiotensin-converting enzyme inhibitor is increased too rapidly, a decline in GFR with a concomitant rise in the serum creatinine will be noticeable. If the increase in the serum creatinine is mild to moderate (an increase of less than 30% from baseline) the medication can be continued.

PRERENAL ACUTE RENAL FAILURE

Prerenal ARF results from hypoperfusion of the renal parenchyma, with or without systemic arterial hypotension. Renal hypoperfusion with systemic arterial hypotension may be caused by a decline in intravascular or effective blood volume that can occur in those with acute blood loss (hemorrhage), dehydration, hypoalbuminemia, or diuretic therapy. Renal hypoperfusion without systemic hypotension is most commonly associated with bilateral renal artery occlusion, or unilateral occlusion in a patient with a single functioning kidney. The initial physiologic responses to a reduction in effective blood volume by the body includes activation of the sympathetic nervous and the renin–angiotensin–aldosterone systems, and release of antidiuretic hormone if hypotension is present. These responses work together to directly maintain blood pressure via vasoconstriction and stimulation of thirst to increase fluid intake and the promotion of sodium and water retention. Additionally, GFR may be maintained by afferent arteriole dilation and efferent arteriole constriction. In concert, these homeostatic mechanisms are often able to maintain arterial pressure and renal perfusion, potentially averting the progression to ARF.[15] If, however, the decreased renal perfusion is severe or prolonged, these compensatory mechanisms may be overwhelmed and ARF will then

TABLE 45-2 Classification of Acute Renal Failure

Category	Abnormality Causing Acute Renal Failure	Possible Causes
Prerenal	Intravascular volume depletion resulting in arterial hypotension	Dehydration
		Inadequate fluid intake
		Excessive vomiting, diarrhea or gastric suctioning
		Increased insensible losses (e.g., fever, burns)
		Diabetes insipidus
		High serum glucose (glucosuria)
		Overdiuresis
		Hemorrhage
		Decreased cardiac output
		Hypoalbuminemia
		Liver disease
		Nephrotic syndrome
	Arterial hypotension (regard less of volume status)	Anaphylaxis
		Sepsis
		Excessive antihypertensive use
	Decreased cardiac output	Heart failure
		Sepsis
		Pulmonary hypertension
		Aortic stenosis (and other valvular abnormalities)
		Anesthetics
	Isolated renal hypoperfusion	Bilateral renal artery stenosis (unilateral renal artery stenosis in solitary kidney)
		Emboli
		Cholesterol
		Thrombotic
		Medications
		Cyclosporine
		Angiotensin-converting enzyme inhibitors
		Nonsteroidal antiinflammatory drugs
		Radiocontrast media
		Hypercalcemia
		Hepatorenal syndrome
Intrinsic	Vascular damage	Vasculitis
		Polyarteritis nodosa
		Hemolytic uremic syndrome-thrombotic thrombocytopenic purpura
		Emboli
		Atherosclerotic
		Thrombotic
		Accelerated hypertension
	Glomerular damage	Systemic lupus erythematosus
		Poststreptococcal glomerulonephritis
		Antiglomerular basement membrane disease
	Acute tubular necrosis	Ischemic
		Hypotension
		Vasoconstriction
		Exogenous toxins
		Contrast dye
		Heavy metals
		Drugs (amphotericin B, aminoglycosides, etc.)
		Endogenous toxins
		Myoglobin
		Hemoglobin
	Acute interstitial nephritis	Drugs
		Penicillins
		Ciprofloxacin
		Sulfonamides
		Infection
		Viral
		Bacterial
Postrenal	Bladder outlet obstruction	Prostatic hypertrophy, infection, cancer
		Improperly placed bladder catheter
		Anticholinergic medication
	Ureteral	Cancer with abdominal mass
		Retroperitoneal fibrosis
		Nephrolithiasis
	Renal pelvis or tubules	Nephrolithiasis
		Oxalate
		Indinavir
		Sulfonamides
		Acyclovir
		Uric acid

be clinically evident. If renal artery stenosis is present, narrowing bilaterally (both kidneys) or unilaterally (one functional kidney) of the artery responsible for blood flow to the kidney can lead to reduced renal function. The most common cause is atherosclerosis, with severe abrupt occlusion sometimes occurring as the result of an embolism.[16]

INTRINSIC ACUTE RENAL FAILURE

Acute intrinsic renal failure results from damage to the kidney itself. Conceptually, acute intrinsic renal failure can be categorized on the basis of the structures within the kidney that are injured: the renal vasculature, glomeruli, tubules, and the interstitium. Many diverse mechanisms have been associated with the development of intrinsic ARF, many of which are categorized in Table 45–2.

Renal Vasculature Damage

Occlusion of the larger renal vessels resulting in ARF is not common, but can occur if large atheroemboli or thromboemboli occlude the bilateral renal arteries, or one vessel of the patient with a single kidney. Atheroemboli most commonly develop during vascular procedures that cause atheroma dislodgement, such as angioplasty or aortic manipulations. Thromboemboli may arise from dislodgement of a mural thrombus in the left ventricle of a patient with severe heart failure, or from the atria of a patient with atrial fibrillation. Renal artery thrombosis may occur in a similar fashion to coronary thrombosis, in which a thrombus forms in conjunction with an atherosclerotic plaque.

Although smaller vessels can also be obstructed by atheroemboli or thromboemboli, the damage is limited to the vessels involved, and the development of significant ARF is unlikely. However, these small vessels are susceptible to inflammatory processes that lead to microvascular damage and vessel dysfunction when the renal capillaries are affected. Neutrophils invade the vessel wall, causing damage that can include thrombus formation, tissue infarction, and collagen deposition within the vessel structure. Diffuse renal vasculitis can be mild or severe, with severe forms promoting concomitant ischemic acute tubular necrosis (ATN). The S_{cr} is usually elevated as the lesions are diffuse, and thus the area of damage is large. Accelerated hypertension that is not treated may also compromise renal microvascular blood flow, and thus cause diffuse renal capillary damage.

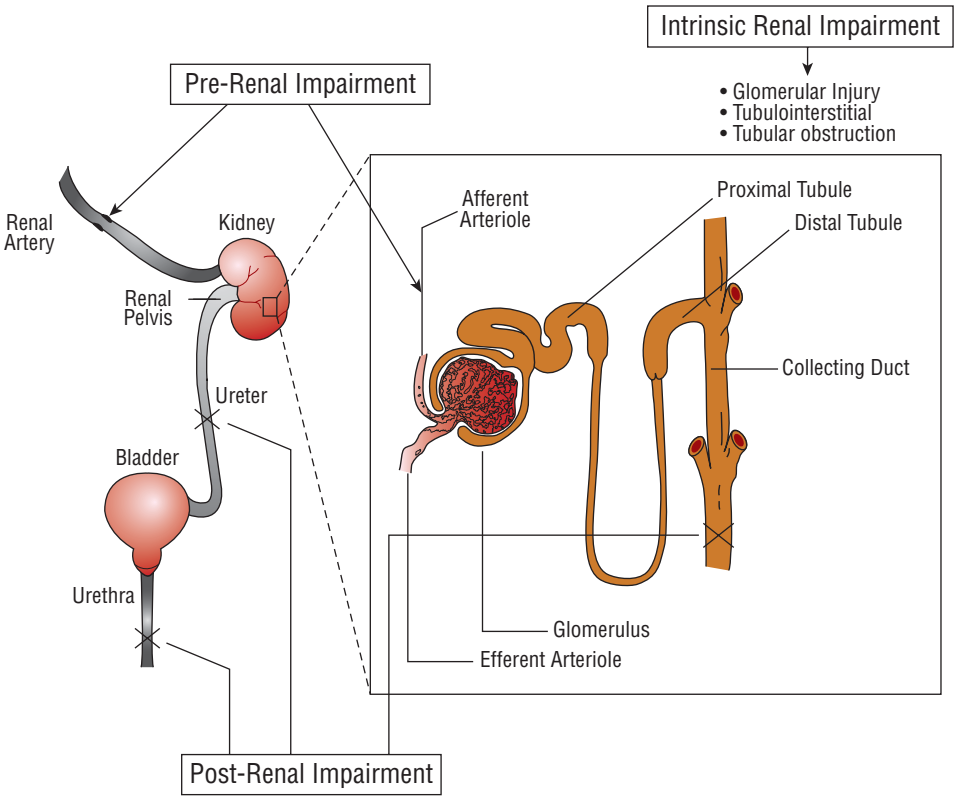

FIGURE 45-2. Physiologic classification of ARF. Blood flows through the afferent arteriole, to the glomerulus and exits through the efferent arteriole. The formation of glomerular ultrafiltrate is dependent on the surface area of the capillaries within the glomerular region, their permeability, and the net hydrostatic pressure across the capillary wall. A decrease in blood flow and renal perfusion can lead to a prerenal reduction in renal function. Under conditions in which renal blood flow is diminished, the kidney maintains glomerular ultrafiltration by vasodilating the afferent and vasoconstricting the efferent arterioles. Medications that may interfere with these processes might result in an abrupt decline in glomerular filtration. Damage to the glomerular or tubular regions leads to intrinsic ARF. Obstruction of urine flow once in the collecting tubule, ureter, bladder, or urethra is termed postrenal failure.

Glomerular Damage

Only 5% of the cases of intrinsic ARF are of glomerular origin. The glomerulus is one of two capillary beds in the kidney, and serves to filter fluid and solute into the tubules while retaining proteins and other large blood components in the intravascular space. Because it's a capillary system, glomerular damage can occur by the same mechanisms described for the renal vasculature, and one additional mechanism, that is, severe inflammatory processes specific to the glomerulus. The pathophysiology and specific therapeutic approaches used to combat the inflammatory processes are described in detail in Chap. 50.

Tubule Damage

Approximately 85% of all cases of intrinsic ARF are caused by ATN, of which 50% are a result of renal ischemia, often arising from an extended prerenal state. The remaining 35% are the result of exposure to direct tubule toxins, which can be endogenous (myoglobin, hemoglobin, or uric acid) or exogenous (contrast agents, heavy metals, or aminoglycoside antibiotics). The tubules located within the medulla of the kidney are particularly at risk from ischemic injury, as this portion of the kidney is metabolically active and thus has high oxygen requirements, yet even in the best of situations, receives relatively low oxygen delivery (as compared to the cortex). Thus, ischemic conditions caused by severe hypotension or exposure to vasoconstrictive drugs preferentially affect the tubules more than any other portion of the kidney.

The clinical evolution of ATN is characterized by the initial injury causing tubule epithelial cell necrosis or apoptosis, followed by an extension phase with continued hypoxia and an inflammatory response involving the nearby interstitium.[17] The onset of ATN can occur over days to weeks, and rarely longer than that depending on the factors responsible for the damage to the tubular epithelial cells.[18] Once tubular cells die, they slough off into the tubular lumen. The debris causes increased tubular pressure and reduces glomerular filtration.[19] Additionally, the loss of epithelial cells leaves only the basement membrane between the filtrate and the interstitium, which results in dysregulation of fluid and electrolyte transfer across the tubular epithelium. Regardless of the etiology, tubular injury leads to a loss in the ability to concentrate urine, to defective distal sodium reabsorption, and, ultimately, to a reduction in the GFR.[20] Continued kidney hypoxia or toxin exposure after the original insult kills more cells, and propagates the inflammatory response and can extend the injury and delay the recovery process. With prolonged ischemia, the tubular epithelial cells in the corticomedullary junction are damaged and die. When the toxin or ischemia is removed, a maintenance phase ensues (typically 2 to 3 weeks), followed by a recovery phase (2 to 3 weeks) during which new tubule cells are regenerated. The recovery phase is associated with a notable diuresis, which requires attention to fluid balance to ensure that a secondary prerenal injury does not occur. However, if the ischemia or injury is extremely severe or prolonged, cortical necrosis may occur, preventing any tubule cell regrowth in the affected areas.

Interstitial Damage

The interstitium of the kidney is rarely the primary cause of end-stage renal disease (ESRD), but it can become severely inflamed and lead to ARF. Acute interstitial nephritis is most commonly caused by medications (see Chap. 49), or bacterial or viral infections.[21] Up to 30% of cases have no identifiable cause.[22] Whatever the inciting event, interstitial nephritis is characterized by lesions comprised of monocytes, macrophages, B cells, or T cells, clearly identifying an immunologic response as the injurious process affecting the interstitium.[23] Because of the interwoven nature of the interstitium and the tubules, the widespread inflammation and edema affect the function of the tubules, and may cause fibrosis if the administration of the nephrotoxin is not discontinued and inflammation quickly controlled.[24]

POSTRENAL ACUTE RENAL FAILURE

Postrenal ARF may develop as the result of obstruction at any level within the urinary collection system from the renal tubule to urethra (see Table 45–2). However, if the obstructing process is above the bladder, it must involve both kidneys (one kidney in a patient with a single functioning kidney) to cause significant ARF. Bladder outlet

obstruction, the most common cause of obstructive uropathy, is often caused by a prostatic process (hypertrophy, cancer or infection) causing a physical impingement on the urethra and thereby preventing the passage of urine. It may also be the result of an improperly placed urinary catheter. Neurogenic bladder or anticholinergic medications may also prevent bladder emptying and cause ARF. The blockage may occur at the ureter level, secondary to nephrolithiasis, blood clots, a sloughed renal papillae, or physical compression by an abdominal process such as retroperitoneal fibrosis, cancer, or an abscess. Crystal deposition within the tubules from oxalate and some medications severe enough to cause ARF is uncommon, but is possible in patients with severe volume contraction and in those receiving large doses of a drug with relatively low urine solubility (see Chap. 49). In these cases, patients have insufficient urine volume to prevent crystal precipitation in the urine.[25] Extremely elevated uric acid concentrations from chemotherapy-induced tumor lysis syndrome should be minimized by the initiation of an aggressive fluid regimen and pharmacologic preventative therapies in at-risk patients. Wherever the location of the obstruction, urine will accumulate in the renal structures above the obstruction and cause increased pressure upstream. The ureters, renal pelvis, and calyces all expand, and the net result is a decline in GFR. If renal vasoconstriction ensues, a further decrement in GFR will be observed.

CLINICAL PRESENTATION

4 The initiating sign or symptom prompting the eventual diagnosis of ARF is highly variable, depending on the etiology. It may be an elevated S_{cr}, decreased urine output, blood in the urine, pain during voiding, or severe abdominal or flank pain. The first step is to determine if the renal complication is acute, chronic, or the result of an acute change in a patient with known CKD. BUN, potassium, phosphorous, and, potentially, magnesium concentrations in serum will likely become elevated and should be promptly evaluated. For those presenting in the outpatient environment it may be difficult to determine when the onset was as the initial presentation of ARF may have been asymptomatic. The onset of ARF may, in fact, trigger independently symptoms of a concurrent medical condition or excessive drug response from a renally eliminated agent.

PATIENT ASSESSMENT

A past medical history for renal disease-related chronic conditions, such as poorly controlled hypertension or diabetes mellitus, previous laboratory data documenting the presence of proteinuria or an elevated S_{cr}, and the finding of bilateral small kidneys on renal ultrasonography suggests the presence of CKD. A thorough medical history and a review of past medical records, if available, that includes recent procedures and illnesses, should be done as soon as possible. The medication and recent procedure history may suggest causes for acute interstitial nephritis or other nephrotoxic effects. An exhaustive review of their recent prescription, as well as nonprescription, complementary, and alternative medications, should be completed. Special attention should be focused on diuretics, NSAIDs, antihypertensives, recent contrast dye exposure and any other recent additions or changes in the patient's medications. Patients may have noticed an acute change in their voiding habits with an increase in urinary frequency or nocturia, both suggesting a urinary concentrating defect. A decrease in the force of the urinary stream may suggest an obstruction. The presence of cola-colored urine also often stimulates people to seek medical care and its presence is indicative of blood in the urine, a finding commonly associated with acute glomerulonephritis. The onset of flank pain is suggestive of a urinary stone; however, if bilateral, it may suggest swelling of the kidneys secondary to acute glomerulonephritis or acute interstitial nephritis. Complaints of severe headaches may suggest the presence of severe hypertension as a result of ARF. A recent increase in the patient's weight or complaints of tight-fitting rings secondary to salt and water retention also may be helpful in defining the time of onset of renal failure.

Patients who develop renal insufficiency while hospitalized usually have an acute initiating event that can be identified from a review of the laboratory data, urine output record, and the medication administration and procedure records. In addition to its prognostic significance, changes in urine output may be helpful in characterizing the cause of the patient's ARF. Acute anuria is typically caused by either complete urinary obstruction or a catastrophic event (e.g., shock or acute cortical necrosis). Oliguria (<500 mL/day of urine output), which often develops over several days, suggests prerenal azotemia, whereas nonoliguric (>500 mL/day of urine output) renal failure usually results from acute intrinsic renal failure or incomplete urinary obstruction.

CLINICAL PRESENTATION OF ACUTE RENAL FAILURE

General

- Community-dwelling patients often are not in acute distress.
- Hospitalized patients may develop ARF after either a notable reduction in blood pressure or intravascular volume, significant insult to the kidney, or sudden obstruction after catheterization. Generally, an acute reduction in urine output coinciding with a rise in BUN and S_{cr} is observed.

Symptoms

- *Outpatient:* Change in urinary habits, sudden weight gain, or flank pain.
- *Inpatient:* Typically, ARF is recognized by clinicians before the patient, who may not experience any obvious symptoms.

Signs

- Patient may have edema; urine may be colored or foamy; orthostatic hypotension in volume-depleted patients, hypertension in the fluid-overloaded patient or in the presence of acute or chronic hypertensive kidney disease.

Laboratory Tests

- Elevations in the serum potassium, BUN, creatinine, and phosphorous, or a reduction in calcium and the pH (acidosis), may be present. The clinical findings are different based on the cause of the ARF.
- An increased serum white blood cell count may be present in those with sepsis-associated ARF, and eosinophilia suggests acute interstitial nephritis.
- Urine microscopy can reveal cells, casts, or crystals that help distinguish among the possible etiologies and/or severities of ARF.
- An elevated urine specific gravity suggests prerenal ARF, as the tubules are concentrating the urine. Urine chemistry also indicates the presence of protein, which suggests glomerular injury, and blood, which can result from damage to virtually any kidney structure.

Other Diagnostic Tests

- Renal ultrasonography or cystoscopy may be needed to rule out obstruction; renal biopsy is rarely used, and is reserved for difficult diagnoses.

A physical examination, including assessment of the patient's volume and hemodynamic status, is an important step in evaluating individuals with ARF. Table 45–3 lists common physical findings in patients with ARF. The physical exam should be thorough, as clues regarding the etiology of the patient's ARF can be evident from the patient's head (eye exam) to toe (evidence of dependent edema).

TABLE 45-3 Physical Examination Findings in Acute Renal Failure

Physical Examination Finding	Possible Diagnosis	Category of Acute Renal Failure
Vital signs		
Orthostatic hypotension	Volume depletion	Prerenal
Febrile	Sepsis	Intrinsic–tubule necrosis
Skin		
Tenting	Volume depletion	Prerenal
Rash	Hypersensitivity reaction	Intrinsic–interstitial nephritis
Petechiae	Thrombotic thrombocytopenic purpura Hemolytic uremic syndrome	Intrinsic–vasculitis
	Sepsis	Intrinsic–tubule necrosis
Splinter hemorrhages Janeway lesions Osler nodes	Endocarditis	Intrinsic–glomerulonephritis
Edema	Total-body volume overload	Intrinsic or prerenal because of heart failure Other types of prerenal unlikely
HEENT		
Hollenhorst plaque	Cholesterol emboli	Intrinsic–vascular
Roth spots	Endocarditis	Intrinsic–glomerulonephritis
Elevated jugular venous pressure	Heart failure Pulmonary hypertension	Prerenal
Heart		
S_3 heart sound	Heart failure	Prerenal
New or increased murmur	Endocarditis	Intrinsic–glomerulonephritis
Lung		
Rales	Heart failure	Prerenal
Abdomen		
Renal artery bruit	Renal artery stenosis	Prerenal
Ascites	Liver failure or right-heart failure	Prerenal Hepatorenal syndrome
Bladder distension	Bladder outlet obstruction	Postrenal
Genitourinary		
Prostatic enlargement	Prostatic hypertrophy or cancer	Postrenal
Gynecologic		
Abnormal bimanual examination	Possible bilateral ureteral obstruction or cervical cancer	Postrenal

HEENT, head, eyes, ears, nose, and throat.

Observations will either support or refute the cause as prerenal, intrinsic or postrenal. In those with prerenal ARF, low effective arterial blood volume may be evidenced by the presence of postural hypotension and decreased jugular venous pressure (JVP). Fluid overload as a consequence of ATN on the other hand is often reflected by rales in the lower lung fields and/or the presence of peripheral edema. If ascites or pulmonary edema is present, the effective arterial blood volume perceived by the kidneys may be low and thus suggest the diagnosis of functional ARF.

When the interstitium of the kidney is damaged (e.g., acute allergic interstitial nephritis), the concentrating gradient within the kidney may be attenuated and ammonia handling disrupted, resulting in a very dilute-appearing urine. Consequently, patients presenting with acute interstitial nephritis frequently are unable to concentrate the urinary solutes. Blood pressure should be evaluated for elevations that may accompany intrinsic renal damage. Any recent history of an infection may suggest postinfective glomerulonephritis. Although uncommon, thromboembolism occurring in the renal artery or vein can potentially result in ischemic damage, and should be a component of the physical assessment. Physical examination may detect possible postrenal obstruction, such as the presence of a urinary catheter, an enlarged prostate in males or cervical/uterine abnormalities in females. Renal artery stenosis can be identified via Doppler ultrasound by measuring changes in flow distal to the narrowing if visible, or by computed tomography (CT) angiography, which can describe the anatomy of the renal vessels.

TABLE 45-4 Diagnostic Parameters for Differentiating Causes of Acute Renal Failure

Laboratory Test	Prerenal Azotemia	Acute Intrinsic Renal Failure	Postrenal Obstruction
Urine sediment	Normal	Casts, cellular debris	Cellular debris
Urinary RBC	None	2–4+	Variable
Urinary WBC	None	2–4+	1+
Urine sodium	<20	>40	>40
FE_{Na} (%)	<1	>2	Variable
Urine/serum osmolality	>1.5	<1.3	<1.5
Urine/S_{cr}	>40:1	<20:1	<20:1
BUN/S_{cr}	>20	~15	~15

ARF, acute renal failure; BUN, blood urea nitrogen; FE_{Na}, fractional excretion of sodium; S_{cr}, serum creatinine; RBC, red blood cell; WBC, white blood cell.
Common laboratory tests are used to classify the cause of ARF. Functional ARF, which is not included in this table, would have laboratory values similar to those seen in prerenal azotemia. However, the urine osmolality-to-plasma osmolality ratios may not exceed 1.5, depending on the circulating levels of antidiuretic hormone. The laboratory results listed under acute intrinsic renal failure are those seen in acute tubular necrosis, the most common cause of acute intrinsic renal failure.

LABORATORY TESTS AND INTERPRETATION

The commonly available laboratory tests used to evaluate the patient with renal insufficiency are described in Chap. 44, and those of particular value in the assessment of renal function in patients with ARF are highlighted in Table 45–4. There is currently no consensus on the degree and time frame of changes in S_{cr} values that clearly defines the presence of ARF. The difficulty of using S_{cr} as a diagnostic laboratory test for patients with ARF is its lack of sensitivity to rapid changes in GFR. An abrupt cessation in glomerular filtration will not yield an immediate measurable change in S_{cr}. The reasons for this are: creatinine generation and accumulation is relatively slow, there is a lag time between test and clinical event, lab tests may not be very sensitive to small changes in GFR, and fluid retention that commonly accompanies ARF dilutes the retained creatinine.[26] Additionally, when decreased filtration of creatinine occurs, functional tubules can increase the secretion of creatinine into the urine, further complicating the interpretation of S_{cr}.

An example of this phenomenon is illustrated by an acute renal artery thrombus that results in abrupt cessation of GFR in one kidney as a consequence of the complete obstruction of blood flow to that kidney (Fig. 45–3). Although 5 minutes following the event GFR is decreased 50% (assuming the other kidney is functioning and unaffected), the serum creatinine remains unchanged. Assuming a standard daily creatinine production of approximately 20 mg/kg of lean body weight, one can expect approximately 1.4 g of creatinine production in a 24-hour period in a 70-kg individual. In pharmacokinetic terms, daily creatinine production is analogous to a continuous infusion, and GFR determines the elimination rate of creatinine. In the patient with normal renal function (GFR of 120 mL/min), the half-life of creatinine is 3.5 hours with 95% of steady state achieved in approximately 14 hours. If GFR declines to 60, 30, or 12 mL/min, the half-life of creatinine increases, resulting in prolongation of the time to reach 95% of steady state, specifically taking 1, 2, and 4 days, respectively.[27]

Other biomarkers for acute renal injury and failure are being explored. One such marker, serum cystatin C (see Chap. 44) has been explored as a more sensitive and rapid means to detect renal dysfunction and injury.[28] Although an elevation in serum creatinine or

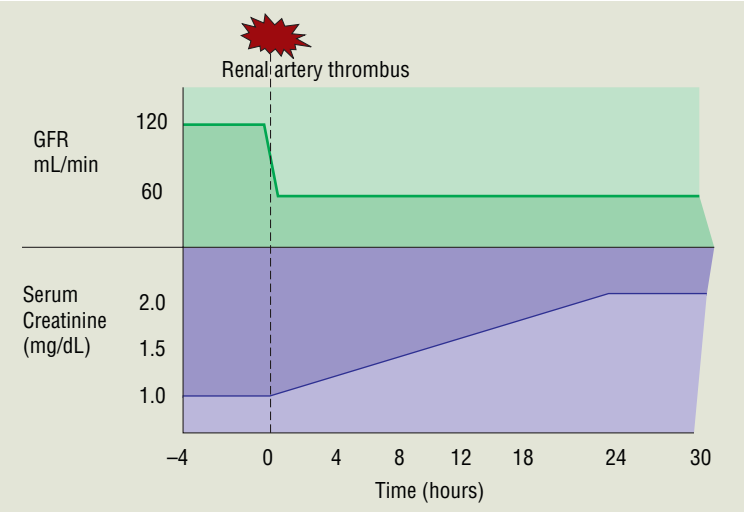

FIGURE 45-3. Glomerular filtration rate (GFR; mL/min) and serum creatinine (S_{cr}; g/dL) versus time following acute renal injury. Prior to time 0, a GFR of 120 mL/min and a S_{cr} of 1.0 g/dL exist. At time 0, an abrupt renal artery thrombus forms, depriving one kidney of renal blood flow. Composite GFR immediately declines by 50% to approximately 60 mL/min. However, S_{cr} does not increase immediately, as it is dependent on creatinine production and attainment of steady-state serum concentrations.

cystatin C may be clearly indicative of a reduction in renal function, these are not quantitative indices that allow one to ascertain the degree of remaining function the patient has. Although several methods, such as the Cockcroft-Gault or one of the Modification of Diet in Renal Disease equations (see Table 44–4), have been extensively used to estimate GFR in patients with CKD, they are not applicable for ARF patients with changing S_{cr} values because by the nature of the condition, renal function is unstable. In ARF, these equations can overestimate GFR when the ARF is worsening, and underestimate it when the ARF is resolving. To avoid missing changes in renal function when relying on equations to predict renal function, consider looking at the sequence of S_{cr} values to determine if renal function is potentially improving (values declining) or worsening (values rising). The most recent S_{cr} value reflects the time-averaged kidney function over the preceding time period. Assessment of urine output can assist in verifying observed serum laboratory values, as well as providing an up-to-the-moment means of identifying any changes in the kidney function. While dependent on several factors such as hydration status and medications, urine output measured over a finite period of time (e.g., 4 hours) is a useful short-term assessment of kidney function. An abrupt decline or increase compared to previous values is highly suggestive of a change in functional status. Because of the shortcomings associated with serum creatinine, urine output is an extremely useful parameter in the assessment of the patient with ARF. Anuria, defined as <50 mL/day of urine, suggests complete kidney failure. Conversely, oliguria (<17 mL/h urine output) certainly indicates kidney damage; however, some function is present. In the setting of ARF, any urine production >17 mL/h indicates the presence of nonoliguric ARF. Despite reasonable urine output, the quality of the urine being produced is not reliably composed of the expected waste products and solutes. Damaged tubules may allow substantial urine to be produced; however, the electrolyte, protein, and acid–base functions of the kidney may be severely compromised. For these reasons, urine output alone is an unreliable marker of kidney function.

Instead of using fixed numbers to determine renal function, changes in the value, even if it remains within the normal range, may indicate marked impairment of renal function. For example, patients with reduced creatinine production, such as those with low muscle mass either because of being bedridden for long periods of time or a concurrent emaciated state, may have very low baseline S_{cr} values (<0.6 mg/dL) and thus the presence of a gradual S_{cr} rise to normal values (0.8 to 1.2 mg/dL) may actually indicate reduced GFR. When coupled with a decline in urine output, this might suggest the presence of ARF. However, in the presence of improved nutrition and an expanding muscle mass, it may be a true representation of the person's current renal status. In contrast, a high S_{cr} value may be present if drawn prior to removal of a postrenal obstruction, such as a nonfunctional Foley catheter, with liters of urine now being voided over a relatively short period of time (hours). S_{cr} and BUN are extensively removed during acute hemodialysis treatments, so when assessing any change in these parameters in the ARF patient, one must pay close attention to when the lab specimens were collected relative to the dialysis procedure.

Several mathematical approaches to estimate GFR in patients with unstable S_{cr} that incorporate the principles of creatinine accumulation and elimination have been proposed[29–31] and are discussed in detail in Chap. 44. These methods have not been extensively validated in the setting of acute alterations in renal function and their value for adjusting medication dosing is questionable. Additionally, these equations are complex, rendering bedside implementation difficult and highly likely to be complicated by calculation errors.

Another approach to measuring renal function when S_{cr} values alone are not reflective of function is to directly measure urine Cl_{cr} over a short period of time, such as 4 to 12 hours.[32] Although potentially precise and fairly simple to do, accuracy is questionable because the urine output is generally low and if the collection is incomplete, the lost urine can have a dramatic impact on the clearance determination.

To facilitate its diagnosis and management, ARF can be classified into several broad categories based on precipitating factors (see Table 45–2). Traditionally this includes prerenal (resulting from decreased renal perfusion), acute intrinsic (resulting from structural damage to the kidney), and postrenal failure (obstruction of urine from removal). A fourth category, functional acute renal failure, is characterized by hemodynamic changes at the glomerulus independent of decreased perfusion or structural damage. Identifying the cause of ARF, which strongly influences potential outcomes and therapies, is of paramount importance.

Selected blood tests in addition to BUN and S_{cr} can be quite valuable in differentiating the cause of ARF and also contribute to optimal patient management. For example, infectious causes of ARF can be assessed using a complete blood cell count with differential. Serum electrolyte values are likely to be abnormal because of the acute decline of the kidney's ability to regulate electrolyte excretion, and particular attention should be paid to serum potassium and phosphorus values, which can be markedly elevated and cause life-threatening complications.

In individuals with normal renal function, the ratio between the BUN and S_{cr} is usually less than 15:1. In the presence of prerenal ARF, reabsorption of BUN exceeds that of creatinine and thus one often sees a ratio greater than 20:1. Given the limited usefulness of solely using S_{cr} or BUN concentrations to differentiate the etiology of ARF, urinary electrolytes and osmolality should be determined, and both a micro-

TABLE 45-5 Urine Analysis Findings as a Guide to the Etiology of Acute Renal Failure

Presence of	Suggestive of
Leukocyte esterase	Pyelonephritis
Nitrite	Pyelonephritis
Protein	
Mild	Tubular damage
Moderate	Glomerulonephritis, pyelonephritis, tubular damage
Large	Lupus nephritis
Hemoglobin	Glomerulonephritis, pyelonephritis, renal infarction, papillary necrosis, renal tumors, kidney stones, tubular necrosis from rhabdomyolysis
Specific gravity	
Low	Tubular necrosis
High	Prerenal
Myoglobin	Rhabdomyolysis-associated tubular necrosis
Urobilinogen	Hemolysis-associated tubular necrosis

TABLE 45-6 Differential Diagnosis of Acute Renal Failure on the Basis of Urine Microscopic Examination Findings

Urine Sediment	Suggestive of
Cells	
Microorganisms	Pyelonephritis
Red blood cells	Glomerulonephritis, pyelonephritis, renal infarction, papillary necrosis, renal tumors, kidney stones
White blood cells	Pyelonephritis, interstitial nephritis
Eosinophils	Drug-induced allergic interstitial nephritis, renal transplant rejection
Epithelial cells	Tubular necrosis
Casts	
Granular casts	Tubular necrosis
White blood cell casts	Pyelonephritis, interstitial nephritis
Red blood cell casts	Glomerulonephritis, renal infarct, lupus nephritis, vasculitis
Crystals	
Urate	Postrenal obstruction
Phosphate	Alkaline urine, possibly secondary to *Proteus* sp. infection, postrenal obstruction

scopic and chemical analysis of the urine should be performed (Table 45–5). The finding of a high urinary specific gravity, in the absence of glucosuria or mannitol administration, suggests an intact urinary concentrating mechanism, and that the cause of the patient's ARF is likely prerenal azotemia. The presence of urinary protein is often difficult to interpret, especially in the setting of acute on chronic renal failure. A patient with CKD may have a baseline proteinuria, thus clouding the clinical presentation, unless this is known at the time of ARF assessment. Classically, proteinuria is a hallmark of glomerular damage. However, tubular damage can also result in proteinuria, as the tubules are responsible for reabsorbing small proteins that are normally filtered by all glomeruli. The presence of blood also results in a positive urine protein test, so this confounder must always be assessed for when a positive urine protein is obtained. Hematuria suggests acute intrinsic ARF secondary to glomerular or injury to other kidney tissue. On microscopic examination, the key findings are cells, casts, and crystals, and the presence of one or more of these suggests specific etiologies of the ARF (Table 45–6). The presence of crystals may suggest nephrolithiasis and a postrenal obstruction. If red blood cells or red blood cell casts are present, one should consider the presence of a physical injury to the glomerulus, renal parenchyma or vascular beds. The finding of white blood cells or white blood cell casts suggests interstitial inflammation (i.e., interstitial nephritis), which can be secondary to an allergic, granulomatous, or infectious process.

Simultaneous measurement of urine and serum electrolytes is also helpful in the setting of ARF (see Table 45–4). From these values a fractional excretion of sodium can be calculated. The equation for the calculation of the fractional excretion of sodium (FeNa) is:

$$\text{FeNa} = (\text{excreted Na/filtered Na}) \cdot 100 = (U_{vol} \cdot U_{Na})/(\text{GFR} \cdot S_{Na}) \cdot 100$$

where

$$\text{GFR} = (U_{vol} \cdot U_{cr})/(S_{cr} \cdot t)$$

Thus

$$\text{FeNa} = (U_{Na} \cdot S_{cr} \cdot 100)/(U_{cr} \cdot S_{Na})$$

where U_{vol} is urine volume; U_{cr} is urine creatinine concentration; U_{Na} is urine sodium; S_{cr} is serum creatinine concentration; S_{Na} is serum sodium concentration, which usually does not vary much; GFR is the glomerular filtration rate; and t is the time period over which the urine is collected.

The fractional excretion of sodium is one of the better diagnostic parameters to differentiate the cause of ARF. A low urinary sodium concentration (<20 mEq/L) and low fractional excretion of sodium (<1%) in a patient with oliguria suggest that there is stimulation of the sodium-retentive mechanisms in the kidney and that tubular function is intact. These findings are most characteristic of prerenal azotemia. Unfortunately, diuretic use in the preceding days limits the usefulness of the fractional excretion of sodium calculation by increasing natriuresis, even in hypovolemic patients. The fractional excretion of urea (FeUrea), which can be calculated similarly to the FeNa, is sometimes used as an alternative means to assess tubule function.

The inability to concentrate urine results in a high fractional excretion of sodium (>2%), suggesting tubular damage is the primary cause of the intrinsic ARF. Diagnosing the type of ARF using fractional excretion of sodium is not absolute, as there are some intrinsic causes that can be associated with a low fractional excretion of sodium (e.g., contrast nephropathy, myoglobinuria, and interstitial nephritis). Highly concentrated urine (>500 mOsm/L) suggests stimulation of antidiuretic hormone and intact tubular function. These findings are consistent with prerenal azotemia.

DIAGNOSTIC PROCEDURES

When the source of renal failure is unclear after a history, physical examination, and assessment of laboratory values, then imaging techniques such as abdominal radiography (kidneys, ureters, and bladder), CT, or ultrasonography may be helpful. These may reveal small, shrunken kidneys indicative of CKD, and postrenal obstruction can often be identified with a renal ultrasonogram and/or CT scan. Renal ultrasonography is a useful means to detect obstruction or hydronephrosis. Nephrolithiases as small as 5 nm, or narrowing of the ureteral tract can be detected by ultrasonography. No contrast dye is required, and it is noninvasive, simple, portable, and rapid to accomplish. In selected conditions under the guidance of a nephrologist, more invasive procedures, such as cystoscopy or biopsy, may be considered to detect the presence of malignancy, prostate hypertrophy, uterine fibroids, nephrolithiases or ureterolithiases.

If insertion of a urinary catheter into the patient's bladder after the patient has voided or attempted to void does not yield a large volume of urine (>500 mL), then one can usually exclude postrenal obstruction distal to the bladder as the cause of ARF. Cystoscopy with retrograde pyelography may be helpful if the possibility of obstruction exists, and the insertion of a catheter did not result in a significant volume of urine.

In cases in which the cause of ARF is not evident, renal biopsies are useful in determining the cause in the majority of patients.[33] Because of the associated risk of bleeding, a renal biopsy is rarely undertaken and should only be performed in those rare circumstances when a definitive diagnosis is needed to guide therapy, such as the precise etiology of glomerulonephritis (see Chap. 50).

PREVENTION AND TREATMENT

Acute Renal Failure

DESIRED OUTCOME

5 Given the dismal outcome of established ARF, prevention is critical. In some cases, the risk of developing ARF may be predictable, such as decreased perfusion secondary to abdominal surgery, coronary bypass surgery, acute blood loss in trauma, and uric acid nephropathy, where preventative strategies can be effective. When patients with risk factors for developing ARF are scheduled for surgery, the clinician should be aware that the likelihood of the patient developing ARF is high and consider preventative measures, including discontinuation of medications that may enhance the likelihood of renal damage (e.g., NSAIDs, angiotensin-converting enzyme inhibitors). Consequently the goals are (a) to prevent ARF, (b) avoid or minimize further renal insults that would worsen the existing injury or delay recovery, and (c) provide supportive measures until kidney function returns.

GENERAL APPROACH TO PREVENTION

The general approach to the prevention of ARF is dependent on the setting the patient is in. To prevent the development of ARF, healthcare professionals should educate the patient on preventative measures. The patient should receive guidance regarding their optimal daily fluid intake (approximately 2 L/day) to avoid dehydration, and if they are to receive any treatment that can pose a risk for insult to the kidney (e.g., chemotherapy or uric acid nephropathy). The patient's fluid balance can be evaluated by measuring acute changes in weight, as other typical sources for weight changes in an adult occur over more prolonged periods, and blood pressure changes. If the patient has a history of nephrolithiasis, they may benefit from dietary restrictions, depending on the type of stones that were present in the past. If a patient has a Foley catheter in place, proper care and monitoring needs to be performed to ensure that postobstructive ARF does not develop. Selected strategies to prevent drug-related ARF are discussed briefly below and in detail in Chap. 49.

NONPHARMACOLOGIC THERAPIES

There are many situations in which administration of a nephrotoxin cannot be avoided, such as when radiocontrast dye is to be administered. In these settings, one of several nonpharmacologic therapies can be employed in an attempt to prevent the development of ARF. Adequate hydration and sodium loading prior to radiocontrast dye administration have been shown to be beneficial therapies. A trial comparing infusions of 0.9% NaCl or 5% dextrose with 0.45% NaCl administered prior to radiocontrast dye infusion conclusively demonstrated that normal saline was superior in preventing ARF.[34] The intravenous solution infusion rate used in this study was 1 mL/kg per hour beginning the morning that the radiocontrast dye was going to be given, and all subjects were encouraged to drink fluids liberally as well. The benefits of 0.9% NaCl infusions have been found in similar studies,[35] suggesting this regimen should be used in all at-risk patients who can tolerate the sodium and fluid load. In addition to the correction of dehydration, saline administration may result in dilution of contrast media, prevention of renal vasoconstriction leading to ischemia, and avoidance of tubular obstruction. The results of one recent study suggest that hydration with sodium bicarbonate provides more protection than saline, perhaps by reducing the formation of pH-dependent oxygen free radicals.[36]

In some cases, when nephrotoxic agent use cannot be avoided, there may be ways to administer them in a manner that reduces their nephrotoxic potential. A good example of this is the use of amphotericin B to treat fungal infections. Amphotericin is a highly nephrotoxic agent, causing ARF in approcimately 30% of patients who receive it.[37] However, there are many infections for which no good alternative treatment exists. The nephrotoxic potential of amphotericin B deoxycholate can be reduced significantly simply by slowing the infusion rate from a standard 4-hour infusion to a slower 24-hour infusion of the same dose.[38] In a patient with risk factors for the development of ARF, liposomal forms of amphotericin B can be used. These liposomal formulations are more expensive, but have been associated with a lower incidence of kidney damage.[39]

Preventive Dialysis

A novel approach to reducing the incidence of nephrotoxicity associated with radiocontrast dye administration is to provide RRT prophylactically to patients who are at high risk of ARF. Hemofiltration initiated prior to and continued for 24 hours after dye administration has resulted in a significant reduction in mortality and a reduced need for dialysis.[40] In contrast, the use of hemodialysis within 1 hour of contrast dye infusion did not yield an improvement in nephrotoxicity rates, possibly because the toxicity caused by dye occurs within minutes of its administration.[41] Overall, evidence to date does not support any consistent significant benefit with the routine use of extracorporeal blood purification to prevent radiocontrast dye–induced nephropathy over standard medical therapy.[42]

PHARMACOLOGIC THERAPIES

Dopamine and Diuretics

Given the dismal outcome of established ARF, many drugs have been investigated for its prevention. Almost all of these approaches have been shown to be of little to no value. Low doses of dopamine (≤2 mcg/kg/min) increase renal blood flow and might be expected to increase GFR. Theoretically, this could be considered beneficial, as an enhanced GFR might flush nephrotoxins from the tubules, minimizing their toxicity. Furthermore, loop diuretics may decrease tubular oxygen consumption by reducing solute reabsorption.[43] Despite these theoretical suggestions, controlled studies have not supported these theories. Dopamine (2 mcg/kg/min) worsened renal perfusion indices compared to saline in a crossover study in patients with ARF.[44] A blinded and randomized trial conducted in patients who were undergoing cardiac surgery compared dopamine at 2 mcg/kg/min, furosemide at 0.5 mcg/kg/min, and a 0.9% NaCl given at initiation of surgery to determine whether any of the these interventions is beneficial.[45] Postoperative increases in S_{cr} occurred significantly more often in the furosemide-treated patients than in the other two groups. Dopamine afforded no benefit compared to the 0.9% NaCl infusion, and thus also should not be used routinely in this manner.

CLINICAL CONTROVERSIES

Despite most studies not showing improved patient outcomes with its use, low-dose dopamine continues to be commonly used. The risks associated with dopamine use (extravasation and the potential for significant dosing errors) suggest that its use should be avoided whenever possible.

Giving low-dose dopamine infusions (≤2 mcg/kg/min) for the prevention of ARF is a surprisingly common practice given the paucity of data to support its use. Although most studies do report an increase in urine output when low-dose dopamine is administered, almost none report that this practice yields a benefit to the patient. A meta-analysis of all low-dose dopamine studies conducted from 1966 to 2000 concluded that low-dose dopamine does not prevent ARF and its use cannot be justified.[46]

The use of diuretics to prevent nephrotoxicity may actually result in intravascular volume depletion and thereby increase the risk of ARF. A trial of forced diuresis, in which mannitol, furosemide, and/or dopamine were given, and the resultant urinary losses were replaced with intravenous solutions, found that diuretic use resulted in little benefit compared to the administration of IV solutions alone.[47] Interestingly, these investigators noted that patients who were unable to increase their urine output after diuretic administration were more likely to develop ARF than were patients who did respond to diuretics. While this unresponsiveness to diuretics might simply be an indication of preexisting kidney damage, similar reports have linked diuretic unresponsiveness to increased mortality rates in critically ill patients with ARF.[48]

Fenoldopam

Fenoldopam mesylate is a selective dopamine A-1 receptor agonist that increases blood flow to the renal cortex that has been investigated for its ability to prevent the development of ARF in many settings including contrast dye induced nephropathy (CIN). Originally approved for use as an intravenous antihypertensive agent, several small studies suggested that fenoldopam had salutary properties for the prevention of drug-induced nephrotoxicity. The largest, multicenter, randomized, placebo-controlled trial of fenoldopam conducted to date in patients with CKD found that fenoldopam use did not reduce the risk of CIN.[49] Indeed, the CIN Consensus Working Panel stated that, fenoldopam along with dopamine, calcium channel blockers, atrial natriuretic peptide, and 1-arginine, were not effective preventative therapeies to reduce the incidence of CIN.[50] However, a recent systematic review of randomized controlled trials of critically ill patients or those undergoing major surgery, revealed that fenoldopam significantly reduced the risk of acute kidney injury and the need for renal replacement therapy. This analysis suggests that fenoldopam may be a viable entity to prevent the development of ARF in some clinical settings.[51] A prospective, appropriately powered trial will need to be performed to validate this observation.

Acetylcysteine

N-acetylcysteine is a thiol-containing antioxidant that may effectively reduce the risk of developing CIN in patients with pre-existing kidney disease, although a therapeutic benefit has not been consistently demonstrated.[52,53] The mechanism for *N*-acetylcysteine's ability to reduce the incidence of contrast dye induced nephrotoxicity is not clear, but likely is due to its antioxidant effects. Given the consistent findings of its efficacy and its relatively low cost, *N*-acetylcysteine should be given to all patients at risk for CIN.[52,54–57] The recommended *N*-acetylcysteine dosing regimen for prevention of CIN is 600 mg orally every 12 hours for 4 doses with the first dose administered prior to contrast exposure. Several other drugs have been investigated for the prevention of ARF with varying degrees of success.[42,52,53]

Theophylline may reduce the incidence of CIN with an efficacy that is perhaps comparable to that reported in studies of *N*-acetylcysteine. However, findings are inconsistent across studies.[58] A large, well-designed trial that incorporates the evaluation of clinically relevant outcomes is required to more adequately assess the role of theophylline in CIN prevention.

Glycemic Control

Perhaps the most promising agent for the prevention of hospital-acquired ARF is a very old drug, but its use in the prevention of ARF is new. Van den Berghe et al. randomized patients in a surgical intensive care unit to receive either standard control (<200 mg/dL) or intensive glucose control measures (goal blood glucose concentrations of 80 to 110 mg/dL).[59] Tight blood glucose resulted in significant improvements in mortality and a 41% reduction in the development of ARF. While it appears that blood glucose control was the key factor associated with the mortality benefit, the reduction in ARF may have been a consequence of the total dose of insulin used to treat the patient, suggesting a direct protective effect of insulin.[60] Strict glycemic control is recognized as an important goal for outpatient diabetics[61]; however, intensive insulin therapy may now also become the standard of care for all critically ill patients to prevent ARF and improve mortality.

MANAGEMENT

Established Acute Renal Failure

■ DESIRED OUTCOMES

Short-term goals include minimizing the degree of insult to the kidney, reducing extrarenal complications, and expediting the patient's recovery of renal function. The ultimate goal is to have the patient's renal function restored to their pre-ARF baseline.

■ GENERAL APPROACH TO TREATMENT

Prerenal sources of ARF should be managed with hemodynamic support and volume replacement. If the cause is immune related, as may be the case with interstitial nephritis or glomerulonephritis, appropriate immunosuppressive therapy must be promptly initiated. Postrenal therapy focuses on removing the cause of the obstruction. It is important to approach the treatment of established ARF with an understanding of the patient's comorbidities and baseline renal function. Loss of kidney function combined with other clinical conditions, such as cardiac and liver failure, are associated with higher mortality than that associated with the development of ARF alone.[62] At times, the most efficacious remedy for ARF is management of the comorbid precipitating event. Appreciation of the baseline renal function is also important at the outset of ARF management, because the presence of CKD indicates the highest degree of renal function that can be attained after ARF resolution. Finally, the presence of CKD indicates that the kidneys have less reserve, and thus there is a greater likelihood that the individual may not fully recover from the current insult.

6 Once acute renal failure is established, the cause is known, and any specific therapy implemented, supportive care is the mainstay of ARF management regardless of etiology. RRT may be necessary to maintain fluid and electrolyte balance while removing accumulating waste products. The slow process of renal recovery cannot begin until there are no further insults to the kidney. In the case of ATN, the recovery process typically occurs within 10 to 14 days after resolution of the last insult. The recovery period will be prolonged if the kidney is exposed to repeated insults.

■ NONPHARMACOLOGIC

Initial modalities to reverse or minimize prerenal ARF include removal of medications associated with diminished renal blood flow or the physical removal of a prerenal obstruction. If dehydration is evident, then appropriate fluid replacement therapy, as described below, should be initiated. Moderately volume-depleted patients can be given oral rehydration fluids; however, if intravenous fluid is required, isotonic normal saline is the replacement fluid of choice, and large volumes may be necessary to provide adequate fluid resuscitation. Typically, IV fluid challenges are initiated with 250 to 500 mL of normal saline over 15 to 30 minutes with an assessment after each challenge of the patient's volume status. Unless profound dehydration is present, as may be seen in diabetic ketoacidosis or hyperosmolar hyperglycemic states, 1 to 2 L is usually adequate. Patients with diabetic ketoacidosis or a hyperosmolar hyperglycemic state often have a 10% to 15% total-body water deficit, and more

aggressive fluid replacement is necessary. The patient should be monitored for pulmonary edema, peripheral edema, adequate blood pressure (diastolic blood pressure >60 mm Hg), normoglycemia and electrolyte balance. Urine output may not be promptly observed, as the kidney continues to retain sodium and water until rehydration is achieved. Up to 10 L may be required in the septic patient during the first 24 hours, because of the profound increase in vascular capacitance and fluid leakage into the extravascular, interstitial space. [63]

Patients with ARF on top of preexisting CKD should not be expected to produce urine beyond their preexisting baseline. In patients with anuria or oliguria, slower rehydration, such as 250-mL boluses or 100 mL/h infusions of normal saline, should be considered to reduce the risk for pulmonary edema, especially if heart failure or pulmonary insufficiency exists. Other replacement fluids may be considered if the dehydration is accompanied by a severe electrolyte imbalance amenable to large and relatively rapid infusions. For example, dehydration resulting from severe diarrhea is often accompanied by metabolic acidosis caused by bicarbonate losses. A reasonable IV rehydration fluid in this situation is 5% dextrose with 0.45% NaCl plus 50 mEq of sodium bicarbonate per liter, administered as boluses as described above, followed by a brisk continuous infusion (200 mL/h) until rehydration is complete, acidosis corrected, and diarrhea resolved. This fluid will remain mostly in the intravascular space, providing the necessary perfusion pressure to the kidneys, and also provide a substantial amount of bicarbonate to correct the acidosis.

If the prerenal ARF is a result of blood loss, or complicated by symptomatic anemia, red blood cell transfusion to a hematocrit no higher than 30% is the treatment of choice.[64] Although albumin is sometimes used as a resuscitative agent, its use should be limited to individuals with severe hypoalbuminemia (e.g., liver disease, nephritic syndrome) who are resistant to crystalloid therapy. These patients have severe hypoalbuminemia-associated third spacing that complicates fluid management, and albumin may be useful in this setting.

The most common interventions that must be made when treating patients with intrinsic or postobstructive ARF involve fluid and electrolyte management. Most patients with these types of ARF, as well as those with a prerenal cause who are excessively fluid resuscitated ultimately become fluid overloaded. This means drug infusions and nutrition solutions must be maximally concentrated. So-called keep vein open or maintenance intravenous infusions should be minimized unless the patient is euvolemic or is receiving RRT to maintain fluid balance. Supportive care goals for the hospitalized patient with any type of ARF include maintenance of adequate cardiac output and blood pressure to allow adequate tissue perfusion. However, a fine balance must be maintained in anuric and oliguric patients unless the patient is hypovolemic or is able to achieve fluid balance via RRT. If fluid intake is not minimized, edema may rapidly develop, especially in hypoalbuminemic patients. In contrast, vasopressors, like dopamine at doses of ≥2 mcg/kg/min or norepinephrine when used to maintain adequate tissue perfusion, may also induce kidney hypoxia as the result of a reduction in renal blood flow. Consequently, Swan-Ganz monitoring may be necessary for critically ill patients (see Chap. 25).

7 Because there is no current definitive therapy for ARF, supportive management remains the primary approach to prevent or reduce associated complications or death. In the presence of severe ARF, RRTs are commonly prescribed to manage uremia, metabolic acidosis, hyperkalemia and complications of excess fluid retention, such as pulmonary edema or accumulation of renally cleared medications. Although precise indications for starting RRT are unclear, some general guidelines for therapy have been proposed (Table 45–7).

Renal Replacement Therapies

RRTs can be administered either intermittently or continuously. The optimal mode for hemodialysis is unclear, and varies depending on the clinical presentation of the patient. It is unclear in many situations if dialysis can improve survival in ARF. Some recent data suggest that more aggressive approaches using RRTs in a more liberal fashion may improve survival in critically ill ARF patients.[65] The choice of whether continuous therapies or intermittent RRTs are used is a matter of debate and is usually determined by physician preference and the resources available at the hospital.

TABLE 45-7 The AEIOUs That Describe the Indications for Renal Replacement Therapy

Indication for Renal Replacement Therapy	Clinical Setting
A Acid–base abnormalities	Metabolic acidosis resulting from the accumulation of organic and inorganic acids
E Electrolyte imbalance	Hyperkalemia, hypermagnesemia
I Intoxications	Salicylates, lithium, methanol, ethylene glycol, theophylline, phenobarbital
O fluid Overload	Postoperative fluid gain
U Uremia	High catabolism of acute renal failure

Intermittent Hemodialysis

Intermittent hemodialysis (IHD) is the most frequently used RRT and has several advantages. IHD machines are readily available in most acute care facilities and healthcare workers are familiar with their use. Hemodialysis treatments usually last 3 to 4 hours with blood flow rates to the dialyzer typically ranging from 200 to 400 mL/min. Advantages of IHD include rapid removal of volume and solute, and rapid correction of most of the electrolyte abnormalities associated with ARF. IHD can be scheduled at times to maximize staffing availability and treatments per day per machine, while minimizing inconvenience to the patient. The primary disadvantage is hypotension, typically caused by rapid removal of intravascular volume over a short period of time. Venous access for dialysis can be difficult in hypotensive patients and can limit the effectiveness of IHD, leading to ineffective solute clearance, lack of acidosis correction, continued volume overload, and delayed recovery because of further renal ischemia insults. If hemodialysis is carefully monitored and hypotension avoided, better patient outcomes can be achieved.[66] Patients with stage 5 CKD generally achieve adequate solute and volume control with thrice-weekly dialysis, but hypercatabolic, fluid-overloaded patients with ARF may require daily hemodialysis treatments.[67] The use of daily versus thrice-weekly IHD in the setting of ARF patients is associated with a reduction in dialysis-related hypotension and a shorter period of time to full recovery of kidney function.[68] Chapter 48 provides a more detailed explanation of the principles and processes of hemodialysis.

Continuous Renal Replacement Therapies

In contrast to IHD, CRRTs that were developed over the past 15 years have proven to be a viable management approach for hemodynamically unstable patients with ARF.[69] Several CRRT variants have been developed, including continuous venovenous hemofiltration (CVVH), continuous venovenous hemodialysis (CVVHD), and continuous venovenous hemodiafiltration (CVVHDF). They differ in the degree of solute and fluid clearance that can be clinically achieved as a result of the use of diffusion, convection, or a combination of both. Although solute removal is slower, a greater amount can be removed over a 24-hour period compared to IHD, which is associated with improved outcomes in critically ill patients with ARF.[70]

In CVVH, solute and fluid clearance is primarily a result of convection where passive diffusion of fluids containing solutes is removed while volume absent of the solutes is replaced to the patient (Fig. 45–4). Continuous venovenous hemodialysis (CVVHD) provides extensive solute removal primarily by diffusion, where solute molecules at a higher concentration (plasma) pass through the dialysis membrane to a lower concentration (dialysate) and some fluid is removed as a

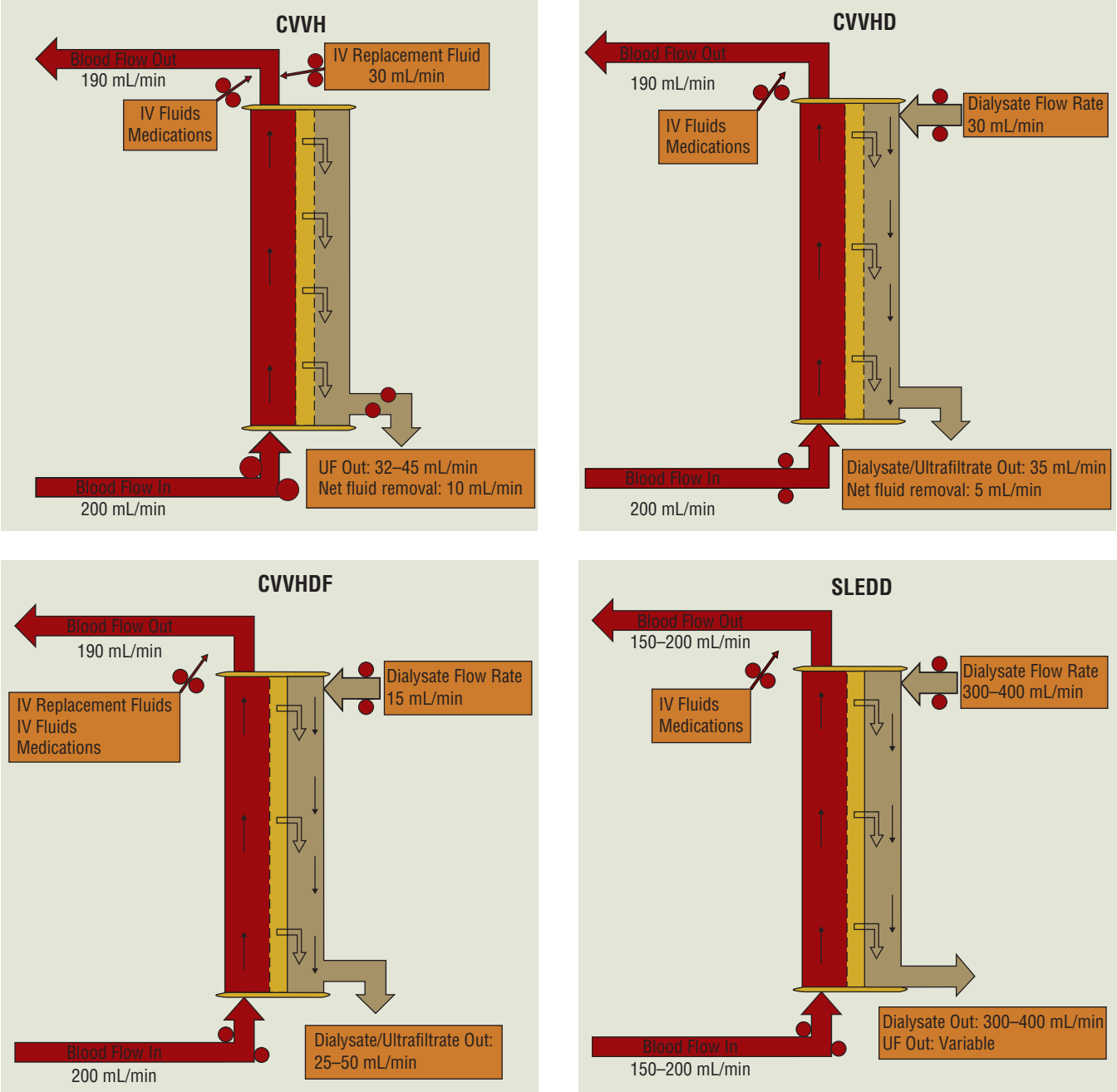

FIGURE 45-4. Several RRTs are commonly utilized in ARF patients including one of the three primary CRRT variants: (a) continuous veno-venous hemofiltration (CVVH), (b) continuous veno-venous hemodialysis (CVVHD), (c) continuous veno-venous hemodiafiltration (CVVHDF), and the hybrid intermittent hemodialysis therapy (d) slow extended daily dialysis (SLEDD). The blood circuit in each diagram is represented in red, while the hemofilter/dialyzer membrane is yellow and the ultrafiltration/dialysate compartment is depicted in brown. Excess body water and accumulated endogenous waste products are removed solely by convection when CVVH is employed. With CVVHD, waste products are predominantly removed as the result of passive diffusion from the blood where they are in high concentration to the dialysate. The degree of fluid removal which is accomplished by convection is usually minimal. CVVHDF utilizes convection to a degree similar to that employed during CVVH as well as diffusion, and thus is often associated with the highest clearance of drugs and waste products. Finally, SLEDD employs lower blood and dialysate flow rates that IHD, but due to its extended duration it is a gentler means of achieving adequate waste product and fluid removal.

function of the ultrafiltration coefficient of the dialyzer. Because the dialysate flows in a countercurrent direction to the plasma flow on the other side of the membrane, the concentration gradient is maximized. This procedure is associated with a lower incidence of clotting than CVVH because of reduced hemoconcentration as there is less fluid removal during the process. CVVHDF combines both hemofiltration and hemodialysis, achieving even higher solute and fluid removal rates (Fig. 45–4). The ultrafiltration rate is an important determinant of the effectiveness of all three forms of CRRT: achievement of a removal rate of 35 mL/kg/h is associated with improved survival.[70]

Because of the reduced blood flow rates relative to IHD, thrombosis is a significant concern with CRRT, and thus some form of anticoagulation is generally necessary for almost all patients. Typical anticoagulation is achieved by the administration of unfractionated heparin, or in some cases, a low-molecular-weight heparin, a direct thrombin inhibitor, or citrate solution.[71] Replacement fluids can be infused either just before or after the dialyzer/hemofilter. Infusing fluids after the hemofilter can result in hemoconcentration within the filter, a factor associated with an increased risk of thrombosis of the dialyzer. Replacing fluids before the filter reduces thrombosis risk, but also reduces solute clearance.

Disadvantages of CRRT are that not all hospitals have the special equipment necessary to provide these treatments, they require intensive nursing care around the clock, and they are more expensive than IHD because of the need to individualize the intravenous replacement and dialysate fluids. There is also very little known about drug-dosing requirements for those who are receiving these therapies. CRRT use is most commonly considered for those patients with higher acuity because of their intolerance of IHD-associated hypotension. In one meta-analysis, no difference in clinical outcomes between the two approaches was seen until there was an adjustment for severity of illness. CRRT was then found to be associated with a lower mortality rate.[72] Because patients treated with continuous therapies are almost always more critically ill than those treated by IHD, comparisons of outcome must control for illness severity.

CLINICAL CONTROVERSY

Some clinicians believe that CRRTs are preferable to IHD because they provide more consistent fluid and waste product removal. Others suggest that IHD is preferable because the nursing and medical staff is more familiar with its use and round-the-clock nursing is not needed. New hybrid approaches with slower removal over a prolonged time period may potentially appeal to both groups.

CRRT and hybrid extended-duration intermittent hemodialysis are now being commonly used for critically ill patients with ARF. With CRRT, more solute and water removal can be achieved than with the thrice-weekly hemodialysis treatments used for patients with ESRD. This has influenced how dialysis is prescribed in the intensive care unit for hypercatabolic patients with ARF. Daily IHD is associated with improved survival and faster resolution of ARF compared to dialysis given every other day.[62] Daily delivery of IHD presents challenges to clinicians prescribing drug and nutrition therapy, as most of these dosing guidelines are based on thrice-weekly dialysis, and application of these guidelines may yield inappropriate outcomes.

Hybrid IHD therapies have a variety of names, with the two most common being sustained low-efficiency dialysis[73] and slow, extended, daily dialysis (see Fig. 45–4).[74] These therapies use slower blood (150 to 200 mL/min) and dialysate flow rates (300 mL/min) with extended treatment periods of 6 to 12 hours. Unlike CRRT, these therapies do not require any new equipment.[74] Anticoagulation is still required, but the amount necessary compared to CRRT is lower.[74] Although the use of hybrid hemodialysis therapies is increasing, our knowledge of the impact of these therapies on drug removal is very limited.[75,76]

■ PHARMACOLOGIC

Once the kidney has been damaged by an acute insult (e.g., reduced perfusion or exposure to exogenous or endogenous nephrotoxins), initial therapies should be directed to prevent further insults to the kidney, thereby minimizing extension of the injury.[20] If sepsis is present, antibiotic therapy regimens should be adjusted for decreased renal elimination, the potential for increased elimination if the agent is removed by hemodialysis, and the ability to treat the infection to prevent further damage to the kidney. The time to recovery from ARF is determined from the most recent insult to the kidney, not the first insult. Hospitalized patients with ARF are at high risk for repeated episodes of kidney injury as the result of repeated exposures to nephrotoxic agents and hypotensive episodes, among other problems. These increased risks, coupled with the fact that no drugs have been found to accelerate ARF recovery, dictate the way clinicians approach the ARF patient.

To date, no pharmacologic approach to reverse the decline or accelerate the recovery of renal function has been proven to be clinically useful. Many agents have looked promising in animal trials, only to be found ineffective in human trials. Numerous agents have been investigated and shown no benefit in the treatment of established ARF.[77] In recent years thyroxine,[78] dopamine,[79,80] and loop diuretics[47,81,82] have all been documented to either be of no help or to worsen patient outcomes. For example, a 77% increase in mortality or nonrecovery of renal function was reported in patients with ARF who received a loop diuretic compared to patients who did not receive loop diuretics.[47] These findings may be explained by the fact that sicker, fluid-overloaded patients may be more likely to receive diuretics, nonetheless no benefit to loop diuretic use could be found in any subanalysis. Consequently, loop diuretic use should be reserved for fluid-overloaded patients who make adequate urine in response to diuretics to merit their use.[81] Prevention of pulmonary edema is an important goal, and it is preferable that it be accomplished with diuretics instead of more invasive RRTs, despite the previously mentioned finding that diuretic use may be associated with diminished outcomes.[47] The most effective drugs in producing diuresis in the patient with ARF, mannitol and the loop diuretics, have distinct advantages and disadvantages. Mannitol, which works as an osmotic diuretic, can only be given parenterally. A typical starting dose is mannitol (20%) 12.5 to 25 g infused intravenously over 3 to 5 minutes. It has little nonrenal clearance, so when given to anuric or oliguric patients, mannitol will remain in the patient, potentially causing a hyperosmolar state. Additionally, mannitol may cause ARF itself, so its use in ARF must be monitored carefully by measuring urine output and serum electrolytes and osmolality.[83] Because of these limitations of mannitol, some clinicians recommend that it be reserved for the management of cerebral edema.[84]

Furosemide, bumetanide, and torsemide are the most frequently used loop diuretics in patients with ARF. Ethacrynic acid is typically reserved for patients who are allergic to sulfa compounds. Furosemide is the most commonly used loop diuretic because of its lower cost, availability in oral and parenteral forms, and reasonable safety and efficacy profiles. A disadvantage with furosemide is its variable oral bioavailability in many patients and potential for ototoxicity with high serum concentrations that may be attained with rapid, high-dose bolus infusions. Consequently, initial furosemide doses, which should not exceed 40 to 80 mg, are usually administered intravenously to assess whether the patient will respond. Torsemide and bumetanide have better oral bioavailability than furosemide. Torsemide has a longer duration of activity than the other loop diuretics, which allows for less-frequent administration but which also may make it more difficult to titrate the dose. Loop diuretics all work equally well provided that they are administered in equipotent doses. In a patient who is unresponsive to aggressive intravenous loop diuretic therapy, switching to another loop diuretic is unlikely to be beneficial.

Diuretic Resistance

8 Inability to respond to administered diuretics is common in ARF and is associated with a poor patient outcome (Table 45–8).[47] An effective technique to overcome diuretic resistance is to administer loop diuretics via continuous infusions instead of intermittent boluses. Less natriuresis occurs when equal doses of loop diuretics are given as a bolus instead of as a continuous infusion. Furthermore, adverse reactions from loop diuretics (myalgia and hearing loss) occur less frequently in patients receiving continuous infusion compared to those receiving intermittent boluses, ostensibly because higher serum concentrations are avoided. However, these adverse effects still may occur with continuous infusion of loop diuretics and should be monitored.[85] The finding that the continuous infusions of loop diuretics have efficacy that is at least as good as intermittent bolus dosing, with fewer adverse effects, appears to be consistent for all agents, including furosemide,[86] bumetanide,[87] and torsemide.[88] When a continuous loop diuretic infusion is used, an initial loading dose is given (equivalent to furosemide 40 to 80 mg) prior to the initiation of a continuous infusion at 10 to 20 mg/h of furosemide or its equivalent. Patients with low

TABLE 45-8 Common Causes of Diuretic Resistance in Patients with Acute Renal Failure

Causes of Diuretic Resistance	Potential Therapeutic Solutions
Excessive sodium intake (sources may be dietary, IV fluids, and drugs)	Remove sodium from nutritional sources and medications
Inadequate diuretic dose or inappropriate regimen	Increase dose, use continuous infusion or combination therapy
Reduced oral bioavailability (usually furosemide)	Use parenteral therapy; switch to oral torsemide or bumetanide
Nephrotic syndrome (loop diuretic protein binding in tubule lumen)	Increase dose, switch diuretics, use combination therapy
Reduced renal blood flow	
Drugs (NSAIDs ACEIs, vasodilators)	Discontinue these drugs if possible
Hypotension	Intravascular volume expansion and/or vasopressors
Intravascular depletion	Intravascular volume expansion
Increased sodium resorption	
Nephron adaptation to chronic diuretic therapy	Combination diuretic therapy, sodium restriction
NSAID use	Discontinue NSAID
Heart failure	Treat the heart failure, increase diuretic dose, switch to better-absorbed loop diuretic
Cirrhosis	High-volume paracentesis
Acute tubular necrosis	Higher dose of diuretic, diuretic combination therapy, add low-dose dopamine

ACEIs, angiotensin-converting enzyme inhibitors; NSAIDs, nonsteroidal antiinflammatory drugs.

creatinine clearances may have much lower rates of diuretic secretion into the tubular fluid; consequently, higher doses are generally used in patients with renal insufficiency.[84] Diuretic resistance may occur simply because excessive sodium intake overrides the ability of the diuretics to eliminate sodium. However, other reasons for diuretic resistance often exist in this population. Patients with ATN have a reduced number of functioning nephrons on which the diuretic may exert its action. Other clinical states, like glomerulonephritis, are associated with heavy proteinuria. Intraluminal loop diuretics cannot exert their effect in the loop of Henle because they are extensively bound to proteins present in the urine. Still other patients may have greatly reduced bioavailability of oral furosemide because of intestinal edema, often associated with high preload states, which further reduces oral furosemide absorption. Table 45–8 includes possible therapeutic options to counteract each form of diuretic resistance. Combination therapy of loop diuretics plus a diuretic from a different pharmacologic class may be an alternative approach in the setting of ARF.[89] Loop diuretics increase the delivery of sodium chloride to the distal convoluted tubule and collecting duct. With time, these areas of the nephron compensate for the activity of the loop diuretic and increase sodium and chloride resorption. Diuretics that work at the distal convoluted tubule (chlorothiazide and metolazone) or the collecting duct (amiloride, triamterene, and spironolactone) may have a synergistic effect when administered with loop diuretics by blocking the compensatory increase in sodium and chloride resorption. The combination of loop diuretics and usual doses of thiazide diuretics may be effective in renal disease despite the accumulation of endogenous organic acids in renal disease that blocks the transport of loop diuretics into the lumen. If oral thiazides cannot be given to the patient, chlorothiazide 500 mg can be administered parenterally.

Several drug combinations with loop diuretics have been investigated, including the addition of one or more of the following: theophylline, acetazolamide, spironolactone, thiazides, or metolazone.[83] Of these combinations, oral metolazone is used most frequently with furosemide. Metolazone, unlike other thiazides, produces effective diuresis at a GFR below 20 mL/min. This combination of metolazone and a loop diuretic has been used successfully in the management of fluid overload in patients with heart failure, cirrhosis, and nephrotic syndrome. Despite a lack of supporting evidence, oral metolazone at a dose of 5 mg is commonly administered 30 minutes prior to an intravenous loop diuretic to allow time for absorption. Additionally, this combination has been found to be efficacious in pediatric patients in addition to adults.[90] The combination of mannitol plus intravenous loop diuretics is used by some practitioners,[51] but no convincing evidence of the superiority of this combination regimen to conventional dosing of either diuretic alone exists.

ELECTROLYTE MANAGEMENT

Hypernatremia and fluid retention are frequent complications of ARF, and thus sodium restriction is a necessary intervention. In general, patients should receive no more than 3 g of sodium per day from all sources, including intravenous fluids, drugs, and enteral intake. Clinicians should be vigilant about sources of sodium. Excessive sodium intake is a common reason diuretic therapy fails. Commonly administered intravenous antibiotics, as well as other medications, may contain significant amounts of sodium; for example, 1 L of 0.9% NaCl yields 154 mEq (3.5 g) of sodium. At usual doses, intravenous metronidazole provides 1.3 g of sodium per day, ampicillin up to 800 mg, piperacillin approximately 700 mg, and fluconazole 500 mg. The cumulative effect of a few sodium-containing medications and fluids can be significant.

In continuous and intermittent RRTs there usually is less concern about hyponatremia developing because these therapies often incorporate isonatremic (135 to 140 mEq/L of sodium) solutions as the dialysate or ultrafiltrate replacement solutions. Serum sodium concentrations should be monitored daily. Hyperkalemia, hyperphosphatemia, and, to a lesser extent, hypermagnesemia are electrolyte disorders that are frequently seen in patients with ARF. This is generally not a serious concern in those who are receiving RRT, but electrolytes should be monitored closely in all patients with ARF.

The most common electrolyte disorder encountered in ARF patients is hyperkalemia, as more than 90% of potassium is renally eliminated. Life-threatening cardiac arrhythmias may occur when the serum potassium is over 6 mmol/L, so potassium restriction is essential. All patients with ARF should have serum potassium monitored at least daily, and twice daily for those who are seriously ill. This frequency is a consequence of the seriousness of the potential arrhythmias, the dynamic nature of potassium serum concentrations in the acutely ill patient, the potential for metabolic acidosis leading to increased extracellular potassium concentrations, and potassium's ubiquitous presence in foods and some medications. Commonly encountered medications that contain substantial amounts of potassium include oral phosphorous replacement powders (e.g., Neutra-Phos and Neutra-Phos-K) and alkalinizers (Polycitra). Many foods are high in potassium, including potatoes, beans, and various fruits. Some medications may promote potassium retention by the kidneys, and should also be avoided or closely monitored (see Chap. 54). Typically no potassium should be added to parenteral solutions unless hypokalemia is documented. Patients receiving enteral nutrition should be limited to a 3-g potassium diet. Patients receiving RRT should also have their serum potassium concentration measured at least daily. Some centers add no potassium to their CRRT solutions and hypokalemia can result unless one is prospectively monitoring for its development. Chapter 54 discusses the treatment of hyperkalemia in detail.

Other electrolytes that require monitoring include phosphorous and magnesium. Both are eliminated by the kidneys and are not removed efficiently by dialysis. In the early stages of ARF, hyperphosphatemia might be more common than hypophosphatemia. Patients who have significant tissue destruction (e.g., trauma, rhabdomyolysis, tumor lysis syndrome) may have significant phosphorus released from the destroyed tissue. Treatment of the hyperphosphatemic state can include CRRT. Calcium-containing antacids should be avoided to prevent precipitation of calcium phosphate in the soft tissues. Typically, the dietary intake of phosphorous and magnesium is restricted,

but in patients receiving prolonged renal replacement, deficiency states can occur, particularly in pediatric patients because of their reduced body stores. In contrast to the patient with CKD, calcium balance is usually not an important issue for the ARF patient because of the limited duration of the illness. One exception to this is in patients who are receiving CRRT with citrate as the anticoagulant. Citrate binds to serum calcium and without an adequate concentration of calcium, blood cannot form a clot. Citrate is thus typically infused before the dialyzer/hemofilter to maintain the dialyzer circuit calcium levels between 0.35 and 0.50 mmol/L. Calcium chloride (10 g of CaCl diluted in 500 mL normal saline), or gluconate (20 g of calcium gluconate to 500 mL normal saline) is then administered prior to returning the blood to the patient to maintain systemic ionized calcium levels between 1.11 to 1.31 mmol/L.[92] The citrate that reaches the systemic circulation is subsequently metabolized by the liver. Severe hypocalcemia can result in arrhythmias, and even death, so frequent monitoring of unbound serum calcium concentrations is essential.

NUTRITIONAL INTERVENTIONS

Baseline nutritional status is a strong predictor of outcomes in patients with ARF.[93] The provision of enteral nutrition to patients with ARF in intensive care units is associated with an improvement in outcomes.[94] Parenteral nutrition, however, has not demonstrated the same benefit and some have questioned whether it should be used in this population.[95] (see Chapter 147 for a detailed discussion.)

Because fluid intake often must be restricted in severely volume-overloaded ARF patients, the design and provision of adequate parenteral or enteral nutrition are problematic (see Chap. 147). Septic patients with ARF usually are hypercatabolic and normalized protein catabolic rates of up to 1.75 g/kg/day have been reported, but this value varies widely among patients.[96] Most patients with ARF have difficulty tolerating the amount of intravenous fluid required to replace catabolized protein unless they are receiving CRRT or daily hemodialysis.

Although patients with ARF typically experience elevated levels of potassium, magnesium, and phosphorus, which often necessitate restriction of these from nutrition formulas, it is not uncommon for deficiency states to occur in patients receiving CRRT, despite incorporation of these electrolytes into the replacement fluid solutions. The effect of CRRT on the delivery and removal of macro- and micronutrients must also be taken into account. The dextrose contained in CRRT replacement solutions may contribute a significant amount of calories to the patient's regimen. The removal of protein during dialysis, especially during peritoneal dialysis, may necessitate an increase of the protein intake up to 2.5 g/kg/day in some patients (see Chap. 147).

Another nutritional consideration for patients receiving CRRT is the heat losses as a consequence of the cooling of the patient's blood as it traverses the extracorporeal circuit and as a result of the use of room-temperature intravenous ultrafiltrate replacement solutions.[97] The energy loss for patients who are receiving continuous hemofiltration is estimated to be as high as 800 kcal/day.[98] Most of this heat loss can be attenuated by warming the intravenous ultrafiltrate replacement solution.[98] However, many hospitals are unable to heat intravenous solutions as they are infused, so recognition of this large source of energy loss is necessary so that the clinician can design an adequate nutritional prescription.

DRUG-DOSING CONSIDERATIONS

9 Optimization of drug therapy for patients with ARF is often quite challenging. The multiple variables influencing responses to the drug regimen include the patient's residual drug clearance, the accumulation of fluids, which can markedly alter a drug's volume of distribution, and delivery of CRRT or IHD, which can increase drug clearance and impact the patient's fluid status to further complicate the clinician's projection of the optimal dosage regime. For renally eliminated drugs (>30% excreted unchanged in the urine), particularly for agents with a narrow therapeutic range, serum drug concentration measurements and assessment of pharmacodynamic responses are likely to be necessary. If hepatic function is intact, choosing an agent eliminated primarily by the liver may be preferred. However, any renally eliminated active metabolites may accumulate to a point where they can elicit an undesired pharmacologic effect. Renal failure can also independently impair drug metabolism.[99] Clinical experiences and pharmacokinetic studies in patients with established ARF are fairly limited. The use of dosing guidelines based on data derived from patients with stable CKD, however, may not reflect the clearance and volume of distribution in critically ill ARF patients (see Chap. 51).[100]

Edema, which is common in ARF, can significantly increase the volume of distribution of many drugs, particularly water-soluble ones with relatively small volumes of distribution. Increased fluid distribution into the tissues (i.e., sepsis, anasarca in heart failure) can also contribute to a larger volume of distribution for many drugs and thereby reduce the proportion of drug in the plasma that is available to be removed by CRRT or IHD. ARF frequently occurs in critically ill patients and thus multisystem organ failure must often be contended with. Reductions in cardiac output or liver function in addition to volume overload can significantly alter the pharmacokinetic profile of many drugs such as vancomycin, aminoglycosides, and low-molecular-weight heparins.[101,102]

In almost all cases where rapid onset of activity is desired, a loading dose may be necessary to promptly achieve desired serum concentrations because the expanded volume of distribution and the prolonged elimination half-life result in an extended time (3.5 times the half-life) until steady-state concentrations are achieved. Maintenance dosing regimens should be reassessed frequently and be based on the patient's current renal function. A dose that provides the desired serum concentration on one day may be inappropriate only a few days later if the patient's fluid status or renal function has changed dramatically.

CLINICAL CONTROVERSY

In the volume-depleted patient requiring a renally eliminated medication, dosing regimens based on the initial S_{cr} prior to fluid therapy have the potential to underestimate renal function and drug elimination, resulting in subtherapeutic serum concentrations. Although not accepted as a standard practice, an initial 24-hour dosing regimen with a bolus might be optimal for many patients.

Drug therapy individualization for the ARF patient who is receiving any form of renal replacement therapy is complicated by the fact that patients with ARF may have a higher residual nonrenal clearance than CKD patients who have a similar CL_{cr}. This has been reported with some drugs, such as ceftriaxone, imipenem, and vancomycin.[103–106] Alterations in the activity of some, but not all, cytochrome P450 enzymes have been demonstrated in patients with CKD.[99] The nonrenal clearance of imipenem in patients with ARF (91 mL/min) is between the values observed in stage 5 CKD patients (50 mL/min) and those with normal renal function (130 mL/min).[106] This may be the result of less accumulation of uremic waste products that may alter hepatic function. A nonrenal clearance value in a patient with ARF that is higher than anticipated based on data from individuals with CKD would result in lower-than-expected, possibly subtherapeutic, serum concentrations. For example, to maintain comparable serum concentrations, the imipenem dose requirement in patients with ARF would be 2,000 mg/24 hours as compared to the recommended dosage for patients with ESRD of 1,000 mg/24 hours.[106] As ARF persists, the nonrenal clearance values appear to approach those observed in patients with CKD.[107,108] Finally, the clearance of ami-

noglycosides has been reported to be higher and the elimination half-life shorter in those with severe ARF compared to ESRD patients requiring hemodialysis.[100] Thus, application of dosing regimens derived from studies in patients with CKD and ESRD may result in underdosing of these agents and thereby contribute to less than optimal clinical outcomes.

IHD Compared to CRRT

In addition to patient-specific differences, there are marked differences between IHD and the three primary types of CRRT—CVVH, CVVHD, and CVVHDF—with regard to drug removal.[109–111]

CRRT During CVVH, drug removal primarily occurs via convection/ultrafiltration (the passive transport of drug molecules at the concentration at which they exist in plasma water into the ultrafiltrate). Convective removal is most efficient for smaller agents, typically less than 15,000 daltons in size, and those that are primarily unbound in the plasma. The clearance of a drug by either of these methods is thus a function of the membrane permeability for the drug, which is called the sieving coefficient (SC) and the rate of ultrafiltrate formation (UFR). Alteration in the pore size of the filter and surface charge relative to the molecule being removed may vary between different dialyzers. If diffusion of the drug is not dependent on the filter pore size, then the SC can be calculated as follows:

$$SC = (2 \times C_{UF})/[(C_a) + (C_v)]$$

where C_a and C_v are the concentrations of the drug in the plasma going into and returning from the dialyzer/hemofilter, respectively, and C_{UF} is the concentration in the ultrafiltrate. The SC is often approximated by the fraction unbound (f_u) because this information may be more readily available. Thus the clearance by CVVH can be calculated as:

$$Cl_{CVVH} = UFR \times SC$$

or approximated as:

$$Cl_{CVVH} = UFR \times f_u$$

In CVVHDF, clearance is a combination of both diffusion and convection. The Cl_{CVVHDF} can be mathematically approximated providing the blood flow rate is greater than 100 mL/min and the dialysate flow rate (DFR) is between 8 and 33 mL/min as:

$$Cl_{CVVHDF} = (UFR \times f_u) + Cl_{diffusion}$$

where $Cl_{diffusion}$ is the clearance via diffusion from plasma water to the dialysate. In the clinical setting, it is not possible to separate these two components (UFR and DFR) of Cl_{CVVHDF}. In essence the Cl_{CVVHDF} is calculated as the product of the combined ultrafiltrate and dialysate volume (V_{df}) and the concentration of the drug in this fluid (C_{df}) divided by the plasma concentration (C_p^{mid}) at the midpoint of the V_{df} collection period.

⑩ Individualization of therapy for a patient receiving CRRT therapy is dependent on the patient's residual renal function and the clearance of the drug by the mode of CRRT the patient is receiving. There are differences in the rate of drug removal, not only between the three primary modes of CRRT, but also within each mode.[105,109–112] This is a result of differences in the filter membrane composition, variable degrees of drug binding to the membrane, and the permeability characteristics of the membrane.[113–116] The primary factors that influence drug clearance during CRRT are thus ultrafiltration rate, blood flow rate, and dialysate flow rate. For example, clearance in CVVH is directly proportional to the ultrafiltration rate, whereas clearance during CVVHDF, which depends on both the ultrafiltration rate and the dialysate flow rate, increases as either flow rate increases. An increase in ultrafiltration flow rate (5 to 45 mL/min) and dialysate flow rate (8.3 to 33.3 mL/min), however, can have dramatic effects on clearance of agents such as ceftazidime during CVVH and CVVHD, respectively (Fig. 45–5).[116]

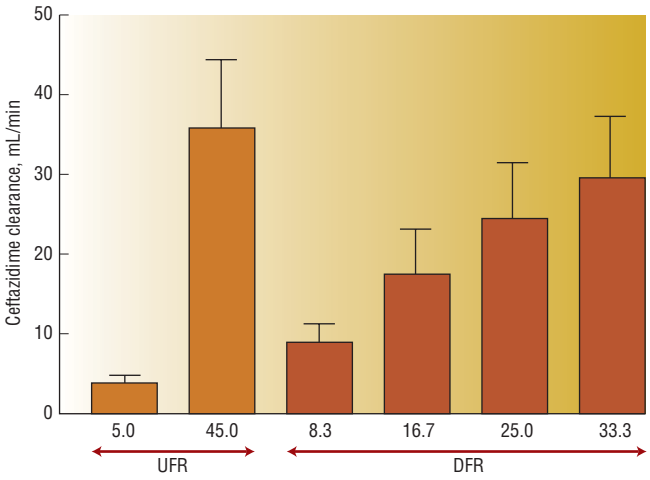

FIGURE 45-5. The effect of increasing ultrafiltration rate (UFR in milliliters per minute) and dialysate flow rate (DFR in milliliters per minute) on the clearance of ceftazidime. *(Adapted from reference 116.)*

Another readily apparent factor that changes drug dosing is the type of RRT used in the patient. CRRT can rapidly remove excess fluid from edematous patients, thereby changing the volume of distribution (V_D) of drugs with limited distribution (low V_D suggesting a greater proportion in the plasma or extracellular fluid) fairly rapidly. Drug clearances attained by IHD, CRRTs, and hybrid RRTs all differ from each other and must be added to any endogenous drug clearance that the patient generates.[105] An algorithmic approach for drug dosage adjustment in patients undergoing CRRT has been proposed.[110] In CRRT, the clearance of a given agent may be ascertained from published reports.[110,117,118] Table 45–9 summarizes the

TABLE 45-9 Predicted and Measured Sieving Coefficients of Selected Drugs

Drug	Predicted	Measured
Amikacin	0.95	0.88
Amphotericin	0.01	0.32–0.4
Ampicillin	0.80	0.6–0.69
Cefepime	0.97	0.47-0.97
Cefoperazone	0.10	0.27–0.69
Cefotaxime	0.62	0.55–1.1
Cefoxitin	0.30	0.32
Ceftazidime	0.90	0.38–0.78
Ceftriaxone	0.10	0.71–0.82
Clindamycin	0.25	0.49–0.98
Digoxin	0.75	0.96
Erythromycin	0.25	0.37
5-Fluorocytosine	0.96	0.98
Gentamicin	0.95	0.81–0.75
Imipenem	0.80	0.78
Metronidazole	0.80	0.80
Mezlocillin	0.68	0.68
N-acetylprocainamide	0.80	0.92
Nafcillin	0.20	0.47
Netilmicin	–	0.85
Oxacillin	0.05	0.02
Phenobarbital	0.60	0.86
Phenytoin	0.10	0.45
Procainamide	0.80	0.86
Theophylline	0.47	0.85
Tobramycin	0.95	0.78–0.86
Vancomycin	0.90	0.5–0.8

Adapted from references 109–112, 117 and 118.

sieving coefficients of frequently used drugs. These data can be used to design initial dosage regimens for patients receiving CVVH.[109,112]

For example, IM is a 48-year-old, 60-kg male with a S_{cr} that has increased from 2.3 mg/dL to 7.2 mg/dL over 3 days. The residual Cl_{cr} value in this patient, calculated using the Jeliffe and Jeliffe equation (see Chap. 44) is 4.8 mL/min. The consulting nephrologist recommends that CVVHDF be initiated using a Fresenius F-80 filter at blood, ultrafiltrate, and dialysate flow rates of 150, 15, and 33.3 mL/min, respectively. The patient is to receive cefepime while on CVVHDF. The patient's residual cefepime clearance (Cl_{RES}) can be estimated using the following regression equation relating Cl_{cr} and cefepime clearance:

$$Cl_{RES}\ (mL/min) = [0.96 \times (Cl_{cr})]\ + 10.9$$

$$Cl_{RES} = [0.96 \times (4.8)]\ + 10.9 = 15.5\ mL/min$$

The total clearance while on CVVHDF would be the sum of the patient's residual clearance and the cefepime clearance associated with CVVHDF (which can be approximated as described above) as follows:

$$Cl_{CVVHDF} = [(UFR + DFR) \times f_u)]$$

$$Cl_{CVVHDF} = [(15 + 33) \times 0.97]$$

$$Cl_T = CL_{RES} + CL_{CVVHDF}$$

$$Cl_T = 15.5\ mL/min + 47\ mL/min = 62.1\ mL/min$$

This patient's clearance value can be used to adjust the cefepime dose as described below. The cefepime clearance in a patient with normal renal function would be calculated as:

$$Cl_{norm}\ (mL/min) = [0.96 \times (Cl_{cr})]\ + 10.9$$

$$Cl_{norm} = [0.96 \times 120]\ + 10.9$$

$$Cl_{norm} = 126.1$$

The dosage adjustment factor would then be:

$$Q = Cl_T/Cl_{norm}$$

$$Q = 62.1 \div 126 = 0.49$$

For this patient's situation, the normal regimen of cefepime would be 2,000 mg (D_n) every 12 hours (τ_n). If one wanted to maintain D_n and extend the dosing interval, then τ_f would be calculated as:

$$\tau_f = \tau_n/Q$$

$$\tau_f = 12\ hours/0.49$$

$$\tau_f \approx 24\ hours$$

This approach suggests the patient should receive cefepime 2,000 mg every 24 hours. If the additional clearance associated with CVVHDF (40.2 mL/min) was not considered, the calculated dosing interval would have been considerably longer. Several variables can impact the outcome of these calculations, including the multiple variables within the dialysis therapy—for example, UFR, blood flow rate, and DFR—and interpatient variability in nonrenal and renal drug clearance, to name just two.

Intermittent Hemodialysis Limitations of IHD-based dosing charts include variability in the patients' individual pharmacokinetic parameters, differences in the dialysis prescription, such as dialyzer blood flow or duration, and the use of new IHD dialyzers. The approach to hemodialysis may also change on a daily basis, especially in unstable individuals with ARF. This could include, for example, the dialyzer/filter used, the duration, the degree of hemofiltration compared to convection, and blood flow rate. Individualization of a dosing regimen may require daily assessment of the clinical status of the patient and any planned or recently administered hemodialysis.

CLINICAL CONTROVERSY

Some clinicians use a standard ESRD dosage regimen despite the fact that renal function can fluctuate such that the patient may be in one dosing range one day and in another the next. Others believe, however, that the patient's clinical need for the drug and any change in the volume of distribution or the RRT therapy should be considered if one has any chance of achieving the target serum concentrations.

Overall, there are a tremendously large number of potential pharmacokinetic and pharmacodynamic alterations to be aware of in the patient with ARF. Unfortunately, there is a dearth of data to quantify these changes, and even less evidence to prove that if one incorporates these considerations into patient care that the associated outcomes will be improved.

EVALUATION OF THERAPEUTIC OUTCOMES

Vigilant monitoring of patients with ARF is essential, particularly in those who are critically ill (Table 45–10). Once the laboratory-based tests (e.g., urinalysis, fractional excretion of sodium calculations) have been conducted to diagnose the cause of ARF, they usually do not have to be repeated. In established ARF, daily measurements of urine output, fluid intake, and weight should be performed. Vital signs should be monitored at least daily, more often if patient acuity of illness is high. Daily blood tests for electrolytes, BUN, and a complete blood cell count should be considered routine for hospitalized patients.

Therapeutic drug monitoring should be performed for drugs that have a narrow therapeutic window that can be measured by the hospital laboratory. If results from these serum drug concentrations cannot be obtained in a timely fashion (<24 hours) to the patient's care team, then their value is limited. When considering approaches to measuring serum concentrations, consensus is limited. Measuring a serum drug concentration prior to hemodialysis has the advantage of allowing time for the result to be reported and redosing done shortly

TABLE 45-10 Key Monitoring Parameters for Patients with Established Acute Renal Failure

Parameter	Frequency
Fluid ins/outs	Every shift
Patient weight	Daily
Hemodynamics (blood pressure, heart rate, mean arterial pressure, etc.)	Every shift
Blood chemistries	
Sodium, potassium, chloride, bicarbonate, calcium, phosphate, magnesium	Daily
Blood urea nitrogen/serum creatinine	Daily
Drugs and their dosing regimens	Daily
Nutritional regimen	Daily
Blood glucose	Daily (minimum)
Serum concentration data for drugs	After regimen changes and after renal replacement therapy has been instituted
Times of administered doses	Daily
Doses relative to administration of renal replacement therapy	Daily
Urinalysis	
Calculate measured creatinine clearance	Every time measured urine collection performed
Calculate fractional excretion of sodium	Every time measured urine collection performed
Plans for renal replacement	Daily

after dialysis with minimal delay. This is especially important if the desired pharmacologic effects are lost during or after hemodialysis is complete because the serum concentrations have become subtherapeutic. Knowledge based on previous observations of how a particular agent is removed for a given dialysis approach and any prehemodialysis serum concentration of the agent can assist in estimating the amount removed and predicting any necessary postdialysis dose. Serum concentrations drawn after hemodialysis may reflect plasma concentrations that are transiently depressed until the drug can reequilibrate from the tissues (plasma rebound effect). The advantage with an after-dialysis level is the greater accuracy in determining how much drug was cleared during hemodialysis, but may delay reestablishing target effects. Greater therapeutic drug monitoring may be necessary in patients with ARF than what is done routinely for other patients because of the potential changes in dynamic status (changing volume status, changing renal function, and RRTs) of ARF patients.

PHARMACOECONOMIC CONSIDERATIONS

ARF is a large financial burden on the healthcare system. Much of this cost is because many of these patients are in intensive care units where daily costs are high. It is estimated that the average total hospital cost of a patient with ARF who requires RRT is approximately $50,000.[119] Most patients who survive ARF regain life-sustaining renal function, but the 5% who do not regain renal function[14] continue to incur the economic and personal costs of dialysis or kidney transplantation. The financial burden is estimated to be $50,000 per year greater than the non–dialysis-dependent patient whose kidneys recovered from ARF. Nonetheless, patients who required RRT for their ARF generally have a good quality of life after recovery.[119]

Medical intervention costs can be normalized to assess total costs using quality-adjusted life-years (QALYs) gained by the intervention. The use of a QALY approach to treatment of critically ill patients with ARF indicates that treating these patients is very expensive relative to other common medical interventions.[120] For example, in 2001, the treatment of critically ill ARF patient cost per QALY was $168,711, compared to treatment of acute myocardial infarction cost per QALY of $45,000, and the routine treatment of hypertension cost per QALY of $31,321.[6] A typical cost per QALY of <$100,000 is considered cost-effective. Although nobody is suggesting that serious ARF not be treated, it is clear that research needs to be done to improve the ARF survival rate to reduce this cost per QALY. Furthermore, it underscores the need to prevent the occurrence of ARF in the first place.

CONCLUSIONS

The unique characteristics of ARF compared to CKD can lead to notable differences in how renal function is measured and how treatment regimens are developed. Most management approaches currently involve prevention and support of the patient once ARF is established, so as to minimize the potential for additional harm to either the patient or kidney. Understanding the constantly changing status inherent to ARF, and how to adjust management regimens is a key component to optimizing therapy.

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ABBREVIATIONS

ARF: acute renal failure

ATN: acute tubular necrosis

BUN: blood urea nitrogen

CKD: chronic kidney disease

CL_{cr}: creatinine clearance

CRRT: continuous renal replacement therapy

CT: computed tomography

CVVH: continuous venovenous hemofiltration

CVVHD: continuous venovenous hemodialysis

CVVHDF: continuous venovenous hemodiafiltration

FE_{Na}: fractional excretion of sodium

GFR: glomerular filtration rate

IHD: intermittent hemodialysis

NSAID: nonsteroidal antiinflammatory drug

QALY: quality-adjusted life-year

RRT: renal replacement therapy

S_{cr}: serum creatinine

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