

# Chapter 26

## ACUTE RENAL FAILURE

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### SUMMARY

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## INTRODUCTION

Acute renal failure (ARF) is a disorder manifested by a sudden decline in renal function and is characteristically accompanied by (a) changes in the concentrations of electrolytes and nitrogenous waste products in the blood and (b) a reduction in urinary output. While ARF has diverse etiologies, most patients sustain injury from renal ischemia, nephrotoxins, or both. ARF usually occurs in the setting of serious injury or illness, and as such, substantially affects morbidity and mortality.

The morbidity and mortality of ARF depend on several factors including the etiology and clinical features of the disease as well as the patient's underlying condition. The mortality of ischemic, oliguric ARF, usually occurring in patients who have sustained trauma or patients with medical or surgical illnesses with shock, exceeds 50%, and may be higher depending on the patient population under study. Conversely, ARF accompanied by substantial urinary output (ie, nonoliguric ARF, in which nephrotoxins play an important role in the pathogenesis<sup>1</sup>) is usually associated with a lower mortality.<sup>2</sup> Finally, covariables such as age and associated extrarenal organ involvement adversely affect outcome.

These patients do not die of renal failure per se, but the presence of renal failure substantially increases the mortality. The availability of dialysis to control fluid and electrolyte imbalances and nitrogenous waste retention has prolonged the duration of illness, with patients surviving 4 to 6 weeks instead of several days. Nonetheless, many

eventually succumb to overwhelming infections (approximately 70%) or pulmonary complications (approximately 30%). The impact of multiple organ failure on survival with ARF is such that when ARF develops without concomitant extrarenal organ failure, as is often seen in obstetrical and radiocontrast injury, the mortality is usually lower than 10%.<sup>3</sup>

Although we have the capability to provide dialysis to the combat casualty, it has become axiomatic that dialysis and modern critical care medicine have not exerted an important effect on the mortality associated with ARF. The reasons for this are not clear; they may relate to an increase in the mean age of the population that sustains ARF or to increased comorbidity in this population. Nonetheless, our current efforts are directed toward preventing ARF, providing better nutrition, and developing more effective drugs to treat infection. Because there is little reason to believe that improvements in dialysis will affect outcome in the majority of patients, we have sought to expand our understanding of the pathophysiology of ARF, with the ultimate goal of preventing renal injury.

It is not the purpose of this chapter to exhaustively review the literature on either experimental or clinical ARF. Such purpose, given the thousands of papers that have been written on this subject, would be unrewarding. The principles outlined herein are designed to assist medical officers, including nephrologists, in the prevention, diagnosis, and management of ARF in combat casualties.

## MILITARY HISTORY

### World War II

ARF has been recognized as a serious problem for military physicians since 1941, when E. G. Bywaters and D. Beall<sup>4</sup> published their classic description of rhabdomyolysis and myoglobin-induced ARF in four patients who sustained crush injuries in the bombings of London, England, during World War II. Since then, our understanding of the pathophysiology of ARF has increased, and our treatment options have expanded substantially. However, posttraumatic ARF continues to be associated with a persistently high mortality,<sup>5</sup> and is a complex medical problem for those who plan the delivery of military healthcare during wartime.

The salient features of the incidence, treatment, and outcomes of combat casualty-associated ARF in U.S. military forces in modern armed conflicts have been reviewed in detail<sup>6</sup> and are summarized here to emphasize the lessons learned.

During the World War II era, blood chemistry analyzers were primitive and not widely available; thus, ARF was usually recognized by the presence of oliguria, hypertension, and pulmonary edema, and only occasionally by azotemia—making it likely that only severe ARF was recognized. Nonoliguric ARF was undoubtedly under-diagnosed. Using data that had been collected and analyzed during 1944 and 1945, but not published until 1952, the Board for the Study of the Severely Wounded<sup>7</sup> included records of patients who were oliguric dur-

ing shock and died within 24 hours of injury. Inclusion of these patients probably led to over-emphasis of the role of parenchymal ARF in their mortality. The cited mortality of ARF—90%—is therefore problematic, although that figure became accepted as the standard mortality of ARF in its untreated state. A more accurate interpretation of the data would place the mortality between 70% and 80%. ARF's severity may well have been increased by the medical realities of the war: evacuation times exceeded several hours, and shock was treated with plasma because supplies of blood and crystalloid fluids like saline were limited. Accordingly, some of the lessons learned from the study of ARF during the World War II era may not be applicable currently: more effective therapy of shock in subsequent conflicts radically changed the apparent incidence and clinical characteristics of ARF.

### Korean War

Nonetheless, recognition of the impact of ARF in World War II led to anticipation of the problem of posttraumatic ARF in troops engaged in the Korean War. At that time, early forms of hemodialysis had been developed and were utilized at a center for kidney treatment established at Wonju, Korea, in 1951. The incidence of ARF during the Korean War was approximately 1 per 200 seriously wounded. The decrease in the mean duration of shock and more-rapid evacuation of wounded, in conjunction with successful use of hemodialysis in the combat zone, resulted in substantial reductions in the observed mortality due to ARF: down to 53% to 60%. In this conflict, ARF was the subject of careful clinical observation, which indicated that the mortality was often due to shock and multiple organ failure.<sup>8,9</sup> Concomitantly, although the overall mortality of patients with ARF remained quite high, two tenets of the treatment of established ARF were developed:

1. Attempts were made to provide nutritional support utilizing high-caloric, low-volume fluid regimens developed for use in oliguric patients.
2. Hemodialysis was utilized in an effort to attenuate the effects of uremia.

### Vietnam War

Many of the lessons learned in Korea were used to advantage during the Vietnam War. The 629th Medical Renal Detachment was formed at Brooke

General Hospital in 1965 and was attached to the Third Field Hospital in Saigon in 1966. Other renal units were placed at Clark Air Force Base in the Philippines and on two U.S. Navy hospital ships. These renal intensive care units had the capability of delivering complete care to casualties with ARF. Nephrologists prescribed and supervised dialysis, which was performed by nurses and corpsmen trained in dialysis. These personnel comprised "K" teams, which gained a substantial body of experience in the management of ARF and the numerous medical problems with which it was associated.

During the Vietnam War, two factors contributed to the decrease in the incidence of ARF to approximately 1 per 600 seriously wounded:

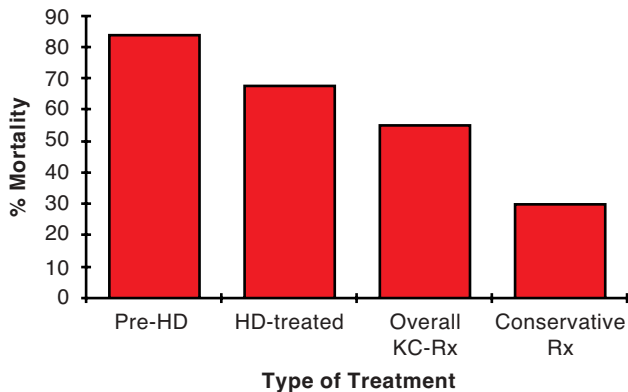
1. Rapid volume resuscitation of casualties, instituted near the geographical site of injury, was widely practiced in Vietnam and reduced the duration of shock.
2. The use of helicopters substantially reduced evacuation times.

Nonetheless, the 55% to 65% mortality of ARF was nearly identical to that seen in the Korean War, despite the facts that hemodialysis was utilized extensively for more severe forms of ARF and peritoneal dialysis was utilized in milder forms of ARF (eg, hemoglobinuria associated with malaria).

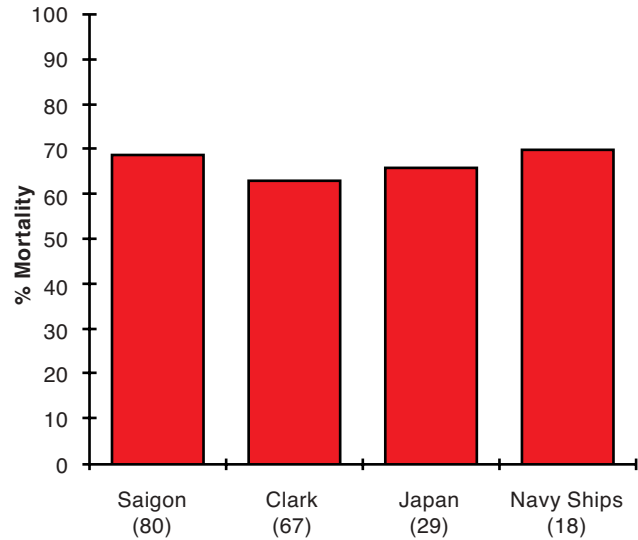
During the Vietnam War, medical officers reported several landmark studies of casualties with ARF. In 1974, W. J. Stone and J. H. Kneppshield<sup>10</sup> described their experience with 62 casualties with ARF who received care in the renal unit of the 629th Medical Detachment in Saigon, and noted a 69% mortality despite the liberal use of dialysis. Sepsis, respiratory failure, bleeding, and hyperkalemia were the causes of death; the two former causes accounted for 89% of the total mortality. In 1972, R. E. Lordon and J. R. Burton<sup>11</sup> described their experience with 67 casualties with ARF treated at Clark Air Force Base. Although frequent dialysis was utilized, the mortality was 63%. These investigators also emphasized the role of infection in ARF, which accounted for 72% of the deaths. In 1975, J. D. Conger<sup>12</sup> conducted a prospective trial of "prophylactic" dialysis compared with dialysis for more conventional indications in 18 patients treated for ARF aboard the USS *Sanctuary*. This study purported to examine the role of prophylactic dialysis; however, it is more accurately characterized as a study of intensive dialysis. Although differences in mortality between patients who received intensive prophylactic dialysis compared with those dialyzed for

conventional indications failed to reach statistical significance, the former group suffered fewer complications. The collective experience with the management of ARF in the Vietnam War served to validate the role of hemodialysis in the management of posttraumatic ARF. Because hemodialysis was simultaneously being widely applied in the civilian treatment of ARF, due in part to the pioneering efforts of R. C. Swann and J. P. Merrill<sup>13</sup> in Boston in 1953, it became an accepted treatment modality for most patients with ARF. Selected features of the experience with ARF in conflict are presented in Figures 26-1 and 26-2.

A new expression of ARF, in which renal dysfunction developed over several days, became evident in both the Vietnam War and the civilian sector during the period 1965 through 1974.<sup>14,15</sup> ARF was noted to develop in critically ill patients with multiple organ failure and was attributed to multiple etiologies, including sepsis and exposure to nephrotoxic drugs. Although some patients required only conservative management, others required dialytic support. At present, the concept of ARF developing without overt shock has reached its fullest expression in the patient with multiple organ failure.<sup>16</sup> Patients with ARF in association with multiple organ failure now represent a large fraction of patients with ARF seen in peacetime, and providing support to them represents a major mechanism for regular and reserve medical officers' maintaining their "go-to-war" skills.



**Fig. 26-1.** Mortality of casualties from acute renal failure during the Vietnam War. Pre-HD refers to patients who were treated before hemodialysis was available. KC refers to patients who were treated in the specialized Kidney Center in the 3rd Field Hospital in Saigon. Data source: Butkus DE. Post-traumatic acute renal failure in combat casualties: A historical review. *Milit Med.* 1984;149:117-124.

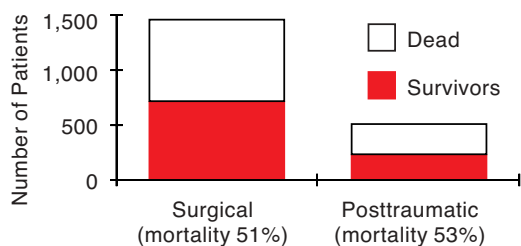


**Fig. 26-2.** Mortality of casualties from acute renal failure in the Vietnam War, stratified as to the location of their dialysis treatment. The numbers in parentheses represent the number of patients treated in each location. Adapted with permission from Butkus DE. Post-traumatic acute renal failure in combat casualties: A historical review. *Milit Med.* 1984;149:121. *Military Medicine*, Official Journal of the Association of Military Surgeons of the United States (AMSUS).

### Military and Civilian Experience Since Vietnam

The experience gained from the wartime treatment of ARF, augmented by knowledge gained from the care and study of patients with ARF since the mid-1970s, has engendered several principles that guide our planning for the care of combat casualties:

1. ARF is a substantial problem in casualties with serious injuries and is often heralded by oliguria due to shock.
2. Identification of patients at high risk for ARF is possible, although there is surprisingly little objective evidence that such identification has been clinically effective.
3. ARF may develop at any time during the treatment and management of the seriously wounded, and even after initial stabilization may result from injury induced by anesthesia, hemolysis, sepsis, or drug toxicity.
4. Given the widespread application of dialysis, casualties rarely die of ARF but instead die of the infections and sequelae of multiple organ failure that accompany severe injuries.



**Fig. 26-3.** Mortality of acute renal failure between 1970 and 1979 in surgical and trauma patients. Data source: Finn WF. Recovery from acute renal failure. In: Brenner BM, Lazarus M. *Acute Renal Failure*. Philadelphia, Pa: WB Saunders; 1983: 755.

A comprehensive review of the mortality of different forms of ARF, factored for the era in which it occurred, has been provided by W. F. Finn,<sup>17</sup> part of whose data are summarized in Figure 26-3.

### Deployable Medical Systems

To provide healthcare for casualties of future conflicts, the Department of Defense has revised doctrine to include the concept of Deployable Medical Systems (DEPMEDS).<sup>18</sup> Military and civilian medical experts, many with experience in conflict, drew up a list of disorders likely to be encountered in combat. Projected incidence data and treatment protocols were defined for each of these patient conditions (this subject is discussed more fully in Chapter 6, Deployable Hospitals). More than 20% of identified patient conditions would be expected to be accompanied by the development of ARF in at least a cohort who sustain the illness or injury. In general, it is estimated that 5% of casualties who sustain either moderately severe, multiple, fragment injuries to the thorax or abdomen; isolated extremity injuries with muscle damage; or severe malaria will potentially require dialytic support at the fourth echelon. Ten percent of casualties who sustain either severe injuries to the thorax or abdominal cavities, alone or in combination, or major crush injuries, particularly of the lower extremities, are expected to require dialysis. Obviously, such

figures could vary depending on the location of the conflict, its intensity, the types of weapons systems utilized, and the triage and evacuation policies of the theater commander. For example, given equal rates and severity of injury, there would likely be more ARF in a conflict in an arid environment, in which water supplies are limited and personnel are dehydrated, than in a more temperate climate.

Under the DEPMEDS doctrine, all equipment and consumable supplies required to perform hemodialysis are in a self-contained module. Only electrical generators are not included in the module. The cohort of personnel required to provide dialysis are delineated, and include a nephrologist, a dialysis-trained nurse, and corpsmen trained in dialysis. This team is similar to the “K” teams of Korea and Vietnam.

### Civilian Disasters

Although much of the contingency planning for the delivery of care to patients with ARF in future conflicts is based on experience gained in prior conflicts, these concepts have been validated recently in a peacetime situation analogous to combat. The earthquake in 1988 in Armenia produced more than 600 patients with ARF secondary to crush injury. An international team of medical personnel, in conjunction with support from the dialysis industry, was rapidly mobilized to provide personnel and supplies for over 400 patients, at times administering 150 dialysis treatments per day. The magnitude of the disaster required that more than 80,000 lb of dialysis supplies be shipped from the United States. Intrinsic resources in Armenia and in Moscow were utilized for at least one third of the patients.<sup>19</sup> Because much more ARF could have been encountered if more casualties had survived, the magnitude of the problem of ARF in this setting underscores the need for the capability to rapidly mobilize large quantities of consumable supplies, sophisticated medical equipment, and appropriately trained personnel. It is this expeditious deployability of healthcare—eliminating the need to preposition personnel, supplies, and equipment—that is the basic tenet of DEPMEDS.

## PATHOGENESIS OF ACUTE RENAL FAILURE

### Classic Mechanisms of Renal Failure

The pathogenesis of ARF has been the subject of considerable experimental study, clinical observation, and review.<sup>20–30</sup> Information obtained from

nearly all experimental models of ARF indicates that both renal blood flow and the glomerular filtration rate decline early after the initial insult. This early period, lasting from hours to days, is termed the *initiation* phase. Gradually, renal blood flow

returns toward normal, while the glomerular filtration rate remains depressed. This period, which may last from days to weeks, is called the *maintenance* phase. In general, when ARF persists for longer than 3 months, end-stage renal disease is assumed.

Four mechanisms have been proposed to explain the pathophysiology of ARF (Exhibit 26-1). These mechanisms—renal vasoconstriction, reduction in glomerular filtration, tubular obstruction, and back leak of filtrate—have been identified and delineated using models in which the renal artery is either clamped or infused with norepinephrine, or in which hemorrhage of sufficient severity is produced to result in sustained systemic hypotension. This latter model is of particular interest as it closely mimics the clinical setting of posttraumatic ARF, and because the kidney is exposed to the multiplicity of hormonal and neurogenic alterations that accompany shock. A similar model involves the injection of glycerol into a large muscle of an animal, which results in muscle necrosis and vascular pooling in the involved extremity, and is closely analogous to crush injury.

The classic mechanisms of ARF can be divided into (a) those that exert primarily vascular effects and (b) those that exert tubular effects. The vascular mechanisms include reductions in both renal blood

flow and the intrinsic filtration capability of the glomeruli. The tubular mechanisms include tubular obstruction by casts and back leak of filtrate. Undoubtedly, all four mechanisms participate in the injury seen in existent models of ARF. The contribution of each, however, is likely to differ depending on the model used. Thus, reduced renal blood flow is the prominent feature of ARF induced by hemorrhagic hypotension, while intratubular obstruction by casts is more prominent in ARF induced by glycerol. Models most useful for the study of clinical ARF combine features of all suspected mechanisms.

### *Vascular Mechanisms*

An early decrease in renal blood flow and an increase in renal vascular resistance are consistent findings in virtually all types of experimental ARF. The reduction in renal blood flow results in integrated hormonal, neural, and intrinsic renal responses, all of which are designed to restore the extracellular fluid, renal blood flow, and renal function. ARF is the result when these mechanisms fail.

**Reduced Extracellular Fluid Volume.** Sensor mechanisms for detection of decreased extracellular fluid include baroreceptors located throughout the body. These receptors are sensitive to mechanical stretch and transmural pressure. Intrathoracic volume receptors exist in both the atria and the pulmonary capillaries. Activation of these receptors results in increased traffic both in sympathetic fibers and in cranial nerves IX and X, the latter to centers in the hypothalamus and medulla. Arterial volume sensors in the carotid sinus have been postulated to provide stimuli for the kidney to retain sodium and water, although the mechanisms of their actions have not been completely defined. Finally, baroreceptors located in the juxtaglomerular apparatus of the kidney are exquisitely sensitive to reductions in renal perfusion pressure. Their activation initiates the release of renin and the subsequent formation of the vasoconstrictor angiotensin II, and release of the sodium-retaining hormone aldosterone. Effector mechanisms react to reduced renal blood flow and induce vasoconstriction and sodium and water retention, both of which are designed to restore the extracellular fluid. These mechanisms include catecholamines, angiotensin II, arginine vasopressin, aldosterone, vasoconstrictor prostaglandins, and intrinsic renal tubular events, which participate in an integrated response.

**Decreased Glomerular Filtration.** The second vascular mechanism that occurs is decreased filtra-

#### **EXHIBIT 26-1**

#### **CLASSIC MECHANISMS OF ACUTE RENAL FAILURE**

##### **Vascular Mechanisms**

- Renal vasoconstriction
  - Reduced blood flow
  - Increased resistance
- Reduced glomerular filtration
  - Endothelial morphology
  - Reduced glomerular area

##### **Tubular Mechanisms**

- Luminal obstruction
  - Cellular debris
  - Casts
- Back leak of filtrate
  - Inulin
  - Other markers

tion capability of the glomeruli. Filtration is a function of the intrinsic permeability characteristics of the glomerular capillary membrane, the surface area available for filtration, and the net pressure for filtration (defined by Starling forces) across the glomerular capillaries. The aggregate capability for filtration is expressed by the term  $K_f$ , and is reduced *pari passu* the reduction in renal blood flow, as the latter is a major determinant of glomerular filtration rate. Such reduction may be due either to a direct effect of ischemia on the basement membrane of the capillary or to reduction in the surface area of the capillary, perhaps mediated by angiotensin II.

### *Tubular Mechanisms*

**Obstruction.** Obstructing casts originate from cellular debris, principally sloughed epithelial cell fragments and brush border membranes, which coalesces with Tamm-Horsfall mucoprotein of uroepithelial origin. The resultant obstruction of the tubular lumen raises intratubular pressure in excess of glomerular filtration pressure, so that glomerular filtration ceases.

**Back Leak.** The second tubular mechanism is back leak of filtrate, in which a marker of glomerular filtration rate, usually inulin, can be shown to traverse the damaged tubular epithelium from the tubular lumen into the renal circulation. Such movement of solute could be due either to disruptions in intercellular bridges or, most likely, to impairment in the ability of epithelial cells to restrict the transcellular movement of normally excluded solutes.

### **The Nature of Cellular Injury**

If the four events detailed above were sufficient explanations for the mechanisms of ARF seen after ischemic or nephrotoxic injury, we could infer that maneuvers successful in ameliorating one or more factors might exert a beneficial effect on the incidence or severity of renal injury. Unfortunately, the results of such strategies have been largely inconsistent and only variably successful. The lack of success could result from an inability to distinguish precisely between the initiation phase of ARF, when damage could putatively be reversed, and the maintenance phase, when injury is established. Alternatively, the factors believed to be operative in the classic explanation of the pathophysiology of ARF may be epiphenomena.

Since the early 1980s, our understanding of the pathogenesis of ARF has been amplified substan-

tially by investigation into the cellular basis of ischemic and toxic renal injury.<sup>31</sup> Research utilizing kidney, heart, and liver tissue has formed a base for additional studies with renal tubular epithelia, mesangial and endothelial cells, as well as subcellular constituents. These studies have provided information that has vastly improved our understanding of the mechanisms by which ischemic and nephrotoxic injury occur. Our current research seeks to formulate unifying hypotheses of renal injury, with the understanding that whole-organ injury is predicated on, and best understood in the context of, injury to its constituent cells.

Ischemia initiates a cascade of events that result in cell death. Changes in cellular metabolism, alterations in cation adenosine triphosphatases (ATPases), activation of phospholipases, generation of toxic free radicals, and changes in the intrinsic nature of the renal epithelial membrane itself<sup>32</sup> have been studied in a variety of models of ARF. While the nature of the cellular response to injury varies somewhat depending on the model, these responses are sufficiently homogenous that inferences about possible therapeutic maneuvers can be made.

Two of the central events in the cell's response to ischemia are (a) the simultaneous reduction in the availability of adenosine 5'-triphosphate (ATP) and other high-energy phosphate compounds and (b) an increase in the formation of adenine nucleotide degradation products.<sup>33</sup> Without an adequate supply of ATP to maintain normal function, the cell's ability to maintain its metabolic integrity is severely compromised. Thus, diminished activity of the sodium-potassium ATPase results in the accumulation of intracellular sodium and swelling of the cell. Similarly, inhibition of the calcium ATPase results in cytosolic and mitochondrial calcium overload, with impairment of the functional integrity of the electron transport chain.<sup>34,35</sup> These findings have led to the use of stimulators of sodium-potassium ATPase such as thyroid hormone, which has been found to be beneficial in a number of different models of ARF.<sup>36</sup> Similarly, some investigators<sup>37</sup> have demonstrated a beneficial effect of calcium channel blocking agents such as verapamil.

The results of ischemia are (a) the metabolism of ATP to hypoxanthine and (b) loss of nucleosides from the cell.<sup>30</sup> This latter event inhibits the regeneration of ATP and cell recovery. During reperfusion, the enzyme xanthine oxidase, which is formed during periods of ischemia from xanthine dehydrogenase, converts hypoxanthine to xanthine, with the concomitant generation of toxic free radicals through iron-requiring reactions known as the

Haber-Weiss and Fenton reactions.<sup>38-40</sup> Inhibition of xanthine oxidase by allopurinol prevents the irreversible degradation of hypoxanthine, so that when ischemia resolves, purine salvage pathways can utilize adenine nucleotides for resynthesis into ATP.<sup>41</sup>

Activation of phospholipase A<sub>2</sub> results in peroxidation of lipids in the cell membrane, a phenomenon that can be measured by the accumulation of malondialdehyde. Phospholipase A<sub>2</sub> is activated by excessive concentrations of calcium, which may result from diminished activity of calcium ATPase. Moreover, with reperfusion, enzymatic changes occur that result in the formation of large

quantities of hydrogen peroxide and the hydroxyl ion.<sup>39,40</sup> These moieties are extremely toxic to cell contents. In the laboratory, the use of free radical scavengers such as superoxide dismutase and dimethyl thiourea has shown some promise in abrogating renal injuries caused by oxygen-derived free radicals.<sup>42</sup>

Taken collectively, the voluminous literature that has appeared since the early 1980s on the cellular basis of ARF demonstrates how much our understanding of this condition has expanded. As we will see later, however, the therapeutic maneuvers that follow from this understanding have not yet reached the stage of widespread clinical application.

## CLINICAL ASPECTS OF ACUTE RENAL FAILURE

No single definition of ARF is accepted by all clinicians, although many accept the diagnosis if the serum creatinine concentration increases by 50% above its baseline. The blood urea nitrogen (BUN) concentration is affected by diet, hydration, and medications; therefore, it is not, by itself, a particularly valid marker of renal function. Acute renal dysfunction commonly is detected by alterations in volume of urine, particularly acute *oliguria*, which is defined as urinary output less than 400 mL/d, or approximately 20 mL/h. Acute *anuria* is defined as urinary output less than 50 to 100 mL/d, but this is an uncommon manifestation of ARF. *Polyuria* in the context of acute renal dysfunction should be reserved to describe urinary output of several liters of urine daily. Individuals who excrete urine in these amounts are often found to have partial urinary tract obstruction. The term *nonoliguric* characterizes the substantial portion of patients who have significant ARF, yet maintain urinary output of 1 to 2 L/d.

### Distinguishing Between Acute Oliguria and Acute Renal Failure

Operationally, the differences between acute oliguria and ARF are substantial (Exhibit 26-2). The former term implies that there may be a reversible aspect of the renal dysfunction (ie, prerenal or postrenal injury), while the latter connotes injury that may require days to weeks to resolve.

*Prerenal azotemia* is renal dysfunction that results from any absolute or relative deficiency of blood or extracellular fluid. The consequent reduction in renal blood flow results in activation of the effector mechanisms that already have been mentioned. Urinary flow and sodium excretion decrease be-

cause the physiological response to perceived volume depletion is to conserve salt and water avidly.

*Postrenal azotemia*, which is generally caused by obstruction of the urinary tract, elicits physiological responses that are similar to those seen in prerenal azotemia. The causes of obstructive injury deserve emphasis, as they may not be seen frequently by nonsurgical physicians. First, obstruction of the ureters above the level of the bladder

#### EXHIBIT 26-2

#### DIFFERENTIAL DIAGNOSIS OF OLIGURIA

##### Prerenal Azotemia

- Absolute blood loss
- Absolute or relative loss of extracellular fluid
- Heart failure
- Liver failure
- Nephrotic syndrome

##### Postrenal Azotemia

- Intravesicular obstruction
- Retroperitoneal hemorrhage
- Ureteral injury with single kidney

##### Intrinsic Acute Renal Failure

- Renal ischemia
- Nephrotoxins
- Acute glomerulonephritis
- Acute tubulointerstitial nephritis



may result from pelvic trauma or surgery, in which the ureters can be obstructed by blood or by inadvertent ligation. Rarely, obstruction may be the first sign of a leaking aorta or vena cava. In this situation, blood causes a desmoplastic response resulting in encasement of the ureters. Obviously, supraventricular obstruction will only induce substantial renal failure should both ureters be involved, or if the patient has only one kidney, a condition that occurs in 1 in 900 to 1,000 individuals. Second, individuals who are susceptible to renal calculi may experience episodes of nephrolithiasis if climatic conditions are unfavorable (eg, dehydration in the desert). However, renal calculus disease will cause oliguria or ARF or both if the stones are bilateral, or if the stones form in a patient who has a single kidney. And third, because it is virtually routine to place an indwelling bladder catheter in seriously injured casualties, many cases of oliguria due to postrenal causes should be detected and definitively treated early, before substantial reduction in renal function occurs. The most common cause of urinary tract obstruction is an indwelling bladder catheter that has become occluded or dislodged; therefore, the integrity of the drainage system should be verified at the first sign of diminishing urinary output.

*Intrinsic ARF* has a variety of causes. Moreover, any prerenal or postrenal condition can result in established ARF if uncorrected for sufficient time. The period that must elapse before reversible injury becomes irreversible is variable. Thus, relatively trivial insults result in renal injury in some patients, while substantial insults can be tolerated by others before renal dysfunction is irreversible. Such differences may result from the kidneys' autoregulatory ability. In the otherwise healthy human, the lower limit of mean arterial pressure for autoregulation is approximately 60 to 70 mm Hg. This corresponds to systolic blood pressures of 80 to 90 mm Hg. The time that renal blood flow can be maintained under more severe hypotensive conditions is unknown.

Other factors besides those related to volume depletion—including hypercapnia and hypoxemia, frequent concomitants of acute respiratory failure—can also result in decreased renal blood flow.<sup>43</sup> Cross-clamping of the aorta results in the same response even if a surgically induced alternate pathway for perfusion, around the aortic cross-clamp, is provided to the kidneys.<sup>44</sup> Agents that disrupt the balance between systemic and intrarenal vasoconstrictor and vasodilatory hormones, which participate in the maintenance of renal blood flow, are

associated with marked reductions in renal blood flow. These agents, including the nonsteroidal antiinflammatory agents and angiotensin-converting enzyme inhibitors, are particularly injurious when the extracellular fluid volume is subnormal, and renal blood flow is predicated on the balance between vasoconstrictor and vasodilator hormones.<sup>45</sup> Finally, it is intuitive that renal injury might be more likely or more severe with a combination of injurious factors than with a single factor. Given the dependence of the kidneys on renal blood flow for oxygen delivery, any situation in which oxygen is reduced would make the kidneys more susceptible to either ischemic or nephrotoxic insult.

Renal ischemia accounts for ARF in most patients, although nephrotoxic injury has become increasingly important in peacetime medical practice.<sup>1</sup> Patients who sustain nephrotoxic injury often have sepsis, and the coexistent hemodynamic changes associated with sepsis often result in renal ischemia and undoubtedly enhance the injurious effects of nephrotoxic substances, drugs, or diagnostic agents.

The military physician's task is to distinguish between oliguria that results from correctable causes (ie, prerenal or postrenal failure) and established ARF. Although the spectrum of causes of ARF in a peacetime environment is quite broad, relatively few disorders cause ARF on the battlefield; and many of the rarer causes of ARF in peacetime practice, such as acute glomerulonephritis, are not likely to be encountered at all by medical officers dealing with combat-associated ARF. Finally, the distinction between ischemic and nephrotoxic causes is often artificial because a substantial portion of patients have elements of both types of injury.

### Diagnostic Assessment

Collectively, the history, physical examination, biochemical analyses of serum and urine, urinalysis, and judicious use of renal imaging studies almost always provide the information needed by the clinician to determine whether there is a readily reversible cause of acute renal dysfunction or the patient has established ARF. Medical treatment facilities in the combat zone will have limited laboratory capability, but rearward facilities, particularly fixed general hospitals, may have a wide range of sophisticated diagnostic equipment. At times, the volume status of the patient is difficult to assess, and measurement of central venous pressure or pulmonary capillary wedge pressure is necessary.

However, hemodynamic monitoring, while providing valuable information, can be time-consuming to institute, and may delay fluid resuscitation and prolong renal ischemia.

### ***Patient History***

The medical officer's review of available records, including flow sheets, nurses' notes, and medications, is essential, particularly in patients who develop ARF during hospitalization. Recent hypotension, either profound or subtle but sufficient to cause decreased renal perfusion, may have occurred, and daily weights and accurately measured urinary outputs may be of substantial value.

The patient's history of drug therapy is also important, as many drugs, particularly antibiotics and nonsteroidal antiinflammatory agents, can cause nephrotoxic injury either alone or in concert with decreased renal perfusion. Aminoglycoside antibiotics are associated with nephrotoxicity in approximately 10% of patients. Risk factors for toxicity include heart failure, liver disease, and other states associated with decreased renal perfusion.<sup>46</sup> The most powerful predictor of toxicity is the duration of therapy. Renal toxicity is seldom seen with fewer than 5 to 7 days of therapy; the incidence increases substantially if therapy exceeds 10 days.

Many patients with ARF have few symptoms and signs other than those related to the causative disorder. Symptoms are related to the rapidity of onset and severity of dysfunction and the patient's underlying condition, and may include nausea, vomiting, or altered mental status. A diffuse bleeding diathesis, with gastrointestinal, nasotracheal, and puncture-site hemorrhage, may occur with severe azotemia. Typically, however, azotemia is largely asymptomatic unless the BUN and creatinine exceed 100 to 120 mg/dL and 6 to 8 mg/dL, respectively; or if azotemia develops extremely rapidly (eg, over 24–48 h). Acidemia can be asymptomatic; however, if severe, it may result in hypotension from depression of myocardial performance or reduction in peripheral resistance. Hyperkalemia may result in cardiac arrhythmias and skeletal muscle weakness. The latter may be extremely difficult to detect in the critically ill patient. All the features described above can be caused by factors other than azotemia.

Some patients develop symptoms of volume overload rapidly, which may reflect aggressive fluid therapy. Fluid therapy is frequently continued in oliguric patients for several hours, until the signifi-

cance of diminishing urinary output is finally appreciated. Although oliguria is the most common manifestation, nonoliguric ARF is frequently seen with nephrotoxic injury. As has been mentioned, polyuria is characteristic of urinary tract obstruction, and anuria is typical of vascular catastrophes or complete urinary tract obstruction.

### ***Physical Examination***

The physical examination is useful in helping to determine whether the patient is volume depleted or volume overloaded, or the urinary tract is obstructed. Crucial elements include assessments of skin turgor and edema, and the cardiac, pulmonary, and genitourinary examinations. Accurate weights or fluid flow sheets or both, blood pressure assessment for orthostatic hypotension, and proof of a properly draining urinary tract are essential.

### ***Biochemical Analyses of Blood and Urine***

The concentrations of BUN and creatinine increase steadily during the course of ARF because production remains relatively constant while excretion is profoundly decreased. Daily increments of BUN and creatinine usually average at least 20 to 30 mg/dL and 1.3 to 1.5 mg/dL, respectively. More-rapid incremental changes in the BUN may reflect excessive catabolism or gastrointestinal hemorrhage, while excessive increments in the serum creatinine may reflect muscle necrosis from rhabdomyolysis. Although the measurement of renal function using the serum creatinine concentration is not as accurate as calculating clearances from timed urine collections, it is sufficiently accurate for diagnosing posttraumatic renal dysfunction and for initiating rational therapy.

Other abnormalities commonly encountered include metabolic acidosis, which results from retention of endogenously produced acid. The serum bicarbonate concentration averages 17 to 18 mmol/L in uncomplicated cases. Hyperkalemia may result from limited excretion and acidemia. Potassium concentrations usually range from 5.0 to 6.5 mmol/L. Hyperphosphatemia occurs because phosphate excretion is negligible. In the absence of major tissue destruction, phosphate concentrations rarely exceed 8 mg/dL. However, such levels, in conjunction with the inhibition of the effect of vitamin D and the resistance to the actions of parathyroid hormone that occur in ARF,<sup>47</sup> result in hypocalcemia. In the absence of obvious blood loss, the

hematocrit should fall over 5 to 7 days to a level of 0.23 to 0.27, and may reflect volume overload, covert blood loss, and bone marrow suppression.

### *Urinalysis*

Biochemical and microscopical analyses of the urine are extremely important in treating patients with ARF, as the tests may provide evidence of prerenal or postrenal azotemia, or may support the diagnosis of established ARF. The patient with prerenal azotemia should have concentrated urine with high urine-to-plasma ratios of urea, creatinine, and osmolality, and a low urinary sodium concentration. Similar values are found in patients with acute urinary obstruction. The patient with established ARF usually loses the ability both to concentrate the urine and to conserve urinary sodium, with low urine-to-plasma ratios of solute and high urinary sodium concentrations. Similar values are found in patients with ARF from chronic obstruction of the urinary tract. Indices of renal function such as the fractional excretion of sodium and the renal failure index are manipulations of these basic data, all of which should be interpreted cautiously if the patient has received diuretics in the 12 to 18 hours prior to their determination.<sup>48</sup> Nonetheless, biochemical analyses of urine can accurately distinguish between prerenal or postrenal failure and established ARF in nearly 90% of cases.

The information gleaned from the microscopical examination of the urine is so critical that the physician should examine it personally. The urine sediment is typically relatively unremarkable in prerenal and postrenal azotemia, although it may

contain hyaline and granular casts. Hematuria may be present if a catheter is in place. Conversely, the sediment in ARF contains many granular casts, and, most importantly, renal tubular epithelial cells and other cellular debris, which give rise to a very "dirty" sediment. Experienced observers can distinguish between prerenal or postrenal failure and established ARF on the basis of the sediment in approximately 85% to 90% of cases.

### *Radiographic Studies*

Imaging of the kidneys in patients with ARF should be limited to those studies that demonstrate whether there are two kidneys, calculi, and urinary tract obstruction. Although a technically well-done renal ultrasound examination is the imaging test of choice, ultrasound is not now available in the combat zone, and such capability may be limited even further to the rear. Thus, plain radiographs of the abdomen should be obtained, and may suffice to determine the number of kidneys and to demonstrate radiopaque calculi. Because the renal shadows are often obscured by bowel gas, computed axial tomography, which is available at fourth-echelon hospitals, is far superior and should be performed if the question of urinary obstruction cannot be resolved. Such scans should always be performed without radiocontrast agents to avoid further injury from these agents. Nuclear medicine scans have virtually no role in the evaluation of the patient with suspected ARF. In patients with true anuria, selective angiography of the renal vessels may be required to evaluate whether a vascular catastrophe has occurred.

## PREVENTION OF ACUTE RENAL FAILURE

There has been a resurgence of interest in preventing ARF in patients known to be at high risk since, despite aggressive therapy, established ARF remains associated with substantial mortality. Moreover, advances in the understanding of the abnormalities of cell biology that occur in ARF have suggested avenues for new therapeutic regimens. Finally, we have developed sufficient expertise to be able to predict with some accuracy who is at risk for the development of ARF. Prospective identification of high-risk patients should allow for proactive intervention to prevent the occurrence of ARF. This assumes that preventing ARF may be more rewarding than improving the quality of care of patients with established ARF.

### **Identification of High-Risk Patients**

A number of investigators have conducted studies of patients with ARF and have identified clinical scenarios in which patients are likely to be at high risk for ARF. These studies have also shown that ARF is almost always multifactorial (ie, it seldom results from a single insult).

In 1983, S. H. Hou and her colleagues<sup>49</sup> prospectively studied more than 2,000 consecutive hospital admissions and found 129 episodes of ARF in 109 patients, for an incidence of 4.9%. She further delineated those factors that appeared to be causal in the development of ARF. Decreased renal perfusion accounted for 54 (42%) of the episodes. Among

the causes of decreased renal perfusion were volume depletion in 41%, cardiac dysfunction in 30%, and sepsis in 19%. ARF developed postoperatively in 23 patients (18%); however, only 12 of the patients had documented hypotension. ARF in association with cardiac and vascular surgery had incidence rates of 15% and 8%, respectively. Administration of radiocontrast agents was associated with ARF in 16 (12%) of the episodes, although such injury was only rarely seen in patients who had normal serum creatinine concentrations at the time the contrast medium was administered. Aminoglycoside administration accounted for 9 (7%) of the episodes, while miscellaneous causes, such as the hepatorenal syndrome or unknown causes, were implicated in 27 (21%) of the episodes. Of particular interest was the investigators' inference that 55% of all episodes were partly iatrogenic.

A similar analysis had been performed in 1982 by H. H. Rasmussen and L. S. Ibels,<sup>50</sup> who studied 143 patients with hospital-acquired ARF for the purpose of identifying risk factors and the nature of the acute insults with which ARF was associated. The presence of hypertension, preexistent renal disease, and diabetes were the most prominent risk factors associated with the development of ARF. Sepsis, administration of nephrotoxins such as aminoglycoside antibiotics or radiocontrast agents, myoglobinuria from rhabdomyolysis, and volume depletion were the most common acute insults resulting in ARF. The investigators noted that 48% of the patients had more than one risk factor, and 62% had more than one acute insult. More importantly, analysis of the entire dataset demonstrated that the number of acute insults was additive as a determinant of both the incidence and severity of ARF.

In research published in 1990, F. Jochimsen and colleagues<sup>51</sup> extended and expanded these observations in a prospective analysis of 261 patients who had ARF and were in an intensive care unit. Two groups of patients, 95 with ARF severe enough to require dialytic support, and 166 patients whose ARF did not require dialysis, were studied. Bleeding, volume depletion, sepsis, administration of antibiotics, cirrhosis, and diabetes were identified as the risk factors associated with more-severe ARF. Patients with multiple risk factors were far more likely to develop ARF than patients with a single risk factor.

These studies, in conjunction with the clinical experience of most nephrologists, reinforce the concept that patients without preexisting comorbidity appear to be relatively resistant to the development of ARF and may be able to withstand a single insult

without developing ARF. For example, uncomplicated gastrointestinal hemorrhage in otherwise healthy patients rarely results in ARF.<sup>52</sup> Likewise, uncomplicated myocardial infarction is also infrequently associated with ARF.<sup>53</sup>

In victims of trauma, the nature of the injury in large part determines whether the patient will be at risk for the development of ARF. Thus, patients who sustain only isolated limb or head injuries rarely develop multiple organ failure and ARF. Conversely, injuries to the abdomen, with or without other injuries, are accompanied by the development of ARF in a substantial number of patients.

In the conflict setting, casualties who develop oliguria can be categorized into three groups. The first consists of patients in whom relative or absolute hypotension has been present for varying times before medical care is instituted. These patients are frequently in shock. Resuscitative efforts may be successful in restoring urinary output and renal function. In such patients, the incidence and severity of renal dysfunction, manifested by oliguria and prerenal azotemia, are functions of (a) how long the renal insult has been present and (b) how efficacious are the efforts to restore effective circulatory function. These patients are at high risk for subsequent renal injury, and every effort must be made to prevent further ischemic or nephrotoxic injury.

The second group includes casualties who have sustained severe and prolonged insults, for whom resuscitative efforts have not been successful, and in whom ARF has become established. The duration or intensity of shock may have resulted in additional ischemic injury to the brain, heart, gastrointestinal tract, or liver. These patients may often require surgery, and the presence of multiple organ failure predicts substantial morbidity and mortality. Many of these patients will require prolonged and aggressive nutritional and dialytic support.

The third group of casualties consists of those who develop ARF while under medical care, during or after initial evaluation, stabilization, evacuation, and treatment. These patients may not be oliguric; thus, ARF may be detected by biochemical analysis of their blood. Hypotension may have been part of their presenting picture, and sepsis may have been associated with renal ischemia. Often these patients have undergone or will undergo surgery, or require the administration of nephrotoxic drugs or diagnostic agents. Renal injury may have to be tolerated as part of the cost of effective treatment for the casualty's condition. A small fraction of this group develop ARF because the urinary tract may have been, or has become, obstructed.

While therapeutic efforts may differ somewhat among these three groups, the basic principles of the initial assessment of the patient with ARF are applicable to all. Moreover, the information gained from risk-factor identification and analysis, coupled with an enhanced understanding of the pathophysiology of ARF, has provided opportunities for proactive intervention to protect renal function. Before examining methods of renal protection in detail, we must first discuss volume expansion and the pharmacological agents that are used in such management strategies.

### Volume Expansion

The beneficial effects of volume expansion have been known for years. Although the mechanism or mechanisms by which volume expansion abrogates renal injury are not completely defined, at least four mechanisms are thought to be operative. First, volume expansion exerts a salutary effect on renal hemodynamics by inhibiting intrarenal renin release, with a reduction in the concentration of the vasoconstrictor angiotensin II. Second, it decreases the activity of the catecholamine-mediated renal nerves by direct intranephronal mechanisms; consequently renal blood flow is maintained. Third, volume expansion results in a decrease in the activity of the intrathoracic baroreceptors that play a central role in the control of renal blood flow. Diminution in their activity results in both decreased traffic in the renal nerves and minimal renal vasoconstriction. The importance of these baroreceptors is illustrated by their role in hypotension with cardiac failure. This situation, in which the atrial baroreceptors are distended and less active than when they are collapsed, results in a lesser decrease in renal blood flow than does equivalent hypotension from absolute volume depletion. And fourth, some data suggest that saline may exert a beneficial effect by inducing a solute diuresis, an effect that may be independent of the renin-angiotensin axis.<sup>54</sup>

There is evidence that volume expansion can reduce the incidence or severity of clinical ARF. The reduction in the rate of ARF per seriously injured casualty from the Korean War to the Vietnam War has been mentioned previously, and is undoubtedly due in large part to rapid and aggressive volume resuscitation of casualties prior to their transport to definitive medical care. Other evidence comes from studies of rhabdomyolytic-induced ARF. In 1979, F. Eneas, P. Y. Schoenfeld, and M. H. Humphreys<sup>55</sup> reported a salutary effect of

bicarbonate diuresis in patients with rhabdomyolysis. In other forms of ARF (eg, those induced by cis-platinum and amphotericin), volume expansion with hypertonic saline or mannitol clearly results in attenuation of renal injury.<sup>56</sup> However, studies utilizing mannitol must be interpreted cautiously regarding the effects of volume expansion, because the contribution of mannitol may be as a volume expander, osmotic diuretic, or both.

In summary, volume expansion, usually done with normal saline but occasionally with isotonic fluids containing alkali or other base precursors, is generally accepted as beneficial in the prevention of ARF. This is particularly true if hypovolemia is present, because interpretation of the numerous studies examining the role of volume expansion in the prevention or attenuation of ARF suggests that volume expansion may prevent incipient ARF in many situations of prerenal failure. A trial of volume expansion can be both diagnostic and therapeutic, in the sense that it can reduce the contribution that renal ischemia makes to the pathogenesis of ARF. Moreover, a large body of clinical experience supports the concept that the volume-expanded state confers protection against renal injury. This concept has implications for fluid and nutritional support of troops deployed to arid regions, in whom subclinical volume depletion of several liters may occur rapidly unless adequate salt and water are provided. In such situations, maintenance of an adequate extracellular volume may be the most important mechanism by which ARF can be prevented.

### Pharmacological Interventions

A number of agents have been evaluated in experimental and clinical studies for their ability to abrogate or attenuate the untoward effects of ischemia or nephrotoxins.<sup>57</sup> Many of these have been used in the management and, at times putatively, in the prophylaxis of ARF (Table 26-1). Most studies with loop and osmotic diuretics and vasodilators have been conducted in either laboratory or clinical ARF after the renal injury has been induced. Newer agents—including dopamine, adenine nucleotides, calcium channel-blocking agents, atrial natriuretic factor, and thyroid hormone—and agents that (a) interfere with the generation of or (b) scavenge toxic free radicals have received much attention recently. This discussion concentrates on agents that are presently in unrestricted clinical use, and provides a brief overview of the rationale for the use of the remaining agents.

**TABLE 26-1**  
**AGENTS USED IN THE PREVENTION OF**  
**ISCHEMIC ACUTE RENAL FAILURE**

Agent	Status
Furosemide	In use
Mannitol	In use
Dopamine (low-dose)	In use
Thyroid hormone	Clinical trials
Adenine nucleotides	Causes hypotension
Xanthine oxidase inhibitor	Transplant trials
Free-radical scavengers	Clinical trials
Calcium channel blockers	Clinical trials
Prostaglandins	Causes hypotension
Atrial natriuretic factor	Used with dopamine

### *Loop and Osmotic Diuretics*

The use of loop diuretics (ie, a class of diuretic agents that act by inhibiting reabsorption of sodium and chloride in Henle's loop) in both laboratory and clinical ARF is based on three theoretical constructs. First, furosemide is a renal vasodilator that might contribute to the restoration or maintenance of renal blood flow in the presence of renal ischemia. Second, loop diuretics also increase tubular flow rate, potentially abrogating the effects of intratubular obstruction. Third, because the vast majority of renal oxygen consumption is utilized to reabsorb sodium, inhibiting sodium reabsorption by the renal tubules should reduce renal oxygen consumption and renal work.

Furosemide has been shown in controlled clinical trials to promote urinary output in patients with ARF.<sup>58,59</sup> These trials contained small numbers of patients, so their conclusions may be flawed. Nonetheless, many patients' urinary output increased, although neither the severity, duration, nor outcome of ARF was affected. A more problematic issue is the role of furosemide in "converting" oliguric to nonoliguric ARF. A substantial proportion of oliguric patients increase their urinary output when given furosemide. Whether this is due to abrogation or attenuation of the severity of ARF, or is simply a marker of those patients with reversible, or intrinsically mild, ARF, is not known. No studies have been conducted sufficiently early in the course

of incipient ARF to demonstrate whether furosemide exerted a beneficial effect on renal function.<sup>60</sup>

The osmotic diuretic mannitol has long been considered a renal protective agent, largely based on studies such as those performed in 1961 by K. G. Barry and colleagues,<sup>61</sup> who utilized mannitol infusions prior to aortic cross-clamping in the operating room and demonstrated preservation of renal blood flow. Mannitol is a renal vasodilator and increases tubular flow rate. In contrast to loop diuretics, mannitol expands the extracellular fluid volume, which may account for its beneficial effect in some situations. It has also been shown experimentally to prevent endothelial swelling associated with ischemia.<sup>62</sup> However, there has never been convincing evidence that it exerts a beneficial effect on overall mortality if administered after ARF is established, and no controlled prospective studies utilizing mannitol early in oliguria (ie, in the initiation phase of ARF) have been conducted. Nonetheless, substantial uncontrolled clinical experience suggests that mannitol prevents ARF both in vascular surgery procedures and in rhabdomyolysis.

### *Vasoactive Agents*

A number of vasoactive agents have been utilized in various models of ARF and have been used in a limited fashion in clinical ARF. These agents have been used to promote renal vasodilation with the goal of minimizing the adverse effects of renal vasoconstriction. Acetylcholine, vasodilatory prostaglandins, antibodies to renin, and dopamine have all been utilized. Although many laboratory studies have shown that these agents can restore renal blood flow toward normal values, only dopamine has been widely utilized in clinical ARF because the other agents have unacceptable hemodynamic toxicity.

Both experimental and clinical studies suggest a beneficial role of dopamine in ARF, although in clinical studies, proof of its efficacy is largely anecdotal. In 1979, A. Lindner and colleagues<sup>63</sup> studied the effects of dopamine with and without furosemide in a canine model of nephrotoxic ARF. Treatment with both agents resulted in improvement in both renal blood flow and urinary flow rate, and attenuated the fall in glomerular filtration rate compared with values in control animals or those animals who received either dopamine or furosemide alone. In contrast, in 1988, L. J. Pass and colleagues<sup>64</sup> studied the effects of dopamine with and without mannitol in dogs undergoing thoracic aortic cross-clamping. No beneficial effect on any measure of renal function was noted in any group.

Regarding its use in clinical ARF, low-dose (ie, renal dose) dopamine, 1 to 3  $\mu\text{g}/\text{kg}/\text{min}$ , has been administered in situations characterized by oliguria and incipient decreased renal function. In many circumstances, dopamine is associated with a modest increase in systemic arterial pressure while urinary output increases. Whether the increase results from the effect on systemic arterial pressure or from intrarenal vasodilation cannot be discerned from clinical studies. In 1982, R. F. Davis and colleagues<sup>65</sup> studied (without control subjects) the effects of low-dose dopamine in 15 adults with oliguria after cardiac surgery. Dopamine infusion was associated with (a) improved creatinine and osmolar clearances, (b) improved urinary flow rate and sodium excretion, and (c) reduced plasma renin activity, when compared with such values in the patients prior to administration of dopamine. Moreover, in a prospective trial of patients undergoing liver transplantation, prophylactic dopamine was associated with less ARF. In 1987, R. J. Polson and colleagues<sup>66</sup> studied 34 patients who underwent 36 liver transplants. Nineteen patients (21 operations) received low-dose dopamine prophylactically, while 15 patients did not. The incidence of renal dysfunction was 9.5% in the dopamine group, compared with 67% in the control group. Overt ARF was not seen in the dopamine group but was seen in 27% of the control group. Dopamine is widely used in intensive care units in patients with oliguria or other early signs of renal dysfunction. Although (a) the effects of low-dose dopamine on renal function; (b) the incidence or severity, or both, of ARF; (c) the need for dialysis; and (d) mortality have not been studied in a rigorous fashion, dopamine has been associated with improvement in urinary output in the majority of patients, with minimal toxicity. However, it should not be used in any patient whose extracellular fluid volume is not adequate.

### Experimental Drugs

A number of additional agents have shown promise in experimental ARF. However, there is limited clinical experience with these agents, in some cases because of their toxicity and in others because of their relatively recent availability. Adenine nucleotides, generally in the form of adenosine triphosphate combined with magnesium chloride (ATP-MgCl<sub>2</sub>), have been used extensively, and are of interest because of their ability to attenuate the severity of renal injury even when given after the insult.<sup>67</sup> Their mechanism of action may be twofold: first, they result in a marked increase in renal blood

flow; and second, they provide the precursors necessary for injured cells to resynthesize ATP, levels of which are markedly depressed after an ischemic insult.<sup>68</sup> Unfortunately, ATP-MgCl<sub>2</sub> causes profound hypotension in humans, which severely limits its usefulness.

Other agents, such as calcium channel-blocking agents and atrial natriuretic factor, have shown promise in experimental ARF. Although a substantial literature on the role of calcium channel-blocking agents in ARF is available, it remains unclear whether any beneficial effect is due to hemodynamic effects or effects on intracellular redistribution of calcium.<sup>69</sup> These agents are currently undergoing clinical trials.

The administration of thyroid hormone abrogates or attenuates renal injury in a variety of models of ARF.<sup>36</sup> It appears to operate by increasing either the activity or the amount of the tubular cells' sodium-potassium ATPase. Thyroid hormone is of interest for two reasons. First, it appears to be relatively nontoxic and has few hemodynamic effects. Second, it appears to be effective even after renal injury occurs. Clinical studies with this drug are ongoing.

Finally, free radical scavengers (eg, superoxide dismutase) and inhibitors of reactions that generate free radicals (eg, allopurinol and deferoxamine) have been subjects of intense investigation. As yet, however, controlled clinical studies in patients with ARF are not available. Allopurinol inhibits xanthine oxidase, which contributes to the generation of toxic free radicals during reperfusion via the Haber-Weiss reaction. Superoxide dismutase has been demonstrated to be effective in preventing ischemic damage in kidneys procured for organ transplantation.<sup>70</sup> Of interest is the fact that deferoxamine, an iron-chelating agent, substantially reduces the severity of ARF in glycerol models. Because iron participates in the Haber-Weiss reaction, chelation of iron may reduce toxic free-radical formation. Deferoxamine has been shown to minimize the untoward effects of such radicals on renal function.<sup>71</sup>

Thus, many of the recent investigations into the prevention of ARF have utilized agents that might be beneficial, based on observations of the cellular nature of injury induced by renal ischemia. Investigators have focused more on the response of individual cells or their constituents to injury than on the whole organ's response to injury. The use of these agents may become widespread if efficacy can be demonstrated in clinical trials. Some of these experimental drugs are promising because of their

ability to exert beneficial effects even when administered after renal injury. It is likely that efficacy will be linked to cytoprotective effects rather than to effects on renal hemodynamics. A new genera-

tion of agents that may protect or restore renal function after injury is exciting but unlikely to be available for a few years for use in combat casualties with ARF.

## PROTECTION FOR PATIENTS IN INCIPIENT RENAL FAILURE

Patients with incipient or established ARF may receive pharmacological therapy from our current armamentarium for a number of different goals. One goal is to promote urinary flow, with or without an improvement in glomerular filtration itself. A second goal is to prevent the occurrence, or lessen the severity, of ARF. Based on these goals, the following protocol, for patients with acute oliguria and for those at high risk for renal dysfunction, has been developed.

### Pharmacological Therapy of Acute Oliguria

As early as possible after oliguria ensues, the extracellular fluid must be determined to be adequate—either clinically or by clinical impression validated by the results of invasive hemodynamic monitoring. If the extracellular fluid is not adequate, then normal saline, in 500-mL increments, should be administered intravenously until either the central venous pressure or the pulmonary capillary wedge pressure is higher than 15 mm Hg. Then graded doses of 1, 5, and 10 mg/kg of furosemide are administered—at hourly intervals—to clearly normovolemic patients. Furosemide will often restore urinary output. If there is no response to the 5-mg/kg dose, then 5 mg of metolazone, a proximally acting diuretic, should be given 30 minutes before the 10-mg/kg furosemide dose is administered. If there is no response to this final furosemide-metolazone challenge, then the patient should be considered to be resistant to diuretics. Resumption of urinary output at any dose of diuretic, however, obviates further doses. Low-dose dopamine (1–3  $\mu\text{g}/\text{kg}/\text{min}$ ), which often promotes urinary flow even without affecting systemic arterial pressure, is infused throughout the diuretic challenge. In patients in whom oliguria is associated with rhabdomyolysis, or who have undergone vascular surgical procedures with aortic cross-clamping, or who have undergone cardiac bypass, a mannitol-bicarbonate solution (100 g of 20% mannitol in 5% dextrose in water to which 3 ampules of sodium bicarbonate have been added) can be used to assist in restoring urinary output. Mannitol may serve as a volume expander in these situations. However, accurate assessment of the patient's vol-

ume status is critical if mannitol is to be administered, as it may precipitate pulmonary edema in the borderline hypervolemic patient. Mannitol should not be used in patients with serum sodium concentrations lower than 125 mmol/L: life-threatening hyponatremia may ensue as mannitol causes water to move from the cells into the extracellular fluid. Neither furosemide nor dopamine is likely to be effective, and the former may be harmful if the patient is volume depleted; thus, the extracellular fluid must be adequate.

Concomitant with the measures described above, an indwelling bladder catheter should be placed, or the existent catheter should be flushed. A renal ultrasound examination should be obtained emergently. Ultrasound equipment will not be available in field medical treatment facilities, but integrity of the bladder catheter should be ensured in all patients.

### Prevention of Acute Renal Failure in High-Risk Patients

The same protocol can be used in patients at high risk for developing oliguria or established ARF or both. Many of these patients will need to undergo surgery imminently, and some will have undergone surgery recently. One standard practice is to obtain baseline measures of renal function (ie, a current BUN and creatinine concentration) and a urinalysis. An expanded extracellular fluid should be maintained in these patients, either as determined on clinical grounds or, preferably, with some form of hemodynamic monitoring. For patients who will undergo vascular procedures, a portion of administered fluids should include mannitol 1 g/kg, given as a 20% solution. Maintenance of an expanded extracellular fluid is probably the most powerful protection against renal ischemia associated with alterations in systemic arterial pressure from the adverse hemodynamic effects of anesthesia and blood loss during surgery.

In oliguric patients and in those at high risk for renal injury, potentially nephrotoxic drugs should be used judiciously. Loading doses of drugs are not altered, but the use of known nephrotoxins should be modified by either prolonging the dosing inter-



val or giving reduced doses at regular intervals. Renal function should be assessed by measuring the serum creatinine at least daily. Since measurement of drug levels will not be available in battlefield medical treatment facilities, some nephrotoxic injury is likely. Other drugs, particularly nonsteroidal antiinflammatory agents that are useful as analgesics, should be used with caution; alternative analgesics are available.

To illustrate these principles, medical officers should consider the following discussion, which describes a situation that occurs frequently in combat and is likely to lead to ARF. Rhabdomyolytic-induced ARF, a classic example of posttraumatic ARF,<sup>72</sup> commonly occurs after a missile or crush injury of an extremity (as a result of a compartment syndrome) or with heat stroke. Even though there are a number of nontraumatic causes of rhabdomyolysis (Exhibit 26-3),<sup>73</sup> this discussion is confined to the traumatic causes, as they are likely to be encountered in battle injuries.

Muscle necrosis results from direct trauma or from the impairment of the blood supply. Muscle cells depend on oxygen delivery to maintain their cellular integrity. As ischemic injury occurs, muscle cells swell and eventually lyse. The release of intracellular contents causes predictable alterations in

blood chemical values, and, with sufficient severity, leads to ARF or death. Muscle contains myoglobin, a respiratory protein that contains a globin chain and a heme moiety. The latter contains iron and is the delivery system for oxygen for the muscle cells. Myoglobin is carried in the circulation loosely bound to an  $\alpha_2$  globulin up to a concentration of approximately 23 mg/dL; if this concentration is exceeded, myoglobin circulates freely. As the molecular weight of myoglobin is 17,000 daltons, it is readily filtered by the glomeruli. In normal individuals, myoglobin is excreted if urinary flow rates and pH are optimal. One gram of muscle contains 4 mg of myoglobin.

However, there are situations that preclude the uneventful excretion of myoglobin. These situations include volume depletion and acidic urine. If sufficient quantities of myoglobin reach the kidney in the presence of these conditions, ARF is likely to occur. Volume depletion contributes to the toxicity of myoglobin via four mechanisms:

1. Renal blood flow is reduced, and the kidneys are subject to ischemic injury, with the consequences that have been discussed previously.
2. The relatively low urinary flow rates associated with volume depletion serve to increase the concentration of myoglobin in the tubules. Myoglobin precipitates with low-molecular-weight proteins in tubular fluid, which obstructs the tubular lumen, preventing flow.
3. In acidic urine, myoglobin dissociates into two moieties: globin and ferrihemate. This latter substance is extremely toxic to renal tubular cells.<sup>74</sup>
4. When ferrihemate is transported into cells, iron is released. When reperfusion occurs, the iron is a source of toxic free radicals through the Haber-Weiss and Fenton reactions.

ARF induced by rhabdomyolysis is one of the most severe forms of ARF. A substantial portion of patients who sustain muscle injury sufficient to induce ARF die of shock or hyperkalemia. The latter results from the release of intracellular potassium, the concentration of which in muscle is approximately 140 mmol/L. Other intracellular products released include organic acids; purine precursors such as uric acid; creatine, which is ultimately dehydrated into creatinine; other muscle enzymes; and proteins, which serve as procoagulants on their release.

### EXHIBIT 26-3

#### CAUSES OF RHABDOMYOLYSIS

##### Trauma

##### Electrolyte Disorders

- Hypokalemia
- Hypophosphatemia

##### Myopathies From Enzyme Deficiencies\*

- Phosphorylase deficiency (McCardle's disease, ie, type 5 glycogenosis)
- Phosphofructokinase deficiency (Tarui's disease)
- Carnitine palmityl transferase deficiency

##### Myopathies From Toxins\*

- Alcohol-induced myopathies
- Carbon monoxide-induced myopathies

##### Idiopathic Paroxysmal Myoglobinuria\*

\*Not discussed in this chapter

Patients with rhabdomyolytic ARF present with overt trauma; oliguria or anuria; hypotension; and severe biochemical abnormalities, including hyperkalemia, metabolic acidemia, hyperphosphatemia, hypocalcemia, hyperuricemia; and elevations of enzymes principally found in muscle, particularly creatine kinase. Renal failure develops quickly as a consequence of both renal ischemia (from shock) and the nephrotoxicity of myoglobin. The profound depression of glomerular filtration, in conjunction with an excessive catabolic rate and the release of creatine from damaged muscle, results in a creatinine concentration that is disproportionately elevated compared with the BUN concentration. Moreover, the rate of production of creatinine continues to be excessive as long as damaged muscle is present; thus, the daily increment in the serum creatinine concentration may exceed 4 to 6 mg/dL.

The prevention of rhabdomyolytic-induced ARF follows logically from an understanding of its pathogenesis. First, volume depletion must be corrected rapidly and the extracellular fluid should be expanded. Casualties who sustain crush or other injury of an extremity are often in shock, and may lose liters of extracellular fluid into the injured extremity. In situations where muscle groups are enclosed by nondistensible fascial planes, such swelling may contribute to further muscle necrosis. Nonetheless, volume depletion and shock must be treated aggressively in an effort to correct renal ischemia. Renal blood flow must be restored before

attempts to augment urinary flow can be made.

Tubular flow can be enhanced by expansion of the extracellular fluid with mannitol. In addition to its effects on renal blood flow owing to its ability to expand the extracellular fluid, mannitol is also an osmotic diuretic and will increase bulk fluid flow through the tubules. This effect serves to enhance the excretion of myoglobin and to restore tubular patency. Alkalinization of the urine is also crucial. Because myoglobin dissociates into its toxic components in an acidic milieu, prevention of further dissociation is facilitated by infusing isotonic sodium bicarbonate at rapid rates. This fluid, in addition to serving as a urinary alkalinizing agent, is also an effective volume expander. Low-dose dopamine infusion, even in the presence of normal blood pressure, should be started.

The aggressive character of this form of ARF usually necessitates early and vigorous hemodialysis if renal resuscitation is unsuccessful.<sup>75</sup> These casualties are extremely catabolic, and hemodialysis should be applied early, before the plasma concentrations of potassium or nitrogenous waste result in cardiac death or uremia, respectively. Additionally, surgical expertise is required to determine the extent of surgical debridement necessary, and whether and when fasciotomies should be performed. Because limb salvage is secondary to preservation of life, fasciotomies should be utilized liberally—certainly if there is any question about the vascular integrity of a limb.

## CONSERVATIVE TREATMENT OF ESTABLISHED ACUTE RENAL FAILURE

Despite protective and resuscitative efforts, however, many patients will not respond to the maneuvers outlined above, and are assumed to have established ARF. We must then determine clinically whether conservative or dialytic therapy is indicated. Part of such determination includes an assessment of the optimal timing and type of dialysis, should it be required. Because the fundamental assumption in the treatment of ARF is that injured kidneys can recover, the major goal of therapy is to support the patient until this occurs. An ancillary goal is to provide an optimum milieu for both nutritional support and prevention or treatment of infection (infection being by far the major cause of death in ARF). To these ends, the assistance of experts in nutritional care and infectious diseases is critical in the management of these patients. Two management strategies can be used for patients with established ARF: conservative management

and management with some form of dialysis. Many of the principles of conservative management of course also apply to patients who require dialysis.

Some patients with ARF, particularly those who remain nonoliguric and in whom catabolism is not excessive, can be managed without dialysis. Conservative management requires meticulous attention to nutritional support, fluid and diuretic therapy, and acid–base and electrolyte balance, the use of drugs, and general medical care.

### Nutritional Support

The subject of nutritional support in ARF was reviewed in 1994.<sup>76</sup> One of the seminal studies that supported the use of nutritional support in ARF was conducted in 1967 by H. A. Lee, P. Sharpstone, and A. C. Ames.<sup>77</sup> These investigators studied 45 patients with ARF who were treated with casein

hydrolysate and lipid, and noted diminished weight loss and more prompt recovery of renal function. Then in 1973, R. M. Abel and colleagues<sup>78</sup> prospectively studied 53 patients with ARF. These investigators utilized a combination of hypertonic dextrose and essential amino acids, compared with glucose alone, in cohorts of 28 and 25 patients, respectively. Of the patients receiving the protein-glucose solution, 75% recovered from ARF, compared with 44% of the patients receiving glucose alone ( $P < .02$ ). Of the patients who required dialysis, 65% of those given amino acids and glucose survived, while only 18% of those given glucose alone survived.

In 1975, S. M. Baek, G. G. Makabali, and C. W. Bryan-Brown<sup>79</sup> studied 129 patients with postoperative ARF and noted a reduction in mortality from 70% in patients given glucose alone to 46% in patients treated with amino acids. The improvement in mortality was particularly impressive in patients who had sepsis.

However, the results of a number of other studies of nutritional support of patients with ARF have not been consistently positive, and the optimal nutritional regimen has not yet been defined. Moreover, no studies have been conducted in prospectively defined groups in which disease etiology and severity have been stratified. Nonetheless, many investigators believe that nutritional support of patients with ARF is beneficial, and it is often provided to patients.

A large body of clinical experience suggests that most fluid administered to patients with ARF should be nutritionally supportive, because these patients have limited ability to excrete fluids. All fluids should be administered only as they meet a specific need of the patient, and "maintenance fluids" should be carefully prescribed. Nutritional support should be initiated within the first 48 hours after the injury in most patients with posttraumatic ARF, because nutritional support clearly attenuates the hypercatabolism that many of them exhibit.

Fluids used to provide nutritional support (the "renal-failure" fluids) consist of hypertonic glucose and amino acid solutions, and should be supplemented by lipid emulsions to provide additional calories. Energy requirements are best calculated on the basis of basal metabolic requirements, with additional requirements predicated on a *stress factor* related to the type and severity of the underlying illness. Energy requirements (*ER*) in kilocalories per day can be expressed in the formula

$$ER = \text{basal requirements} \cdot \text{stress factor}$$

A factor of 1.25 accounts for the increased energy requirements of ill patients who are not paralyzed. The stress factor is 1.30 to 1.50 for patients who have sustained multiple trauma or who have infection.<sup>80</sup> Basal metabolic requirements and stress factors are discussed in detail in Chapter 23, Metabolic Derangements and Nutritional Support.

In general, a minimum of 30 to 50 kcal/kg/d is required by most critically ill patients. Carbohydrate should account for 60% to 70% of the calories, while most of the remainder should be provided as fat. Excessive carbohydrate administration will cause carbon dioxide accumulation and respiratory distress; thus, judicious use of lipid emulsions is critical.<sup>81</sup> Fluid regimens should provide as many calories in as small a volume as possible; thus, 50% to 70% dextrose is often required. Lipid can be administered through a peripheral vein, as the solutions are not hypertonic.

Because of azotemia, the quantities of protein must be limited to 0.8 to 1.0 g/kg/d unless the patient is on dialysis. Amino acids are lost across the dialysis membrane at a rate of 10 to 15 g per treatment, and must be replaced in addition to the basal requirement of amino acids.<sup>82</sup> Protein should be of high biological value and contain mostly essential amino acids, including branched-chain amino acids. Solutions containing casein hydrolysates or amino acid preparations in which nonessential amino acids predominate may result in excessive azotemia without attenuation of catabolism.

Enteral alimentation is preferable to parenteral alimentation if the patient's condition permits. Small-diameter polyethylene feeding tubes are placed through the patient's nose for instillation of solutions of either essential amino acids or a mixture of essential and nonessential amino acids. Not only is enteral feeding associated with fewer complications, but some evidence also suggests that feeding facilitates the maintenance of the integrity of the bowel mucosa, which may prevent endotoxemia and gut-associated sepsis, both of which can induce multiple organ failure.<sup>83</sup> Moreover, the presence of nutrients in the bowel will maintain the enzymes necessary for enteral nutrition and permit a smooth transition to enteral feedings when the patient's condition permits. However, enteral solutions will often cause diarrhea if administered in too large quantities or at too rapid a rate. The use of infusion pumps, which facilitate constant instillation of solution, greatly reduces this complication.

However, many patients with posttraumatic ARF will have undergone abdominal surgery, and enteral feedings will not be possible. Moreover, the magnitude of nutritional support required by hypercatabolic patients often precludes the use of enteral feedings. Should total parenteral nutrition (TPN) be required, access to the central circulation is obtained through the subclavian or the internal or external jugular veins. The catheter site should be inspected and redressed daily, using strict aseptic techniques, and the catheter used exclusively for TPN. If these guidelines are followed, catheter-related infection is uncommon.

The composition of enteral or parenteral fluid can be varied according to the needs of the patient. Sodium can be added or deleted depending on the volume status and the serum sodium concentration. Often, sodium is administered as the acetate salt; the eventual metabolism of acetate to bicarbonate tends to abrogate the acidemic effects of TPN solutions. Potassium supplementation is seldom required initially, but is generally required after several days of TPN when the rate of catabolism has slowed and anabolism has begun. The serum phosphate concentration is high initially but can fall to dangerously low levels after several days of therapy, and may require addition of phosphate to the TPN as either the potassium or sodium salt.

The success of nutritional support in patients with ARF depends on

- avoidance of infection in patients treated with TPN,
- attenuation of catabolism,
- establishment of relatively normal biochemical values in plasma, and
- maintenance of stable extracellular fluid.

A standard monitoring scheme should be followed, so that electrolyte disturbances can be anticipated and corrected before they become severe. The serum glucose should be monitored several times daily, and hyperglycemia should be treated with insulin. Although patients with renal dysfunction have prolonged serum half-life of insulin, they also exhibit insulin resistance. In general, insulin administration is required in virtually all patients treated with TPN. Once daily insulin requirements have become stable, the requisite amount of insulin can be administered in the TPN solution by constant infusion. Surveillance of glucose levels should be continued, however, as sudden hyperglycemia is often the first sign of an incipient infection.

## Fluid and Diuretic Therapy

Fluid intake should be limited to the measured urinary output, with additional fluid given for measured gastrointestinal losses and estimated insensible losses. As has been emphasized previously, much of the administered fluid should be nutritionally supportive; the remainder is often required for medication administration. As a general rule, all medications should be administered in as concentrated a form as possible. Most nonoliguric patients excrete no more than 1 to 1.5 L of urine per day. This loss, coupled with gastrointestinal and insensible losses, may be sufficient to allow required fluids in the form of nutrition and medications to be administered. Because most patients excrete urine that is hypotonic to plasma, with urinary sodium concentrations of 60 to 90 mmol/L, fluid that is equivalent in electrolyte composition should be administered. Replacement of urinary fluid and electrolyte losses in this fashion will tend to minimize water excess or deficit and avoid hyponatremia or hypernatremia, respectively. The serum sodium concentration should be monitored frequently as a guide to the patient's water balance, and should be kept in the range of 130 to 150 mmol/L.

Ideally, the patient treated conservatively will lose no more than 0.5 to 1.0 kg of body weight per day. However, some nonoliguric patients will not excrete sufficient urine to allow for effective nutritional support, particularly if large quantities of other fluids (eg, antibiotics) must be administered, and they will gain weight. In such patients, urinary output can be augmented, if necessary, with low-dose dopamine infusions and intermittent doses of loop diuretics. There appear to be few adverse effects of low-dose dopamine infusions. However, excessive use of loop diuretics may result in metabolic alkalemia, deafness, and potassium depletion, the latter of which results in impairment of glucose homeostasis and proper muscle function. Osmotic diuretics such as mannitol should be avoided in most patients with established ARF, as they can induce hyponatremia if a diuresis does not result, hypernatremia if excessive free-water diuresis is induced, or pulmonary edema if urinary output declines. Thiazide diuretics are not effective in ARF, and potassium-sparing diuretics are contraindicated.

## Management of Acid–Base Disturbances

The major acid–base disturbances that occur in patients with ARF are metabolic alkalosis and meta-

bolic acidosis. The more immediate threat is from metabolic acidosis, which results from both excessive generation of acid and the inability to excrete acids. Metabolic alkalosis usually results from inadequate replacement of nasogastric fluid losses, particularly in nonoliguric patients, in whom chloride, and to a certain extent, potassium, loss represents the primary pathophysiological mechanism.

### **Metabolic Acidosis**

Metabolic acidosis is manifested by a depressed serum bicarbonate concentration and, usually in posttraumatic ARF, an anion gap. The concentration of lactic acid is often elevated in these patients, as are concentrations of other organic acids (such as from phosphate and sulfate salts) when renal failure is severe. In uncomplicated cases of ARF, the serum bicarbonate concentration will average 16 to 18 mmol/L, and the serum pH will average 7.34 to 7.37. This degree of acidemia is not associated with untoward effects. In fact, the rightward shift of the oxyhemoglobin curve will result in more effective oxygen delivery to tissue. If acidosis is more severe, cardiovascular complications such as arrhythmias and hypotension may ensue.

The treatment of metabolic acidosis is relatively simple,<sup>84</sup> although recent questions have been raised regarding the efficacy of bicarbonate administration in correcting the hemodynamic abnormalities in critically ill patients.<sup>85</sup> Nonetheless, nonoliguric patients can receive sufficient alkali, usually in the form of sodium bicarbonate, to correct their base deficit and ongoing losses. In patients who are not excessively catabolic, such ongoing losses should amount to approximately 1 mmol HCO<sub>3</sub>/kg/d. In certain patients, the alkali requirement can be met with oral preparations. Sodium bicarbonate tablets, however, result in excessive eructation. A combination of citric acid and sodium citrate (Sholl's solution), which contains 1 mmol HCO<sub>3</sub> equivalent per milliliter, can be used. In severe cases, hemodialysis can be used to remove extracellular fluid volume so that sodium bicarbonate can be administered in large quantities. The concentration of bicarbonate or equivalent base in the dialysate can be manipulated to meet the needs of the patient.

### **Metabolic Alkalosis**

Metabolic alkalosis is characterized by an elevated serum bicarbonate concentration and a depressed serum chloride concentration. The actual

pH of the blood depends on whether (a) the alkalosis is an isolated acid–base disturbance or (b) there are other disturbances. Substantial alkalosis has a number of untoward effects, including

- hypokalemia, which can result in muscle weakness and cardiac arrhythmias;
- respiratory muscle weakness, which may retard successful weaning from the ventilator;
- compensatory respiratory acidosis, because the response to pure metabolic alkalosis is to retain carbon dioxide, and patients on assisted ventilation may become acidotic in an attempt to return the alkaline pH toward more normal values;
- arterial hypoxemia, which is the result of the alveolar hypoventilation required to produce hypercarbia; and
- impaired oxygen delivery to tissues, because the oxyhemoglobin dissociation curve is shifted to the left, for any given partial pressure of oxygen; therefore, less oxygen is delivered to tissue.

Metabolic alkalosis is largely preventable, particularly if intravascular volume (sodium chloride) and potassium depletion are avoided. Excessive diuretic-induced volume and electrolyte losses should be replaced. Moreover, because nasogastric suction removes volume, potassium, and acid from the body, inhibition of gastrointestinal acid secretion by histamine-receptor blocking agents will reduce net proton loss from the body. In this regard, ranitidine is preferable to cimetidine, since alterations in mental status are seen more frequently with the latter.

The treatment of established metabolic alkalosis includes correction of both intravascular volume deficits and potassium depletion. Potassium deficits can be substantial, on the order of several hundred millimoles. In the rare situation in which volume and potassium repletion do not correct alkalosis, carbonic anhydrase inhibitors can be used to promote urinary bicarbonate loss. However, in the vast majority of patients with ARF, these drugs will be ineffective. In oliguric patients, the volume space for correction of volume deficits may not exist. Thus, dilute hydrochloric acid can be infused into a central vein in nonoliguric patients or into the venous return of a dialyzer in patients on dialysis.<sup>86</sup> With this therapy, the difference between the measured and the desired serum chloride concentration

is multiplied by the product of the body weight (in kilograms) and 0.27 (the volume of distribution of chloride). The amount of chloride, in milliequivalents, is administered as an equal amount of 1.0 N hydrochloric acid diluted in dextrose and water. Finally, hemodialysis utilizing especially prepared dialysate solutions can remove excessive bicarbonate and replace potassium and sodium chloride losses.

## Management of Electrolyte Imbalances

### *Hyperkalemia*

Hyperkalemia is potentially the most dangerous of all metabolic complications of ARF, as lethal cardiac dysrhythmias can result with little warning. Hyperkalemia results from a number of different mechanisms, including the following:

- Transcellular shifts of potassium for hydrogen occur during metabolic acidemia, when the body attempts to buffer protons intracellularly. Although it has been classically taught that for each 0.1 change in the pH, there is a reciprocal 0.6 mEq change in the serum potassium concentration, some researchers<sup>87</sup> now think that this does not occur when the metabolic acidosis is due to organic (ie, lactic) acid accumulation. Rather, transcellular shifts occur only when hydrogen is accompanied by an anion such as chloride, which is restricted from transcellular movement.
- Excessive production of potassium also occurs when there is breakdown of tissue in conjunction with inability to excrete potassium. Tissue destruction is common in rhabdomyolysis, but may also be seen with ischemia of the gastrointestinal tract and after vascular surgery, in which tissue viability may be in question.
- Interference with potassium excretion by drugs may also occur. Nonsteroidal agents and  $\beta$ -adrenergic blocking agents may interfere with and impair renal excretion of potassium.
- Finally, renal dysfunction itself severely limits the ability to excrete potassium. Although fecal potassium excretion often increases by as much as 35% in patients with chronic renal failure, this adaptive mechanism is unusual in ARF, and is probably why patients with ARF do not tolerate the

levels of hyperkalemia that are tolerated by patients with chronic renal failure.

The causes of hyperkalemia in ARF include minimal urinary excretion (fecal excretion is possible, but takes days) and release of potassium ions from injured tissue. In addition, hyperkalemia is aggravated by metabolic and respiratory acidemia and insulin resistance; and is worsened by the presence of drugs with potassium effects (eg, nonsteroidal antiinflammatory drugs, extravascular infusion drugs).

Determining the mechanism of hyperkalemia may assist the physician in choosing the most appropriate therapy, because hyperkalemia can be controlled with exchange resins, glucose and insulin, and bicarbonate. The most important therapy, however, is that which antagonizes the effect of hyperkalemia on cardiac muscle. Thus, the initial diagnostic maneuver after hyperkalemia is first noted is to obtain an electrocardiogram. If there are any abnormalities, calcium chloride should be administered immediately. Then, more definitive steps can be taken to resolve the problem.

### *Phosphate Abnormalities*

Hyperphosphatemia is the most common abnormality of divalent ion metabolism in ARF and can usually be controlled by the frequent oral administration of aluminum-containing antacids, either aluminum hydroxide or aluminum carbonate. These agents are administered as suspensions, 30 to 60 mL every 3 to 4 hours, until the serum phosphate concentration approaches normal values, after which they can be administered less frequently. Although such agents bind phosphorus most effectively in the stomach (ie, when given with food), they are effective even in the absence of enteral nutrients, in which situation they interrupt the enteric recirculation of phosphorus. Aluminum toxicity should not be considered a problem in patients with ARF, as it is in those with chronic renal disease. Aluminum-containing antacids are often ineffective until they have been administered for several days. Even then, they may not control the serum phosphate concentration, in which case sucralfate can be administered four to six times daily in doses of 1.0 g. Finally, hyperphosphatemia almost always responds to the provision of adequate nutrition, particularly if appropriate concentrations of branched-chain amino acids and effective nonnitrogen-to-nitrogen caloric ratios are met. Presumably, effective nutritional support retards catabo-

lism and promotes anabolism, so that phosphorus is transported into cells.

Hypophosphatemia has a number of untoward effects, the most common of which are (a) impaired muscle function and (b) reduced extraction of oxygen from hemoglobin.<sup>88</sup> The most frequent adverse clinical effect is diffuse muscle dysfunction, which may involve both skeletal and cardiac muscle. Skeletal muscle dysfunction may severely retard efforts to wean the patient from the ventilator. More-severe hypophosphatemia can result in rhabdomyolysis. The second-most-frequent effect is a shift in the oxyhemoglobin dissociation curve, so that less oxygen is delivered at a given partial pressure. Other effects of hypophosphatemia on the hematopoietic system include (a) hemolytic anemia due to red blood cell ATP depletion and the inability to maintain membrane fluidity and (b) white blood cell dysfunction.

Hypophosphatemia in ARF is commonly a consequence of overaggressive therapy of hyperphosphatemia, and it occasionally occurs in patients who have received TPN. The serum phosphorus can be expected to fall 0.3 mg/dL/d in patients who are receiving TPN. Thus, patients who have baseline normal phosphate concentrations can be expected to develop significant hypophosphatemia in 5 to 10 days. When hypo-

phosphatemia develops, phosphorus should be added to the TPN solution. Symptomatic hypophosphatemia is common when the serum phosphate concentration is below 1.8 mg/dL. In such situations, replenishment of phosphate stores should be considered. Phosphate repletion can be accomplished by a number of different maneuvers.<sup>88</sup>

### Calcium Abnormalities

Hypocalcemia results not only from hyperphosphatemia but also from resistance to the actions of vitamin D and parathyroid hormone. Unless the patient is symptomatic, has signs such as Chvostek's sign, or has electrocardiographic changes associated with hypocalcemia, the more judicious initial treatment is to lower the elevated serum phosphate concentration toward normal. As the serum phosphate concentration becomes more normal, the serum calcium concentration will begin to rise. If necessary, elemental calcium can be administered as enteral or parenteral nutritional supplements. Should clinical symptoms or electrocardiographic changes consistent with hypocalcemia become evident, calcium should be administered intravenously. There are a number of preparations, including the chloride, lactate, or gluceptate salts, that can be utilized.

## APPROACHES TO DIALYSIS

Conservative therapy of ARF requires meticulous management, and attention to the routine details of patient care requires considerable effort. However, the severity of renal dysfunction, with its resultant catabolism and metabolic perturbations, may eventually require dialysis support. Thus, when or if conservative management is inappropriate or unsuccessful, dialysis is indicated. Three approaches to blood-purification therapy can be utilized to attenuate the effects of nitrogenous waste retention, electrolyte imbalance, and circulatory overload: conventional hemodialysis, peritoneal dialysis, and hemofiltration.<sup>89</sup>

### Conventional Hemodialysis

Hemodialysis has traditionally been the therapy of choice for posttraumatic, hypercatabolic ARF, and has been designated as the mainstay of renal replacement therapy in the DEPMEDS doctrine. Removal of urea nitrogen, creatinine, other retained waste products, potassium, sodium, and water is efficient, as metabolic homeostasis can usually be

achieved and then maintained with a 3- to 4-hour treatment conducted three to five times weekly. Modern artificial kidneys achieve BUN and creatinine clearances in excess of 175 mL/min and have ultrafiltration rates of 4 to 5 milliliters per millimeter of transmembrane pressure per hour. With typical operating parameters, BUN and creatinine concentrations can be reduced by 30% to 40%, and 2 to 3 L of extracellular fluid can easily be removed during a 4-hour treatment. Many modern dialysis membranes are made of cuprophane, a substance that may occasionally induce hypoxemia in the initial period of the dialysis treatment by activating components of the complement cascade, resulting in stasis of leukocytes in the pulmonary circulation. Although alternative materials for dialysis membranes are available, they are associated with excessive clotting in the artificial kidney. Fortunately, the hypoxemia associated with cuprophane membranes is transient. The cuprophane membrane is configured in either parallel-plate or hollow-fiber geometry. Although parallel-plate membranes are easier to use, they are associated with slightly higher

rates of clotting than are the hollow-fiber type. Polyethylene tubing to conduct blood flow to and from the artificial kidney is required and must be compatible with both the artificial kidney and the dialysis machine.

Hemodialysis operates through a combination of diffusive and convective transport. Solute removal by diffusion depends on the size of the solute molecules; the thickness and surface area of the artificial membrane; and the rates of blood and dialysate flow, which are countercurrent to each other. Solute removal by convection depends on the rate of fluid (ie, solvent) transport across the membrane. Fluid removal depends on a pressure gradient across the membrane, which is generated by a combination of the patient's blood pressure and resistance to blood flow through the angioaccess, and pressure applied from the dialysate side of the membrane. This cumulative pressure, known as the *transmembrane* pressure, can be varied by the operator to enhance or retard fluid removal.

### **Circulatory Access**

Obtaining access to the circulation for hemodialysis is often quite difficult in critically ill patients. Hemodialysis requires a blood flow of at least 200 to 250 mL/min, which is generated through the use of a blood pump intrinsic to the dialysis machine. Angioaccess is typically achieved with double-lumen dialysis catheters, which are placed percutaneously in the subclavian, internal jugular, or femoral vein. The first location is preferable, since an occlusive bandage can easily be applied to prevent contamination. These catheters should be dressed only by dialysis personnel, and are routinely left in place for several weeks. Catheter-related infection is extremely rare if the catheters are used only for dialysis. Percutaneous access for conventional hemodialysis is preferable to arteriovenous shunts: the latter must be placed surgically and are often complicated by infection and bleeding. Recently, double-lumen catheters that have a synthetic polyester cuff have been used with some success. These catheters are surgically placed in the subclavian vein, where their properties are equivalent to those of conventional percutaneous catheters. However, for rapid access to the circulation for dialysis, we prefer the percutaneous approach.

Although some patients with ARF tolerate hemodialysis without problems, hemodynamic instability and hypotension are relatively common for at least three reasons:

1. The blood pump generates blood flow that is independent of the patient's blood pressure.
2. The efficiency of solute removal with hemodialysis induces osmolar shifts, which are thought to induce hypotension.
3. The use of acetate as a base replacement in the dialysate can result in peripheral vasodilation and impaired myocardial contractility, particularly in patients with liver dysfunction who cannot rapidly metabolize acetate to bicarbonate (this has been abrogated by the virtual universal use of bicarbonate dialysate in critically ill patients).

Anticoagulation of the blood with heparin is generally required, although there are several alternatives to conventional anticoagulation if bleeding is a risk.<sup>90</sup> There is substantial experience utilizing the technique of heparin-free dialysis, in which the artificial kidney is flushed with saline several times each hour. Unfortunately, this not only dramatically reduces the efficiency of the dialysis procedure, it also limits the amount of fluid that can be removed in a standard treatment period. The judicious use of low doses of heparin is associated with acceptable patency of the extracorporeal circuit without untoward bleeding. In general, we should administer 15 units of heparin per kilogram of body weight as a loading dose, then 750 to 1,000 units per hour as a constant infusion. Either dose is easily alterable, depending on the level of anticoagulation, which is measured by the activated clotting time using a portable monitor and disposable tubes coated with platelet activating factor. The desired end point of the test is between 160 and 180 seconds, and this method allows for rapid and repetitive assessment of the effects of heparin administration. Such techniques as regional anticoagulation with heparin or citrate, with protamine or calcium rescue respectively, or anticoagulation with prostacyclin, largely have been abandoned. Prostacyclin produces severe hypotension, which makes maintenance of the extracorporeal circuit impossible.

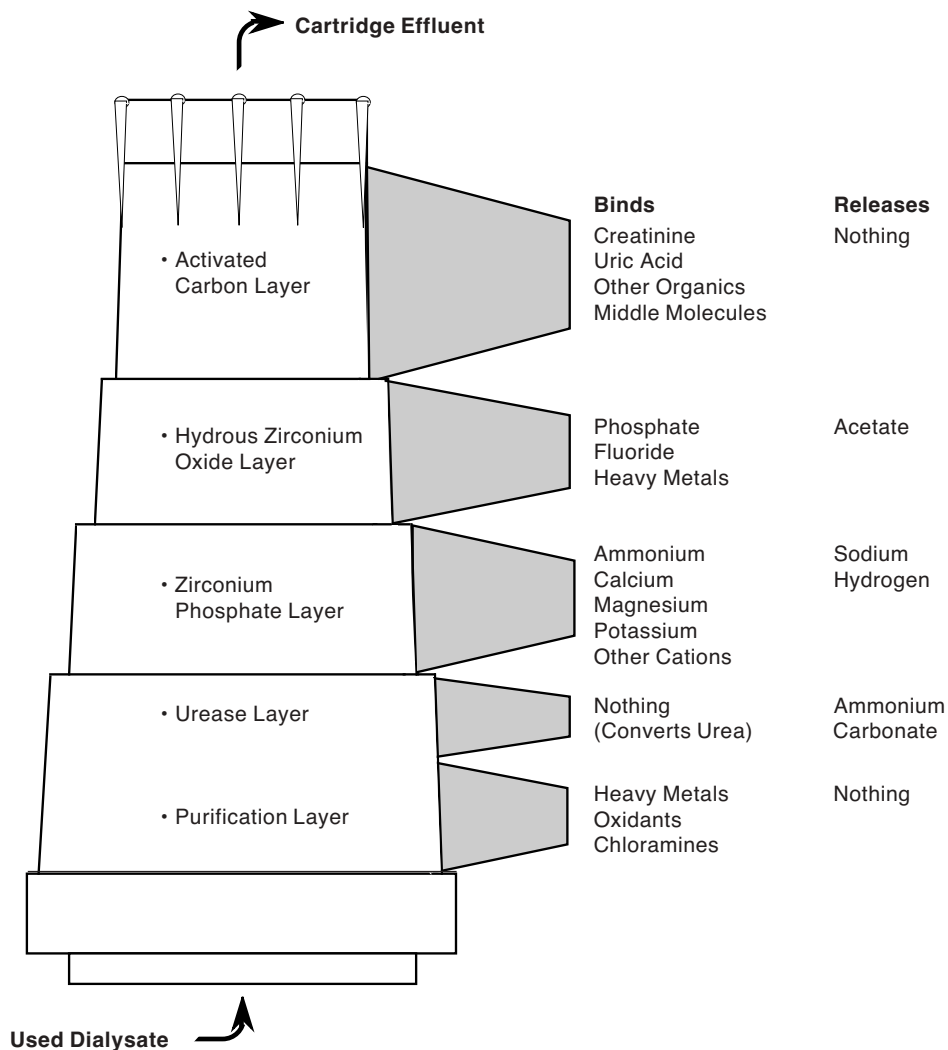
### **Sorbent-Based Dialysis Delivery System**

The large water requirements of conventional hemodialysis can be avoided by the use of sorbent-based dialysis delivery systems.<sup>91</sup> These systems regenerate spent dialysate, and require approxi-



mately 6 L of water, as opposed to the nearly 250 L of water required by conventional hemodialysis. Bicarbonate, calcium, potassium, and other desired solutes can be added to the dialysate as needed.

Waste products that diffuse from the blood into the dialysate are adsorbed onto different layers of a sorbent cartridge, resulting in the maintenance of the desired type of dialysate (Figure 26-4).



**Fig. 26-4.** The single-use sorbent cartridge is commercially available in a number of different sizes. It consists of several components, which, from the bottom of the cartridge up, include scavenger (ie, purification), urease, zirconium phosphate, hydrated zirconium oxide, and activated carbon layers. The scavenger layer consists of activated carbon and zirconium oxide. This layer removes trace metals such as copper and oxidizing agents such as chloramine, which would otherwise inactivate the second layer. The second layer consists of urease. This catalyzes the reaction of urea into ammonia and carbamic acid, which in aqueous solution form ammonium in equilibrium with ammonia, and bicarbonate. The third layer consists of zirconium phosphate, which serves as a cation exchanger. Thus, the ammonium ions that result from the urease layer, in addition to calcium, magnesium, and potassium, are exchanged for sodium and hydrogen ions in a ratio of 8:1 by the zirconium. The fourth layer, of zirconium oxide, serves as an anion exchanger, in which phosphate is exchanged for acetate. The final layer consists of activated carbon, which adsorbs creatinine, uric acid, and other organic compounds. The use of this sorbent-based system allows dialysis to be conducted using potable water, rather than water that would otherwise have to be treated with filters, deionizers, and reverse osmosis membranes. Reprinted with permission from Organon Teknika Corp. *Sorbent Dialysis Primer*. Durham, NC: Organon Teknika Corp; 1988: 3.

The major drawback of the sorbent-based system is that the sorbent cartridge has a finite capacity. That is, the ability of the cartridge to remove urea is limited by the ability of the zirconium-phosphate layer to exchange ammonium, which is derived from the urease-based catalysis of urea, for sodium and hydrogen. When this layer is saturated, additional ammonia cannot be processed and can diffuse into the patient. The capacity of the cartridge to handle urea depends on its size. High-capacity cartridges can remove 28 g of urea nitrogen (ie, 60 g or 1,000 mmol of urea). Detection of ammonia is facilitated by the use of ammonia test strips. When hypercatabolic patients are dialyzed and excessive urea must be removed, either the dialysate must be monitored for ammonia or, more commonly, the cartridge can simply be replaced with a fresh cartridge halfway through the treatment.

### *Equipment and Support*

The machinery and other technical requirements for hemodialysis are substantial. Modern machines are equipped with numerous safety features and monitoring devices. Because many are based on solid-state circuitry, a surge-free electrical current is required. Electrical generators or fixed-facility power plants must be capable of providing 110- to 120-V, 50-Hz power to support machines that are manufactured in the United States. These machines are sufficiently complex that several weeks are required to train operators. Relatively sophisticated medical maintenance support and spare-part backup, primarily in the form of spare circuit boards, are required, as user-based maintenance capabilities are minimal. Supply modules have been configured that contain all the material necessary to conduct dialysis. The machines contained in a DEPMEDS module (deployed at the third echelon) are slightly larger than a large suitcase, and weigh approximately 50 lb.

Hemodialysis is conducted by dialysis technicians, who are corpsmen who have special training in dialysis, and who are supervised by nurses who have undergone similar specialized training. A 6-month course for dialysis technicians is conducted at Walter Reed Army Medical Center (WRAMC) in Washington, D. C., and a course has recently been started for registered nurses who wish to become dialysis nurses. Technicians and nurses alike then receive personnel skill identifiers that facilitate their assignment to facilities where dialysis will be provided. The standards of practice required to care for the typical patient with ARF are that one technician provide treatment to a single

patient. Moreover, a registered nurse with experience in dialysis should be present in any location where patients are being dialyzed. Dialysis personnel are also trained in assisting nephrologists in the placement and subsequent care of catheters for dialysis. Because a typical dialysis treatment requires nearly 1 hour of preparation, 4 hours for the actual treatment, and nearly 1 hour to prepare for the next patient, hemodialysis is a labor-intensive process.

### **Peritoneal Dialysis**

Peritoneal dialysis was used during the Vietnam War for milder forms of ARF. This form of dialysis, in which the peritoneal membrane serves as the dialyzing membrane, is inherently much less efficient than hemodialysis. Access to the peritoneal cavity is achieved via either the percutaneous placement of a stiff peritoneal catheter or, preferably, the placement of a softer, curled catheter through a small incision using local anesthesia and direct visualization of the peritoneal cavity. As with hemodialysis, solutes are removed by a combination of diffusion and convection. Ultrafiltration is caused by the movement of water from the blood into the peritoneal cavity in response to the placement of hypertonic dextrose (1.5%, 2.5%, or 4.25%) into the peritoneal cavity. Solute and fluid removal rates are substantially slower than those achieved with hemodialysis, with BUN and creatinine clearances approximating 15 and 5 mL/min under optimum conditions.

Peritoneal dialysis has some advantages over other forms of dialysis:

- Anticoagulation is not required; thus, patients who are at high risk of bleeding, or in whom bleeding might be catastrophic, can receive therapy.
- There is very little hemodynamic stress, and patients with hypotension who cannot be hemodialyzed can undergo peritoneal dialysis successfully.

However, for military medicine, the disadvantages outweigh the advantages:

- The casualty must have an intact peritoneal cavity. Only rarely can patients successfully undergo acute peritoneal dialysis after abdominal surgery.
- Peritoneal dialysis also requires large quantities of dextrose-containing fluid; delivery, storage, and maintenance of sterility of this fluid represent logistical challenges.

Although peritoneal dialysis has been used in patients with posttraumatic ARF,<sup>92,93</sup> the disadvantages make it of limited use in posttraumatic renal failure, and there is no provision for this form of therapy in our current DEPMEDS planning.

### Hemofiltration

Hemofiltration is the newest form of therapy available and has shown promise in the management of critically ill patients.<sup>94,95</sup> This approach to dialysis utilizes a polysulfone membrane configured in a hollow-fiber geometry. Both hydraulic conductivity and solute passage are substantially greater than they are with hemodialysis. Solute removal occurs through convection, in which transport of the solute depends on the solute's being swept along by the moving stream of solvent (ie, solvent drag) and not on the size of the solute molecule. As long as the size of the solute does not exceed the size of the pore in the membrane, the solute will be cleared with its solvent. However, the concentration of solute in the blood will not change.

The porosity of the hemofilter membrane is such that large volumes of fluid can be removed. Ultrafiltration rates of 50 to 60 mL/min are theoretically achievable; in practice, removal of more than 1 L/h is commonplace. However, because the concentration of undesired substances in the blood does not change, other maneuvers must be utilized to effect a substantial reduction of nitrogenous waste concentration. One such method is to replace fluid removed by the hemofilter concurrently, usually in a postfilter mode, with appropriate quantities of sterile, pyrogen-free, isotonic, electrolyte-balanced fluid. This method is true hemofiltration, and is effective in controlling concentrations of nitrogenous waste products in the blood.

### Continuous Arteriovenous Hemofiltration

No blood pump is required in continuous arteriovenous hemofiltration (CAVH), as the patient's systemic arterial pressure determines the rate of blood flow through the extracorporeal circuit. Other determinants of the efficacy of this system include the type of cannulae used for angioaccess and the length of tubing utilized for ultrafiltrate collection. CAVH requires that a large artery and vein be cannulated or that an external arteriovenous shunt be surgically placed. The term CAVH should be reserved for the use of a hemofilter and postfilter replacement fluid therapy (ie, hemodilution), in which the goal of therapy is control of nitrogenous waste and circulatory overload in the oliguric or

anuric patient with ARF. The enormous quantities of intravenous-quality fluid required to achieve reductions in concentrations of nitrogenous waste make this form of therapy logistically problematic in a wartime setting.

### Slow, Continuous Ultrafiltration

Slow, continuous ultrafiltration (SCUF) is identical to CAVH except that no replacement fluid is administered. Instead, the hydraulic conductivity of the hemofilter is utilized, along with the patient's own blood pressure, to remove an isotonic ultrafiltrate of plasma. This is very effective therapy for volume overload. Concentrations of substances in the blood do not change, and waste removal is limited to the amount of ultrafiltrate removed. Thus this therapy is not effective by itself for azotemia. Conversely, it can be utilized effectively for both acidemia and hyperkalemia, since excessive fluid can be removed, allowing space for bicarbonate, glucose, and insulin. However, because neither acid nor potassium is actually removed from the body in substantial quantities by this procedure, SCUF is probably best considered as a temporizing measure to be utilized until the patient can be treated with hemodialysis.

### Continuous Arteriovenous Hemodiafiltration

The newest form of therapy available is a hybrid of CAVH and SCUF, called continuous arteriovenous hemodiafiltration (CAVH-D).<sup>96,97</sup> In this technique, SCUF is performed with the simultaneous infusion of an electrolytically balanced solution countercurrent to the blood path in the hemofilter apparatus. Such fluid can be pumped with an intravenous fluid-control device, at a rate of 1 L/h; peritoneal dialysate is often used as the fluid. Although the system is relatively inefficient, the mixture of convective- and diffusion-based transport does remove unwanted solutes from the body. Bicarbonate or base-precursors, usually acetate or lactate, diffuse from dialysate into blood, and when metabolized by the liver to bicarbonate, result in the attenuation of acidemia. However, since dialysate flows are approximately 1 L/h, the quantities of fluid required are similar to those required by true CAVH.

There are several advantages of SCUF, with or without hemodiafiltration, over hemodialysis in critically ill patients<sup>98,99</sup>:

1. Because no blood pumps or dialysis machines are required, the machinery and personnel requirements for SCUF are sub-

- stantially less than for hemodialysis. The cognitive and technical requirements that are necessary to be able to supervise or perform SCUF or its variants are readily taught by nephrologists to registered nurses with critical care training, and to internists or intensivists or both.<sup>100</sup> Many of the graduate medical education programs in the military provide this form of training to appropriate resident physicians.
2. Compared with hemodialysis, there is very little hemodynamic instability or hypotension attributable to the extracorporeal procedure itself. The reasons for this are not clear but probably relate to the fact that SCUF does not produce changes in plasma osmolality as does hemodialysis.
  3. The membrane material in hemofilters appears to be more biocompatible than hemodialysis membranes; thus, allergic reactions and sequestration of leukocytes are uncommon.
  4. Critically ill patients with ARF have enormous nutrient requirements; it is not uncommon for such patients to need 3 to 5 L of parenteral nutrition daily. Removal of these substantial volumes of fluid with conventional hemodialysis is often hindered by refractory hypotension; thus, optimal nutritional support cannot be provided.
  5. The use of SCUF does not preclude intermittent hemodialysis. In fact, many patients with ARF who require dialytic support may need virtually continuous volume control, with only intermittent solute removal. Thus, in my experience at WRAMC (1980–1985) with 101 patients dialyzed for ARF, volume overload was by far the most frequent cause for intervention, while azotemia, hyperkalemia, and acidemia were indicated far less frequently.<sup>101</sup> Many patients with oliguric ARF can be treated successfully with SCUF and only intermittent hemodialysis.

## DIALYTIC MANAGEMENT OF ACUTE RENAL FAILURE

The decision to provide dialytic therapy to a critically ill casualty is one that should not be made lightly, and should be made by a nephrologist in consultation with the primary physician after the risks and expected benefits are weighed. At the very least, the decision to provide dialysis involves commitment of substantial personnel, supply, and time. Dialysis should never be offered to casualties who have been triaged as expectant. As a general rule, dialysis should be provided as far rearward in the theater as possible, and should be considered a support measure to allow the casualty to be evacuated as soon as possible to a site of definitive medical care. Given the nature of the injuries and illnesses that are associated with ARF, even with the most favorable circumstances and outcomes, survivors of ARF are virtually never fit to return to any form of duty for 3 to 6 months.

The goals of dialysis are

- to maintain relatively normal electrolyte concentrations;
- to maintain predialysis BUN concentration of 80 to 90 mg/dL and creatinine concentration of 6 to 8 mg/dL;
- to maintain an extracellular fluid volume that permits required fluid administration and acceptable oxygenation-ventilation parameters; and

- to eliminate or prevent manifestations of uremia.

### Indications for Dialysis

In modern nephrologic practice, there are no absolute indications for or contraindications to dialysis, so that virtually any casualty who is not in the expectant triage category may be considered a candidate for dialysis, even those for whom dialysis would have been considered contraindicated in earlier years. The expanded applicability of dialysis is undoubtedly a result of both a better appreciation of the physiological events that accompany dialysis and more advanced physiological monitoring systems. I have successfully dialyzed patients with both closed and open head injuries, patients actively bleeding from gastrointestinal or pulmonary sources, and patients with virtually refractory hypotension. However, these patients require intensive resources that are exceedingly scarce in field hospitals, and the decision to utilize them must be made in the context of the whole theater's need for dialysis support.

The usual indications for dialysis include intrac-table volume overload, refractory metabolic acidemia, uncorrectable hyperkalemia, and substantial azotemia, usually defined as concentrations of BUN and creatinine greater than 110 to 120 mg/dL and 7

**EXHIBIT 26-4****INDICATIONS FOR DIALYSIS OF PATIENTS WITH ACUTE RENAL FAILURE**


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Intractable metabolic acidemia  
 Intractable volume overload  
 Intractable hyperkalemia (dialysis is the definitive therapy)  
 Uremic pericarditis  
 Uremic encephalopathy  
 Dialyzable toxin ingestion  
 Gastrointestinal hemorrhage after localization  
 Bleeding diathesis prior to surgery

to 9 mg/dL, respectively (Exhibit 26-4). These levels of azotemia may prompt many nephrologists to institute dialysis even without uremia. Moreover, overt uremia (manifested by pericarditis, altered mental status, or bleeding diathesis) signifies that dialysis should be instituted as soon as possible. Finally, hypercatabolic ARF, in which the daily incremental changes in BUN or creatinine or both exceed 40 mg/dL and 3 mg/dL, respectively, may occur frequently in wartime and generally requires dialysis.

***Volume Overload***

Intractable volume overload in the oliguric patient is the most common indication for dialytic support, and is manifested by progressive weight gain, substantial edema, and, more importantly, by accumulation of fluid in the lungs with progressive hypoxemia. Accumulation of ascitic fluid may further compromise respiratory function. If possible, a diagnosis of intravascular volume overload made on clinical grounds should be corroborated by central venous pressure or hemodynamic monitoring. Although many patients will exhibit salt and water accumulation secondary to adult respiratory distress syndrome, hypoalbuminemia, or myocardial dysfunction, fluid accumulation in these latter circumstances is exceedingly more difficult to remove with an extracorporeal circuit than is true intravascular volume overload. Injudicious use of SCUF or hemodialysis may result in profound hypotension and retard recovery from ARF.

In patients for whom volume removal is intended, blood pressure can be sustained by a number of different maneuvers:

- Many patients are already receiving vasoactive drugs when dialytic support must be provided. Maintenance of a successful extracorporeal circuit may require that these agents be continued, often in higher doses. Dopamine can be used in doses of up to 10  $\mu\text{g}/\text{kg}/\text{min}$ ; higher doses are not usually effective.
- If myocardial performance is depressed as manifested by low cardiac output, then dobutamine, in doses of 1 to 10  $\mu\text{g}/\text{kg}/\text{min}$ , is the preferred agent. In my experience, there is no added efficacy for the two drugs together compared with their use alone. Levophed, administered as an infusion of 4  $\mu\text{g}/\text{min}$ , may be required for severe hypotension, as may be combinations of isoproterenol, epinephrine, or calcium.
- Correction of metabolic acidemia by infusion of sodium bicarbonate may restore response to pressor agents. Salt-poor albumin (25%) will often reverse hypotension on dialysis by mobilizing edema into the vascular space.<sup>102</sup>
- Similarly, packed red blood cells can be administered through the venous line of the dialysis circuit, particularly if the hematocrit is lower than 0.30. There is little to be gained by raising the hematocrit past this point. Higher hematocrit values (*a*) are associated with an increased incidence of membrane clotting and (*b*) reduce the efficiency of the dialysis procedure by increasing plasma oncotic pressure, which tends to retard fluid removal from the blood across the dialysis membrane. However, in general, if the systolic blood pressure cannot be maintained above 100 mm Hg, dialysis will not be possible. Even with SCUF circuits, a mean arterial pressure of at least 60 mm Hg is required.

***Metabolic Acidemia***

Refractory metabolic acidemia responds to dialysis because organic acids such as lactic acid are readily removed by the dialysis membrane. In addition, the dialysate contains either a base precursor, such as acetate, or a base such as bicarbon-

ate, which diffuses into the patient's blood owing to a favorable concentration gradient. The usual bicarbonate concentration in such situations can range from 25 to 35 mmol/L. Finally, even with SCUF alone, the removal of extracellular fluid will provide space for sodium bicarbonate to be infused into the patient.

### **Hyperkalemia**

Uncorrectable hyperkalemia also favorably responds to dialysis. The removal of potassium is extremely rapid, and overt cardiac toxicity can often be attenuated within the first hour of dialysis. The concentration of potassium in the dialysate should be prescribed for the individual patient. Extremely low potassium dialysate concentrations, such as 0 or 1 mmol/L, should be used only with extreme caution, because rapid shifts of potassium from the blood to the dialysate may be associated with cardiac arrhythmias. It is often more prudent to begin with a 3- to 4-mmol potassium bath and to lower the concentration periodically during the treatment. Although SCUF removes only limited amounts of potassium from the body, removal of extracellular fluid will provide space for the administration of calcium, glucose and insulin, or bicarbonate as necessary.

### **Uremia**

Azotemia is a sign: elevated concentrations of nitrogenous waste products in the blood. Uremia, however, is a syndrome. Thus, patients can be azotemic but not uremic. The detection of severe uremia in critically ill patients can be exceedingly difficult. Classically, uremia is described as a constellation of abnormalities thought to be due to retention of toxins that have not been precisely defined. Elevated concentrations of BUN and creatinine, while considered markers of toxin retention, may not be toxic themselves, as there is not a linear relation between their concentration and the severity of symptoms. Pericarditis, nervous system abnormalities, and bleeding are the typical major clinical features of severe uremia. In general, the medical officer should not attribute any of these disorders to uremia unless the BUN and creatinine concentrations exceed 100 to 120 mg/dL and 6 to 9 mg/dL, respectively. Critically ill patients with ARF will often have coexistent liver, cardiac, hematological, or central nervous system dysfunction from either their primary illness or the effects of drugs or anes-

thetics. The contribution that renal failure makes in such generalized physiological dysfunction is often hard to determine.

**Uremic Pericarditis.** Uremic pericarditis may only be manifested by a three-component friction rub, which can be evanescent and extremely difficult to detect in a patient maintained on a ventilator. The electrocardiographic changes that accompany uremic pericarditis are sufficiently nonspecific as to be unhelpful. In the absence of chest pain, this complication of ARF can be extremely difficult to detect, although it may occur in as many as 15% of patients. Although an echocardiogram can readily detect a pericardial effusion, many patients have pericarditis without effusion. Moreover, echocardiograms will not be available in the combat theater. Thus, increasing size of the cardiac silhouette on chest radiograph or progressive hypotension, particularly if the patient is on dialysis, may be the only clues to the presence of uremic pericarditis. The treatment for pericarditis in this setting is the institution or intensification of hemodialysis.<sup>103</sup> Generally, patients will respond quickly to the former. The development of pericarditis in a patient already receiving dialysis for ARF is of concern, and should lead to a search for pericardial infection.

**Neurological Abnormalities.** The neurological abnormalities seen in ARF are quite diverse and include abnormalities of both central and peripheral nervous system function. Alterations in mental status range from minor abnormalities in sophisticated cortical function to profound coma. The latter is virtually never seen in patients with ARF unless there is a contributing cause besides renal failure. Neuromuscular irritability, manifested by hyperreflexia and clonus, can be seen with severe azotemia. Neurological abnormalities respond only variably to dialysis, because they are seldom caused by renal failure alone. Furthermore, peripheral neuropathies and clonus may be masked by the neuromuscular paralytic agents that are often used in ventilated patients.

**Bleeding Disorders.** Bleeding disorders occur frequently in patients with ARF. It is been my practice to attempt to determine the precise cause of bleeding rather than to attribute it a priori to uremia. These patients may bleed from any of the disorders that cause bleeding in critically ill patients without ARF. For example, gastrointestinal hemorrhage may be due to stress ulcers or ischemic areas of bowel. There may be deficiencies or inhibitors of coagulation factors. Because dialysis generally re-

quires anticoagulation, it is appropriate to eliminate those causes of bleeding that are not due to renal failure before instituting dialysis. Moreover, if hemodialysis is not available or if the patient must undergo surgery before it can be arranged, nondialytic measures can be attempted. One of the most effective is the infusion of desmopressin acetate, a vasopressin derivative, which is administered at a dose of 0.3 µg/kg in 50 mL of 5% dextrose in water 4 to 6 hours prior to surgery or other intervention. This therapy is more effective than the infusion of fresh frozen plasma and can be repeated several times in a 2- to 3-day period.<sup>104</sup>

It has been known for years that uremia is associated with inhibition of platelet function, so that despite adequate numbers, platelets do not function properly.<sup>105</sup> Bleeding due to uremia is usually diffuse and is manifested by oozing from the gastrointestinal tract as well as from venipuncture sites. Bleeding may also involve serous surfaces such as the pleural and pericardial membranes. Uremic bleeding generally improves with the institution of hemodialysis, although it seldom responds to just one treatment. When hemodialysis is instituted for bleeding, the activated clotting time should be followed carefully, as these patients may require little heparin. Moreover, hypotension during dialysis should be avoided, as it is difficult to determine quickly at the bedside whether it is due to fluid removal or bleeding into the pericardial sac with acute pericardial tamponade, and the hemodialysis treatment may have to be aborted.

### ***Hypercatabolism***

Hypercatabolic ARF is the most dramatic form of ARF likely to be encountered after trauma, and is manifested by the rapid development of severe azotemia and concomitant fluid and electrolyte and acid-base disturbances.<sup>106</sup> Rhabdomyolytic-induced ARF commonly results in this syndrome. Casualties with multiple injuries will also occasionally exhibit this picture. Early recognition of the hypercatabolic nature of a patient's ARF is important, as dialytic support, in conjunction with nutrition, is vital if the patient is to have an opportunity to recover. Dialysis is generally begun earlier in this form of ARF than in other forms, as intensive, often daily dialysis is usually required to control metabolic abnormalities. Peritoneal dialysis is ineffective, and SCUF and CAVH are best considered temporizing measures until conventional hemodialysis can be instituted.

### **Complications of Dialysis**

Although the decision to dialyze is made by the nephrologist after the risks and benefits of such therapy are considered, the actual treatment itself is conducted by either a dialysis technician or a nurse. Hemodialysis is associated with a number of potential complications that mandate that it be conducted by trained personnel (Exhibit 26-5).<sup>107</sup> The most common complication is hypotension, which may be seen at any time from the initiation of the treatment until its conclusion. Its management has been previously discussed. Maneuvers to be utilized by dialysis personnel in response to hypotension are outlined by the nephrologist at the onset of each treatment. All agents administered during hemodialysis should be infused into the blood lines distal to the artificial kidney so as to prevent rapid clearance of the drug or clotting of the membrane. Over the first hour of dialysis, the blood flow should gradually be increased from 100 to 125 mL/min to 200 to 250 mL/min. Acutely ill patients may not tolerate higher blood flows; such flows are unnecessary, as very effective dialysis is achieved with blood flows of 250 mL/min.

Other complications are related more to the technical aspects of hemodialysis.<sup>108</sup> These include hemolysis from (a) trace metal contamination of the water used for dialysate or (b) excessive dialysate temperature. With either situation, the blood in the blood lines becomes a translucent, cranberry red. The procedure must be stopped instantly and the entire extracorporeal circuit discarded. Abnormalities in the electrolyte composition of the dialysate

#### **EXHIBIT 26-5**

#### **ACUTE COMPLICATIONS OF HEMODIALYSIS**

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Hypotension  
 Disequilibrium syndrome  
 Hemorrhage  
 Arrhythmias  
 Pulmonary dysfunction  
 Technical errors: dialysate composition, water / air embolism, kidney rupture

may result in progressive hyponatremia or hypernatremia: either situation will result in progressive deterioration in the patient's mental status. If a sorbent-based system is used, the dialysis technician should be instructed to conduct dialysis with dialysate composed of bicarbonate as the base, with a sodium concentration of 128 to 130 mmol/L. The dialysate sodium concentration will rise as dialysis proceeds, since the reaction of urea with the zirconium phosphate layer of the sorbent cartridge will liberate sodium into the bath. Dialysate electrolyte composition is monitored on-line with a conductivity meter, however, and malfunction is uncommon. Occasionally, an artificial kidney will have a defective seal and will rupture during the treatment. The blood pump must be stopped instantly and the lines clamped to prevent the patient's exsanguination. Finally, air may enter the circuit from a defective blood line or if the technician uses an "air rinse" to clear the lines at the conclusion of the treatment. Air will be trapped in the patient's right atrium and ventricle, and may result in cardiac collapse. The treatment involves placing the patient on the left side so that the air rises to the top of the cardiac chamber. Small quantities will gradually be reabsorbed, but larger quantities may have to be aspirated by a percutaneously placed intracardiac catheter.

### Practical Aspects of Dialysis

Monitoring of the patient during the dialysis procedure is extremely important and is the responsibility of dialysis personnel. Vital signs should be recorded every 15 minutes. Bed scales will not be available in the theater; therefore, the blood pressure and pulse are useful indicators of the patient's ability to tolerate removal of extracellular fluid. Often, overt hypotension will be preceded by an increase in the pulse rate, and should be avoided to prevent ischemia from damaging other organs and further injuring the kidneys. In general, critically ill patients should undergo hemodialysis while on a cardiac monitor, and should receive supplemental oxygen to attenuate the almost universal fall in oxygen tension seen with the treatment. No other treatments, including wound care, should be performed during hemodialysis.

Conversely, SCUF or CAVH-D are prescribed and initiated by nephrologists and dialysis personnel but are conducted by intensive care unit personnel. The nephrologist and dialysis personnel should obtain angioaccess, set the operating parameters of

the system, and ensure that the system is operating correctly. Operating parameters to be established include

- the level of anticoagulation that is desired,
- the dosage of heparin that is required to maintain this level,
- limits of ultrafiltration rates that are acceptable, and
- the types and frequency of monitoring techniques that are to be used.

Intensive care personnel should ensure that nurse providers receive in-service training from dialysis personnel, who should remain available for consultation and assistance. However, one of the principal reasons for choosing SCUF or CAVH-D over hemodialysis is that there are relatively few dialysis-trained personnel in the theater. Widespread availability of SCUF and CAVH-D permit dialytic therapy of ARF to be made available to more casualties than could be managed by dialysis personnel alone.

SCUF and CAVH-D are remarkably free of complications, given the severity of illness in the patients to whom these therapies have been applied.<sup>109</sup> Hypotension due to either procedure is uncommon, since the patient's mean arterial pressure is the driving force for ultrafiltration. Should hypotension occur, ultrafiltration will slow down or stop entirely. However, a diminution in the ultrafiltration rate is also a signal that the filter may be clogging with blood clots. If filtration begins to slow, nursing personnel should check both the activated clotting time, to ensure that it is within the prescribed range, and the patient's blood pressure. The only other significant complication of either treatment is bleeding from the catheter sites. This is extremely common in the first few hours after their placement, but will generally respond to a pressure dressing applied for a few hours.

The desired ultrafiltration rate is established by the needs of the patient. In general, most patients will require several hundred milliliters of fluid removal per hour to permit nutrition and antibiotic administration, in addition to removal of the excessive salt and water that have accumulated during the days prior to initiation of the procedure. Fluid removal across a hemofilter is governed by the same Starling forces that govern fluid removal across a capillary. Thus, the forces tending to result in fluid removal include the mean arterial pressure, which is dependent on the blood flow, and the



pressure exerted by the column of fluid in the collection tube. Blood flows in a typical patient may range from 60 to 100 mL/min, depending on the type of angioaccess and the size of the cannulated artery. The pressure exerted by the column of fluid in the collection tube depends on the length of the tube. Excessive ultrafiltration can be slowed by shortening this tube. The principal force that retards fluid removal is the oncotic pressure of the blood, which is predicated on the hematocrit and the protein concentration in the blood. Hematocrits greater than 0.30 and plasma protein concentrations greater than 6 to 7 mg/dL are associated with low ultrafiltration rates. The net ultrafiltration rate is a balance between these forces. A convenient method of determining whether ultrafiltration is too excessive is to check the hematocrit at both the arterial and the venous sides of the hemofilter. The arteriovenous difference should not exceed 10% to 15%.

If CAVH-D is being performed, we should remember that a liter of dialysate will be collected each hour, in addition to the volume of ultrafiltrate. Total ultrafiltrate should be measured each hour; this is greatly facilitated by placing a large-capacity collection bag on a small scale so that weight changes can be monitored, rather than volume changes manually measured, each period.

Because SCUF results in an isotonic ultrafiltrate

of plasma, the biochemical composition of plasma can be checked simply by sampling the ultrafiltrate periodically. This minimizes the need for peripheral venipunctures in fully anticoagulated patients. However, because CAVH-D results in some diffusive transport, this method is not valid in patients undergoing this form of therapy.

### Timing and Frequency of Dialysis

Hemodialysis is an intermittent procedure that requires 3 to 4 hours. It may be required daily in some patients, while two to three treatments per week may suffice in others. With the four goals of dialysis in mind—to maintain relatively normal electrolyte concentrations; predialysis BUN concentration of 80 to 90 mg/dL and creatinine concentration of 6 to 8 mg/dL; extracellular fluid volume that permits required fluid administration and acceptable oxygenation–ventilation parameters; and to eliminate or prevent manifestations of uremia—the decision to dialyze is made anew each day. This decision is made far easier when the patient's biochemical values, weight, and accurate flow sheets are available for the nephrologist on a timely basis. Because dialysis is as scarce a resource as is, for example, the operating room, close coordination between intensivists, surgeons, and nephrologists will permit the patient to receive optimum care.

## PROGNOSIS AND OUTCOME OF ACUTE RENAL FAILURE

The mortality of ARF has remained relatively constant since the introduction of dialysis during the Korean War. This fact can be interpreted in different ways:

- Regarding posttraumatic ARF, it is possible that we now provide dialysis to patients who, because of better resuscitation procedures than in the past, might previously have died of shock without ever developing the need for dialysis.
- Regarding patients who develop ARF in the context of nephrotoxic injury or surgery, it is possible that these patients are older and have more associated comorbidity than patients previously offered dialysis.
- Alternatively, dialysis may not contribute to the overall management of patients with ARF, and may represent an expensive, albeit ineffective, technology.

Most nephrologists feel that dialysis does add substantially to the care of patients with ARF, and that our inability to effectively treat infections and the complications of nonrenal organ failure are the principal reasons why the mortality of ARF has remained so high. To provide insight into better ways to treat patients with ARF, I will review some of the extensive experience that has been gained over 4 decades of treatment of ARF. Several studies examined are probably of more historical than practical interest, as they reflect experience of the decades of the 1960s through the 1980s. General improvements in medical intensive care since the mid-1980s have made analysis of older experiences very problematic in terms of applying their conclusions to current patient populations. Recent studies, which incorporate techniques and practices still in use, may provide more useful information.

In 1960, P. E. Teschan and his colleagues<sup>110</sup> reported their experience with prophylactic hemodialysis in the treatment of 15 patients with ARF at

the Institute of Surgical Research at Brooke Army Medical Center, San Antonio, Texas. Teschan postulated that the uremic syndrome represented a generalized toxic state in which harmful, albeit dialyzable, substances resulted in cumulative injury of many tissues, leading to sepsis and other complications that would result in death. He reasoned that prophylactic dialysis would remove these toxins and prevent both uremia and its lethal sequelae. He dialyzed patients when their BUN concentrations approached 120 mg/dL, and reported a marked attenuation of uremia, as manifested by improved mental status, appetite, and reduced bleeding. Moreover, he noted an improvement in the resistance to infection and a reduction in the severity of infection.

Teschan's results extended those of R. C. Swann and J. P. Merrill,<sup>13</sup> who in 1953 reported their extensive experience with dialysis of patients with ARF in Boston, Massachusetts. These two reports, in conjunction with reports of the results of dialysis being performed in U.S. military hospitals in Korea, led to the widespread application of dialysis for the treatment of ARF. However, the reports of subsequent experience failed to demonstrate a convincing effect of dialysis on the overall mortality of ARF.

In 1973, A. C. Kennedy and colleagues<sup>111</sup> analyzed their experience with 251 patients with ARF treated between 1959 and 1970, including 133 patients (53.8%) with ARF in the surgical setting. Of this group, 32 (24%) sustained ARF from multiple injuries, while the remainder developed ARF after surgical procedures, generally of the abdomen. The mortality in the trauma group was 50%, while the overall mortality in the group was 58%. One hundred twenty-four of the patients underwent dialysis, including all but one of the patients who sustained multiple trauma. The investigators determined that nearly two thirds of the deaths, particularly in the group sustaining trauma, were due to the effects of the trauma itself. Complications including pneumonia, gastrointestinal hemorrhage, cardiac failure, and sepsis played a role in at least 30% of the deaths. Moreover, when analyzed separately, the investigators believed that sepsis was directly responsible for 40% of all deaths.

In 1972, R. B. Stott and his colleagues<sup>112</sup> reported their experience from 1969 to 1971 with 109 patients with established ARF. While the overall mortality of the group was 57%, the investigators stratified their patients into two ARF groups: medical and surgical-traumatic. The latter group, consisting of 55 patients, experienced a 65% mortality. In patients who had proven sepsis, the mortality was

72%; patients in whom sepsis was not suspected had a mortality of 47%.

In 1978, McMurray and colleagues<sup>113</sup> reported their experience with 276 patients with ARF from 1967 to 1975, of whom 240 required dialysis. There were 117 surgical patients and 49 trauma patients, in whom the mortality was 44% and 35%, respectively. These investigators stratified their patients for complications, and found that survivors experienced a mean of 2.2 complications, while nonsurvivors experienced a mean of 3.8 complications ( $P < .001$ ). In contrast to many studies, these investigators were also able to demonstrate an adverse impact of age: older patients fared significantly worse than younger patients. The impact of advancing age has long been considered a powerful predictor variable, although this has not been demonstrated in all studies.

G. S. Routh and colleagues<sup>114</sup> conducted an analysis of 114 patients who were dialyzed for ARF between 1969 and 1978. In their study, published in 1980, the patients were divided into two groups: 58 patients, primarily with multiple organ failure, who were treated in an intensive care unit, and 56 less severely ill patients, who were treated in a renal intensive care unit. The mortality in the former group was 64%; in the latter group, 37%. These investigators also demonstrated the adverse impact of comorbidity and documented that sepsis was the most common cause of death. Of interest is the fact that ARF itself was believed to be the cause of death in only two patients.

In 1972, D. Kleinknecht and colleagues<sup>115</sup> provided a convincing argument for the aggressive use of dialysis in ARF with a study that compared outcomes in two groups of patients treated with different degrees of dialytic support. These investigators analyzed 500 patients with ARF seen between 1966 and 1970. The patients were divided into two groups of 279 and 221 patients. Patients in Group I, who would serve as historical controls, were dialyzed only when their BUN concentration exceeded 350 mg/dL; patients in Group II underwent early and frequent dialysis to maintain BUN concentrations less than 200 mg/dL, and, for the most part, they received nutritional support. Dialysis exerted a salutary effect on two important parameters: (1) the frequency of gastrointestinal hemorrhage was reduced from 26% in Group I to 18% in Group II ( $P < .20$ ), as was the mortality from such hemorrhage (55% vs 27%,  $P < .01$ ). And (2), although the frequency of sepsis was not altered, the mortality from sepsis decreased from 24% in Group I to 12% in Group II ( $P < .02$ ).

The results of J. D. Conger's<sup>12</sup> experience with intensive hemodialysis in the Vietnam War, published in 1975, were discussed earlier in this chapter; in conjunction with the experience of the investigators cited above, Conger's results were partly responsible for providing an intellectual basis for a change in the way patients with ARF were routinely managed after the early 1970s. From then on it would be usual for patients with substantial ARF to receive dialytic and nutritional support prior to the onset of overt uremia and severe biochemical abnormalities. Notwithstanding the lack of properly designed, prospective, controlled studies comparing patients treated with and without dialysis, studies published during the 1980s on the outcome of ARF reflect this aggressive approach to dialysis, and have largely concentrated on identifying risk factors that affect prognosis. Thus, several studies were published in the 1980s on the outcome of ARF. These studies are important because they reflect the practices that will likely be employed in treating future combat-casualty-associated ARF. These practices include the aggressive use of dialysis, combined with intensive nutritional support, general intensive care management, and powerful antibiotics. The current approach of most nephrologists is based on the concepts of Teschan<sup>110</sup> and Champion<sup>106</sup> and incorporates an aggressive, multidisciplinary approach to patients with posttraumatic ARF.

J. Lien and V. Chan<sup>116</sup> conducted a retrospective analysis of 84 patients with ARF treated by hemodialysis between 1980 and 1984. In their study, published in 1985, the overall mortality was 63.7%. These investigators identified several risk factors that were different between survivors and nonsurvivors, including malnutrition, jaundice, hypotension, the need for assisted ventilation, heart failure, and sepsis.

In 1988, J. W. Lohr, M. J. McFarlane, and J. J. Grantham<sup>117</sup> reported on 126 patients who received dialysis for ARF between 1979 and 1985. Dialysis was routinely employed for BUN and creatinine concentrations greater than 100 and 10 mg/dL, respectively. The overall mortality was 75%, and was dependent on five variables that adversely affected survival: hypotension, assisted ventilation, congestive heart failure, proven or suspected sepsis, and gastrointestinal dysfunction. Moreover, these investigators quantified these covariables and demonstrated an inverse relation between survival and the number of covariables. If no factors were present, the survival was 62%, while if four or more factors were present, the survival was only 2.7%.

Also in 1989, F. Liano, F. A. Garcia-Martin, and A. Gallego<sup>118</sup> published the results of a prospective analysis of their experience with ARF (1979–1985), during which period they studied a cohort of 228 patients, of whom 87 were treated with hemodialysis. These investigators found that coma, hypotension, and the requirement for assisted ventilation adversely affected survival, which was only 44%. None of the patients died of ARF directly.

Finally, in 1986, D. M. Gillum and colleagues,<sup>119</sup> one of whom was J. D. Conger, extended Conger's previous observations on the use of dialysis in ARF by conducting a prospective, controlled study of intensive dialysis in ARF. Thirty-four patients with ARF were matched for etiology and a number of clinical characteristics, including nutrition and other support, and were divided into two groups: the first group received intensive dialysis to maintain BUN and creatinine concentrations less than 60 and 5 mg/dL, respectively; the second group was more routinely dialyzed and maintained BUN and creatinine concentrations less than 100 and 9 mg/dL, respectively. There were no significant differences in complication rates or in mortality, which was 59% in the intensive group and 47% in the nonintensive group. This study has been criticized for its small sample size, however, by proponents of dialysis. Interestingly, some investigators<sup>120</sup> questioned whether hemodialysis, because of its hemodynamic stress, delays the recovery from acute renal failure.

The experience at WRAMC has been similar. We analyzed our experience with 101 patients dialyzed for ARF at WRAMC during the period 1980 through 1985 and published the results in 1985.<sup>101</sup> The overall mortality was 64%, and infection was directly responsible for nearly half the deaths. Our experience since then has corroborated that previous experience. Patients rarely die of pericarditis, gastrointestinal hemorrhage, or other features of uremia itself. They die of infection. The lungs and intra-abdominal viscera are the presumed sites of the majority of these infections, based on the types of organisms recovered from blood cultures. We rarely see lethal infections from the urinary tract or indwelling catheters. Instead, the principal organisms are Gram-negative organisms, which are resistant to many antibiotics, and fungi. These infections are notoriously difficult to treat and are often unresponsive to all forms of antibiotics and antifungal agents. Although there are exceptions, in general, patients who develop ARF and require dialysis either recover in the first 10 to 14 days after the renal failure ensues, or they only rarely recover.<sup>121</sup>

The studies described above have been conducted with the goal of identifying factors that affect prognosis, and have largely been based on cohorts in which dialysis was provided. Despite differences in study design, patient populations, and treatment protocols, the findings are consistent.<sup>122</sup> Risk factors, which appear as covariables in statistical analyses, can be identified that exert a predictable effect on outcome, and the more risk factors that are present, the worse the outcome. Dialysis has not measurably reduced the substantial mortality associated with ARF.

The whole problem of the mortality of ARF and the impact of dialysis on its outcome has been reviewed.<sup>2,123,124</sup> Not surprisingly, the vast majority of the available literature implicates the devastating effects of multiple organ failure and infection on mortality. Little evidence exists to suggest that improvements in the quality or quantity of dialysis

would have any impact on outcome. J. S. Cameron<sup>123</sup> summarized the data from a number of different studies, in which the effects of organ failure and sepsis were analyzed for their contribution to mortality. In the aggregate, these data suggest that an identifiable cohort of patients who develop ARF may be doomed despite our best efforts. Predictive functions utilizing clinical variables can predict outcome correctly in 70% to 80% of patients.<sup>49,125</sup> Nonetheless, no predictive equation predicts outcome infallibly, and the datasets on which such equations are based have included patients with substantial comorbidity and advanced age compared with the young, previously healthy soldiers who will develop ARF in wartime. It is possible that casualties in future conflicts who develop ARF will provide the best evidence for the salutary effects of aggressive dialytic and general intensive care support.

## SUMMARY

Casualties with ARF are both a medical and a logistical problem for military medical personnel. The condition was first recognized during World War II and has been associated with a persistently high mortality in subsequent conflicts, despite improvements in the evacuation and treatment of casualties with ARF in the theater.

ARF usually results from either ischemic or nephrotoxic injury; commonly, both forms of injury exist in a given casualty. Multiple theories have been advanced regarding the pathophysiology of ARF. None are completely satisfactory, and knowledge of cellular and molecular biology has increased our understanding of this disorder. Both renal ischemia and nephrotoxic injury result in structural and functional abnormalities of the renal epithelium that subserve clinical injury. A number of promising therapeutic maneuvers, many based on a more in-depth understanding of the disorder, are presently in clinical trials and may soon be available for use.

The approach to the patient with suspected ARF involves ensuring adequacy of the volume of the extracellular fluid, patency of the urinary tract, and elimination of all factors that could potentially damage the kidneys. The determination as to whether oliguria results from prerenal, postrenal, or intrinsic renal causes is critical. The diagnosis of ARF can usually be made from the history, physical examination, microscopical and chemical analyses of the urine, and simple radiographic tests. Patients with oliguria should be challenged with graded doses of

diuretics, after the extracellular fluid volume has been restored, to promote urinary flow. Patients who do not have oliguria are easier to manage in terms of fluid balance, nutrition, and dialysis requirements. Nutritional support is an important aspect of the care of the patient with ARF, who requires a relatively large amount of energy delivered in a small volume of fluid.

The therapeutic options available for casualties with established ARF include conservative management and dialysis. A number of different types of dialysis care are available, including conventional hemodialysis and peritoneal dialysis. With newer, more biocompatible membranes, hemofiltration, ultrafiltration, or a combination of these treatments can be used. The indications for hemodialysis include intractable metabolic and circulatory volume abnormalities. Absolute contraindications include refractory hypotension and having been triaged as expectant. Despite the widespread availability of dialysis, the mortality of combat- and trauma-associated ARF remains high. The most common cause of death is infection, usually associated with multiple organ failure.

The casualty with ARF is a formidable medical and logistical challenge. Despite advancements in our knowledge of renal disease, the mortality of ARF remains high. We can expect improvement in the outcome of this disorder when we have better ways to prevent and treat infection and multiple organ failure.

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