Acute Renal Failure: Pathophysiology and Treatment

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INTRODUCTION

Acute renal failure (ARF) is a clinical syndrome characterized by an acute fall in glomerular filtration rate (GFR), resulting in decreased clearance of metabolic waste products from the blood. ARF can be caused by a number of diseases and pathophysiologic mechanisms. Most cases of ARF, however, occur in the most seriously ill, who often have complex comorbid illnesses, such as sepsis and multisystem organ failure. Despite many advances in critical care medicine, mortality in patients with ARF remains high; in some studies it is greater than 80%. This review discusses pathophysiologic mechanisms involved in the development of ARF, pharmacologic agents with potential therapeutic benefit, and issues surrounding the selection of a modality for renal replacement therapy in ARF patients.

ETIOLOGY AND EPIDEMIOLOGY

ETIOLOGY

The causes of ARF are typically divided into 3 categories: prerenal, renal, and postrenal (Table 1). Pre-renal ARF results from an abnormality in glomerular perfusion that reduces the GFR in the absence of any pathology of the renal parenchyma. It is important to note that this form of renal failure is rapidly reversed when the hypoperfusion is corrected. Postrenal ARF results from obstruction of urinary collection and, again, occurs in the absence of any direct insult to the renal parenchyma. This form of ARF is also completely reversible when the obstruction is relieved. Finally, renal (or intrinsic) ARF occurs when there is direct damage to the renal parenchyma itself; it can
be induced by damage to the vasculature, glomeruli, tubules, or interstitium. Intrinsic ARF is due to ischemia in 50% of cases, nephrotoxins in 35%, and interstitial nephritis or glomerulonephritis in 15%.

The majority of intrinsic ARF cases are associated with acute tubular necrosis (ATN). ATN is the histologic term used to describe the tubular-epithelial cell necrosis and regeneration seen in biopsy specimens of kidney following an ischemic or toxic insult. Patients with ARF, however, usually do not undergo biopsy, and ATN is typically diagnosed based upon a comprehensive clinical evaluation. Most cases of ATN are seen in the critically ill intensive care patient and are usually multifactorial in origin (eg, hypotension, nephrotoxic drug exposure, sepsis, and cardiac, respiratory, or liver failure). Ischemia is the cause of most cases of ATN in hospitalized patients. The development of ATN is closely related to prerenal azotemia, as both are related to hypoperfusion of the kidney. In most cases, the extent of renal hypoperfusion will determine the extent of ATN, and the underlying renal function may play an important role in determining the extent of renal parenchymal damage.

**Morbidity and Mortality**

ARF occurs in approximately 5% of all hospitalized patients, and, historically, it has been associated with a high risk of mortality. Following the introduction of dialysis therapy more than 50 years ago, patient mortality fell from 90% to 50%. However, recent studies have shown that the mortality rate for patients with ARF has not changed significantly, ranging from 50% to 80%. With new advances in intensive care medicine, it has become clear that the current mortality rate is dependent upon underlying comorbid illness. In patients with simple ARF and no underlying comorbidities, the mortality rate is between 7% and 23%; in intensive care patients with other comorbidities it is between 50% and 80%. Several epidemiologic studies have shown that the mortality rate in intensive care patients is correlated with the number of other organ systems in failure (Figure 1).

In addition to being a surrogate marker for severe illness, ARF has been shown to be an independent risk factor for mortality. In a recent study involving patients who received intravenous contrast dye, the mortality rate was 34% in those who developed ARF but only 7% in those who did not develop ARF. After adjusting for comorbid factors, renal failure was associated with an odds ratio of dying of 5.5.

Need for hemodialysis also has an impact on mortality in patients with ARF, as demonstrated in a prospective study of 43,642 patients undergoing open heart surgery. In this study, the mortality rate for patients with ARF requiring dialysis (n = 460; 1.05% of total) was 63.7%, compared with 4.3% for patients without ARF. Thus, patients with ARF requiring dialysis have a 15-fold increased risk of death compared with patients without ARF. These data underscore the fact that ARF is a serious condition that must be treated aggressively at the earliest signs of renal insufficiency.

Severity of illness in the critically ill assessed by the use of

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**Table 1. Causes of Acute Renal Failure**

<table>
<thead>
<tr>
<th>Category</th>
<th>Causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prerenal</td>
<td>Hypovolemia, Hemorrhage, Fluid loss, Hypoalbuminemia, Third-space losses</td>
</tr>
<tr>
<td>Renal</td>
<td>Cardiac failure: myocardial dysfunction, valvular dysfunction, cardiac tamponade, pulmonary hypertension, Systemic vasodilatation: sepsis, cirrhosis, anaphylaxis, anemia, pharmacologic vasodilation, Afferent arteriolar vasoconstriction: sepsis, hypercalcemia, hepatorenal syndrome, drugs, Efferent arteriolar vasoconstriction: angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers</td>
</tr>
<tr>
<td>Postrenal</td>
<td>Urinary tract obstruction</td>
</tr>
</tbody>
</table>

of APACHE scores has not been a good predictor of outcome in patients with ARF. A major advance in the ability to predict mortality in renal failure patients has come from the studies of the Liano Severity of Illness score (Table 2). In this index, renal dysfunction accounts for 21% of mortality (compared with 4% in the APACHE scoring system) and correlates with outcome.

**DIAGNOSIS AND CLINICAL EVALUATION**

ARF is typically diagnosed after serial screening reveals a rise in blood urea nitrogen (BUN) and plasma creatinine concentrations, or after a decrease in urine output is observed over a period of hours to days. Once the diagnosis of ARF is suspected, it is important to correlate the laboratory diagnosis (creatinine value) with renal function. However, plasma creatinine is a suboptimal indicator of renal function during ARF because the creatinine level is influenced by many nonrenal events, such as creatinine generation, volume of distribution, nutritional status, infection, and creatinine excretion. In addition, the relationship between plasma creatinine and GFR is dynamic. Changes in GFR are not reflected in the plasma creatinine value until the creatinine level has stabilized, which can take several days. Therefore, when the GFR is changing (during the early phases of ARF and during recovery from renal failure), plasma creatinine levels are poor indicators of renal function. In such cases, the GFR should be considered to be less than 10 mL/min. Despite the shortcomings of the creatinine value as a clinical indicator of renal function, it will continue to be used until a more effective indicator becomes widely available.

**HISTORY AND PHYSICAL EXAMINATION**

The clinical evaluation of all patients with ARF should include a careful and complete history and physical examination. The medical records of hospitalized patients often provide an important source of information regarding the etiology of renal failure, including drug exposures, vital signs, intravenous fluid records, weights, and urine output. The physical examination should focus on assessment of the patient’s volume status, including evaluation of the patient’s neck veins and cardiac and pulmonary examinations. In some cases, hemodynamic monitoring may be necessary for an accurate evaluation of volume status. On skin examination, findings suggestive of an allergic reaction to a drug associated with acute interstitial nephritis should be sought. Other skin findings such as purpura and livedo reticularis are suggestive of vasculitides or atheroemboli. The abdominal examination may reveal ascites associated with liver disease and heart failure. Renal bruits are often heard in patients with renal artery stenosis, and a distended bladder can be palpated when bladder outlet obstruction is present.

**LABORATORY TESTS**

As mentioned, the diagnosis of ARF typically is based on identification of a rise in BUN and creatinine. These measures also can be used in the differential diagnosis of ARF. The BUN-to-creatinine ratio will be high (> 20:1) during states of decreased urea excretion or increased urea production (eg, prerenal azotemia, urinary tract obstruction, catabolic states, gastrointestinal bleeding, corticosteroid administration, or increased protein intake). Conversely, the ratio is low (< 10:1) when there is reduced urea production, increased release of creatinine, and decreased tubular secretion of creatinine. Other serum chemistries (eg, sodium, potassium, chloride, bicarbonate, calcium, magnesium, phosphorus, uric acid) are helpful for the acute
management of ARF. Urinalysis is essential for evaluating patients with ARF. In particular, microscopic evaluation of the urinary sediment is critical in the diagnosis of an acute glomerulonephritis, acute interstitial nephritis, or ATN. Renal ultrasonography is useful in identifying obstruction of the urinary system. Findings regarding renal size and echogenicity also can be of some diagnostic help (eg, detecting anatomic abnormalities such as solitary kidney, previous undiagnosed chronic renal disease, asymmetric kidney size suggestive of renal artery stenosis).

**PATHOPHYSIOLOGY**

The pathophysiology of ARF is very complex and corresponds to the complexity of the syndrome’s differential diagnosis (Table 1). Studies using both in vitro and in vivo models of ATN have identified several cellular and molecular events that may contribute to kidney dysfunction seen in patients with ARF. Ischemia-reperfusion, one of the most widely studied models, is discussed in the following sections. Knowledge regarding some mechanisms of the ischemia-reperfusion model remains incomplete, and this model is not applicable to all causes of ARF. Nonetheless, understanding the events of ischemia-reperfusion provides insight into ARF pathophysiology.

**HEMODYNAMIC AND VASCULAR FACTORS**

An ischemic injury is the near loss or complete lack of blood flow to an organ. A decrease in the effective arterial blood flow to the kidney results in the release of vasoactive mediators aimed at altering glomerular hemodynamics in an effort to maintain renal perfusion and glomerular filtration. Systemically, epinephrine, vasopressin, and angiotensin II are elaborated to cause vasoconstriction of the efferent arteriole, while prostacyclin and nitric oxide (NO) are produced locally to maintain afferent arteriolar vasodilation. This protective response, known as autoregulation, is maintained as long as the mean arterial pressure stays above 70 mm Hg. When the arterial pressure falls below this level, however, renal blood flow and glomerular filtration cannot be maintained and the vasoconstrictive forces supervene, further decreasing renal blood flow. If renal hypoperfusion persists, ischemia develops and leads to the local production of endothelin and NO, 2 factors important in the regulation of the renal microvascular circulation.

Endothelin-1 (ET-1) is a potent vasoconstrictor that plays an important role in ischemic ARF. It is synthesized by renal endothelial, epithelial, and mesangial cells as a prohormone and is enzymatically converted to its active form, which binds to 1 of 2 receptors: ETₐ or ETᵦ. ETₐ engagement leads to vasoconstriction, further decreasing blood flow, but it also acts as a growth factor, inducing cellular proliferation and matrix deposition in cultured cells. Signaling through ETᵦ leads to vasodilatation and NO release as well as increased synthesis of endothelin.

Exposure to endotoxin, tumor necrosis factor-α (TNF-α), platelet-derived growth factor, transforming growth factor-β, radiocontrast dye, and cyclosporine produces physiologic changes in renal blood flow similar to those seen with ischemic insults, including enhanced renal expression of ET-1 and decreased renal perfusion. In an experimental model of ischemic ARF, blocking the endothelin pathway using either an angiotensin-converting enzyme (ACE) inhibitor, an anti-endothelin neutralizing antibody, or an endothelin-receptor blocker decreased functional renal injury. When this approach was translated to a clinical study in humans undergoing cardiac catheterization, the same effect was not observed.

NO has a complex role in renal hemodynamics and in ischemia-reperfusion injuries seen in the kidney. NO is produced by endothelial cells through the actions of endogenous nitric oxide synthase (eNOS) in response to decreases in renal blood flow. Vasodilation occurs following the release of NO, resulting in increased blood flow in the renal microcirculation. However, the increased blood flow is short-lived, as the NO is inactivated by oxygen-derived free radicals induced during the primary ischemic insult. The protective role of NO was...
demonstrated in an experimental ischemia model in which the infusion of NO reduced reperfusion injury.\textsuperscript{10} Patients with chronic renal failure, diabetes mellitus, atherosclerosis, hypertension, and sepsis have been observed to have defective endothelium-dependent vasodilation, which may contribute to their increased vulnerability to ATN.

In contrast to its beneficial effects, NO also can have deleterious effects on renal function. The kidney can produce large amounts of NO via a form of nitric oxide synthase (iNOS) that can be induced by cytokines and endotoxin. The excess NO reacts with oxygen-derived free radicals generated by injured endothelial cells and adherent leukocytes to form toxic hydroxyl radicals, which in turn cause further renal damage. Because NO has a potential dual role in ARF, inhibiting nitric oxide synthase (eNOS and/or iNOS) may have different effects depending on the model studied. To date, NOS inhibitors have had no beneficial effects in humans.

In summary, the initial ischemic insult leads to the production of vasoactive factors that exacerbate renal ischemia, and these ischemic events precipitate damage to the renal tubular epithelium.

\textbf{TUBULAR EPITHELIAL CELL INJURY AND DEATH}

Injury to and death of renal tubule cells contribute to the alterations in GFR following an ischemic insult. The severity of the injury, in part, relies upon the extent of ischemia. In most cases of ischemic ATN, a range of pathology is seen, from sublethal injury, to apoptosis, to necrosis. Intracellular depletion of adenosine triphosphate (ATP), upon which all cellular processes are dependent, is the hallmark of ischemia. Following depletion of ATP, the function of ATPase is lost and cell homeostasis fails, resulting in cell swelling and acid-base dysregulation, which in turn causes increased levels of intracellular calcium. The increased calcium activates specific enzymes, such as phospholipases, proteases, and endonucleases, that cause loss of cell regulation, cellular detachment, membrane degradation, and cell death. The epithelial-cell barrier loses the ability to regulate its function and loses its polarity and brush border. The loss of function of cellular proteins as well as the activation of destructive proteins leads to cell injury or death and sloughing into the lumen of the nephron. Cell sloughing causes luminal obstruction, increased tubular pressure, and decreased single-nephron GFR. The loss of

\textbf{Figure 2.} Glomerular hemodynamic auto-regulation. $ACE = \text{angiotensin-converting enzyme; } AT_1 = \text{angiotensin I}$. (Reprinted with permission from Iglesias J, Lieberthal W. Clinical evaluation of acute renal failure. In: Johnson RJ, Feehally J, editors. Comprehensive clinical nephrology. London: Mosby; 2000:15.4.)
tubular lumen epithelium results in tubular fluid back-leakage, further decreasing the effective GFR. Following this injury, the kidney has the ability to repair itself through the proliferation and differentiation of new epithelium, a process that is likely promoted by growth factors. Some of the cellular events associated with ischemic ATN are summarized in Figure 3.\textsuperscript{11}

**MANAGEMENT OF ISCHEMIC ACUTE RENAL FAILURE**

**PREVENTION**

Ischemic ATN is best avoided by maintaining systemic hemodynamics and renal perfusion and carefully monitoring the dosing of potentially nephrotoxic drugs. Nonetheless, in most cases of ARF the ischemic insult is unavoidable and the onset is unpredictable. In some clinical situations, the ischemic insult is iatrogenic and occurs when patients are administered intravenous radiocontrast material. Much progress has been made in the prevention of contrast-induced nephropathy, which is caused in part by an acute ischemic injury.\textsuperscript{12} In patients at high risk for contrast nephropathy, the administration of intravenous saline has been used to ameliorate reductions in renal function; calcium antagonists, theophylline, dopamine, and atrial natriuretic peptide have been studied in clinical trials and have not been shown to ameliorate reductions in renal function.\textsuperscript{13} The rationale for administering saline is that it corrects any subclinical intravascular volume depletion, thereby minimizing ischemia induced by the dye. Saline also can prevent intravascular volume depletion induced by the diuresis of the osmotic load. The administration of intravenous fluids has not been studied in a randomized
controlled fashion, but some benefits have been suggested by both retrospective and uncontrolled studies. Most protocols recommend half-normal saline given at a rate of 1 mL/kg/hr beginning 1 to 2 hours before the procedure and lasting for 24 hours. Studies of other agents administered to induce diuresis following intravenous radiocontrast have not shown a clinical benefit. In 2 trials that evaluated the effects of furosemide on renal function in the context of dye exposure, renal impairment was more common in the furosemide group than in the control group. This effect is likely due to the intravascular volume depletion induced by diuresis and the ischemic effects on renal blood flow. Therefore, furosemide cannot be recommended for the prophylaxis of contrast nephropathy. Mannitol also showed no benefit in preventing the effects of dye-induced nephropathy.

In recent studies, reactive oxygen species have been shown to play an important role in contrast-induced ischemia to the kidney. The antioxidant acetylcysteine was evaluated in a randomized controlled clinical trial designed to block reactive oxygen species in patients at high risk for developing contrast-induced nephropathy. In this trial, 12% of the placebo-controlled patients had an increase in creatinine levels compared with 2% of the acetylcysteine treated patients. Thus, prophylactic oral administration of a reducing agent may decrease the risk of contrast-induced renal failure in a high-risk patient population.

**PHARMACOLOGIC TREATMENT OF ESTABLISHED ATN**

The primary therapeutic goals in the treatment of established ischemic ATN are to restore renal perfusion, minimize epithelial damage, relieve tubule obstruction, and promote epithelial repair and regeneration. Many agents shown to be beneficial in experimental models have failed to produce significant beneficial effects in human clinical trials. The following sections briefly discuss some of the potential pharmacologic agents and the rationale for their use in acute ischemic ATN.

**Dopamine**

Agents aimed at restoring renal hemodynamics have been a main focus of attention in the treatment of ATN. “Renal-dose” dopamine is commonly prescribed in the early phase of ARF to enhance renal blood flow and induce diuresis. Dopamine is an endogenous catecholamine, and it acts as a nonspecific vasoactive agonist. It activates both dopaminergic and adrenergic receptors in a dose-dependent manner. At doses of 0.5 to 1.0 µg/kg/min, dopamine primarily acts upon the dopamine receptors, leading to vasodilation and increased renal blood flow. At doses greater than 2 to 3 µg/kg/min, the β1 receptors are stimulated, increasing cardiac output and further augmenting renal blood flow. With doses greater than 10 µg/kg/min, the α-adrenergic receptors are stimulated, causing vasoconstriction.

The dopamine receptors are classified into 2 subtypes: D1 and D2. D1 receptors are located in the proximal tubule, macula densa, and renal arteries, while the D2 receptors are located in brush border and basolateral membranes of the tubules and the renal vasculature. Activation of both results in renal arterial vasodilation. In addition to its vasoactive properties, dopamine inhibits the function of the sodium-hydrogen exchanger and Na+K+-ATPase and inhibits the release of antidiuretic hormone, resulting in diuresis. Based on these physiologic effects, dopamine has theoretic purpose in the treatment of ARF. There have been several uncontrolled case series that have reported increases in urine output and improvements in renal function, but no improvements on mortality or the need for renal replacement therapy.

Recently, the largest prospective randomized placebo-controlled trial comparing low-dose dopamine in the setting of ARF was published. In this trial, 328 patients with systemic inflammatory response syndrome and ARF were studied. Statistically powered to detect a difference of more than 25% in peak serum creatinine between the 2 groups, this study found no difference in peak serum creatinine, need for renal replacement therapy, length of intensive care unit or hospital stay, or mortality.

Dopamine has clinically significant side effects. It can suppress respiratory drive, increase myocardial oxygen demand, and trigger myocardial ischemia or arrhythmias. The drug also can induce hypokalemia and hypophosphatemia and predispose to gut ischemia. There also is evidence that it can suppress T cell function and increase the risk of infection. Because of these potential adverse side effects, low-dose dopamine should not be administered to critically ill patients for the recovery of renal function.

**Dopamine Agonists**

Despite the lack of evidence supporting the use of dopamine, interest remains in dopamine agonists for the prevention and treatment of ARF. Fenoldopam is a selective dopaminergic (D1) agonist that is currently approved for the treatment of hypertensive emergencies. The drug increases renal perfusion at doses that do not lower systemic blood pressure in normal volunteers. As fenoldopam is selective for the D1 receptor, it does not cross-react with the adrenergic receptors and does not exhibit the potential disadvantages of dopamine. In a recent canine study, fenoldopam was shown to ablate the
rerenal tubular response, thus maintaining renal perfusion and GFR in the presence of hypovolemia. This finding suggests that a selective dopamine agonist may confer renal protection during renal ischemia.20 The true test of the effectiveness of this drug will have to await a well-powered randomized controlled study.

**Anaritide**

Anaritide, a synthetic form of atrial natriuretic peptide, has shown great promise in animal and early human studies in the treatment of ARF. This drug has several characteristics that make it theoretically beneficial in the treatment of ARF. Anaritide increases GFR by dilating afferent arterioles while constricting efferent tubules. It also blocks tubular reabsorption of sodium and chloride, redistributes renal medullary blood flow, disrupts glomerulotubular feedback, and reverses endothelin-mediated vasoconstriction. Anaritide also has been shown to increase glomerular filtration and urinary output in animals with acute renal dysfunction. In the first open-label clinical trial, which involved 53 patients with ATN, infusion of anaritide increased creatinine clearance and reduced the need for dialysis.21 This finding led to a large multicenter randomized, placebo-controlled trial in 504 critically ill patients. The administration of anaritide did not improve the overall rate of dialysis-free survival in critically ill patients with ATN.22

**COMPLICATIONS**

A number of life-threatening complications can develop in patients with ARF, and these need to be anticipated from the earliest recognition of renal insufficiency. Measures aimed at preventing these complications must be initiated when a physician first evaluates the patient with ARF. Most medical therapy includes supportive care directed at the management of cardiovascular and respiratory stability. In addition, the metabolic complications must be addressed and managed throughout the course of renal failure (Table 3). Should medical management be unsuccessful at correcting some of the metabolic complications of ARF, renal replacement therapy is indicated. Currently, dialysis is the only FDA-approved treatment for ARF; it is required in about 85% of patients with nonoliguric ARF and 30% of those with oliguric ARF.

**Table 3. Management of Complications of Acute Renal Failure**

<table>
<thead>
<tr>
<th>Complication</th>
<th>Potential Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extracellular volume overload</td>
<td>Salt restriction, diuretics, ultrafiltration</td>
</tr>
<tr>
<td>Hyponatremia</td>
<td>Restriction of oral water and hypotonic intravenous fluid</td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>Restriction of dietary K+; elimination of K+ supplements and K+-sparing diuretics; administration of K+-binding resins, glucose and insulin, sodium bicarbonate, calcium gluconate, dialysis</td>
</tr>
<tr>
<td>Metabolic acidosis</td>
<td>Restriction of dietary protein; administration of sodium bicarbonate, dialysis</td>
</tr>
<tr>
<td>Hyperphosphatemia</td>
<td>Restriction of dietary phosphate; administration of phosphate binders</td>
</tr>
<tr>
<td>Hypocalcemia</td>
<td>Calcium supplementation</td>
</tr>
<tr>
<td>Hyperuricemia</td>
<td>Allopurinol, diuresis, dialysis</td>
</tr>
<tr>
<td>Nutrition</td>
<td>Enteral or parenteral nutrition</td>
</tr>
<tr>
<td>Drug dosing</td>
<td>Adjust doses for GFR &lt; 10 mL/min; avoid NSAIDs, ACE inhibitors, ARBs, radiocontrast, nephrotoxic antibiotics, other nephrotoxins</td>
</tr>
</tbody>
</table>

ACE = angiotensin-converting enzyme; ARB = adrenergic-receptor binder; GFR = glomerular filtration rate; IV = intravenous; NSAID = nonsteroidal anti-inflammatory drug.


Acute renal failure is a form of renal failure characterized by a sudden decrease in kidney function. It can be caused by a variety of factors, including hypotension, dehydration, sepsis, and certain medications. Early recognition and management of complications are crucial to improve outcomes. The table above outlines common complications and their potential treatments, highlighting the importance of a multidisciplinary approach to care.

**RENAL REPLACEMENT THERAPY**

The indications for dialysis are symptoms and signs of uremia, volume overload, hyperkalemia, and metabolic acidosis that is refractory to medical therapy. One of the more difficult issues in the management of ARF is determining the modality of renal replacement therapy. The form of dialytic therapy may affect patient morbidity and mortality and has been the subject of intense investigation in clinical nephrology over the past several years.

**INTERMITTENT HEMODIALYSIS**

Intermittent hemodialysis (IHD) has been the standard form of dialysis used to treat ARF, but some have suggested that this form of renal replacement therapy may actually prolong the course of ARF. It has been hypothesized that intravascular fluid shifts and decreases in blood pressure can exacerbate renal ischemia and delay the recovery of ARF. These hemodynamic effects of IHD may be associated with focal areas of ATN in the recovering kidney.
The role of biocompatibility and delivered dialysis dose are 2 of the many clinical aspects of IHD that have not been adequately studied in the outcomes of patients with ARF. Biocompatibility refers to the magnitude of the activation of the plasma and cellular components of the blood after exposure to the dialysis membrane. These changes are due to activation of complement and the coagulation cascade. In addition, neutrophils, macrophages, and monocytes also are activated. The clinical sequelae of this activation remain speculative, but they may play a role in prolonging recovery of ATN. Several clinical studies have been performed to study the effects of biocompatibility in ARF, and there is some suggestion that biocompatible membranes are beneficial.

Assessment of dialysis adequacy also is an essential issue in the management of patients with ARF. Mortality is inversely related to dialysis adequacy in patients with end-stage renal disease as determined by $K_t/V$ measurements. In recent years, similar studies have begun to emerge for patients with ARF. These studies suggest that patients with ARF are underdialyzed, as the delivered dose of dialysis falls short of the prescribed dose. Dialysis adequacy, some argue, may be a factor contributing to the high mortality seen in ARF. The reasons for the discrepancy between delivered and prescribed dose of dialysis are related to temporary vascular access, catheter recirculation, hypotension, dialyzer clotting, and poor urea clearances.

**CONTINUOUS RENAL REPLACEMENT THERAPY**

Continuous renal replacement therapy (CRRT) can potentially correct some of the problems associated with IHD. This modality has several theoretical advantages over IHD. First, CRRT avoids water, electrolyte, and urea fluctuations. During ARF, metabolites that are normally excreted at relatively constant rates accumulate in the blood. With IHD, these substances are cleared over a period of hours, but they rapidly reaccumulate in the absence of renal function, resulting in a “sawtooth” pattern of metabolite increases and decreases. CRRT provides a more physiologic clearance pattern, avoiding fluctuations in levels of metabolites.

There are several different CRRT modalities (Table 4). Historically, the arterial circulation was used to provide the force to move blood across the dialyzer. Due to the need for arterial access and inherent complications, such as ischemia, atheroemboli, bleeding, and pseudoaneurysm and the technical improvement in venovenous therapies, these methods have been largely abandoned. The venovenous modalities differ primarily in the methods of clearance. Slow continuous ultrafiltration (SCUF) is a method employed to remove volume by taking off fluid filtered by a dialysis membrane by convective force.

**Figure 4.** Sawtooth pattern of blood urea nitrogen level across time in daily intermittent hemodialysis (IHD) and smooth decline of solute concentration of continuous venovenous hemodialysis (CVVHD) in a 70-kg patient with a protein catabolic rate of 2 g/kg body weight/day and a urea generation rate (GU) of 13.79 mg/min. $K_t/V$ is defined as the dialyzer clearance of urea ($K$) multiplied by the duration of the dialysis treatment ($t$, in minutes) divided by the volume of distribution of urea in the body ($V$, in mL [approximately total body water]). (Adapted with permission from Manns M, Sigler MH, Teehan BP. Continuous renal replacement therapies: an update. Am J Kidney Dis 1998;32:185–207.)
Continuous venovenous hemodialysis (CVVHD) provides clearance using diffusive clearance by running dialysate across the membrane. Continuous venovenous hemofiltration (CVVHF) removes fluid by convection (as in SCUF) and then provides replacement fluid back to the patient. Finally, continuous venovenous hemodiafiltration combines the clearance properties of CVVHD and CVVHF.

OUTCOMES OF CRRT AND IHD

Much has been published in the last several years regarding the potential advantages of CRRT versus IHD. To date there is no clear consensus as to whether outcomes are improved in patients treated with CRRT, but clinical trials addressing this specific question are difficult to perform. In a recent study performed in patients with severe ARF requiring dialysis, mortality was almost solely attributed to the underlying medical condition. After adjusting for severity of illness, patients who received CRRT and those who received IHD were equally likely to survive.29

Even though there is no definite advantage of CRRT versus IHD, it is becoming clear that the amount of dialysis delivered to the patient with ARF is important for patient outcome. In a recent trial, the dose of delivered dialysis was shown to impact patient survival in a dose-dependent manner.30 Critically ill patients requiring CRRT were randomized into 3 groups, each receiving an increased dose of dialysis (20, 35, and 45 mL/hour/kg of ultrafiltration by CVVHF). The survival rate for the 3 groups was 41%, 57%, and 58%, respectively, demonstrating a significant difference in survival for those patients receiving more dialysis. The authors concluded that ICU patients with ARF requiring CRRT should receive at least 35 mL/hour/kg of ultrafiltration.

Despite the potential advantages of CRRT, this therapy has several disadvantages, including the need for anticoagulation, patient immobility, and intensive nursing and expense. Furthermore, this form of dialysis is not available at all centers providing renal replacement therapy. Because of these factors, a group recently published a report using conventional dialysis machines in a technique they call extended daily dialysis (EDD).31 With this technique, a conventional dialysis machine is employed and patients are dialyzed for 6 to 8 hours at low blood flow, mimicking CRRT. Their study (not randomized) was done in a controlled fashion in which patients undergoing EDD were compared to a group of patients undergoing CRRT. There were no significant differences between the 2 groups regarding several clinical parameters. Mortality was not a primary end-point in this study; however, 84% of the patients receiving EDD died compared with 65% of those receiving CRRT. Further study of this dialysis technique will have to be performed to determine if it has any clinical benefit.

SUMMARY

Medical management of ARF remains a challenge for clinicians. Increased understanding of some of the pathophysiologic mechanisms of ARF has led to the study of many pharmacologic agents in its treatment. Because of the complex etiology of the syndrome, the benefit of most of these agents has not been recognized. Until further clinical trials are performed, we will not know the true benefit of pharmacologic treatments to prevent or treat ARF. In addition, renal replacement therapies are now available to support ARF patients; determining which therapies improve survival outcomes will be beneficial.

REFERENCES


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