CHAPTER 9

ACUTE RENAL FAILURE

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Acute renal failure (ARF) is defined as a rapid deterioration in renal function sufficient enough to result in accumulation of nitrogenous wastes in the body. However, a different definition has been proposed which defines it as the sudden inability of the kidney to regulate water and solute imbalance. Although this loss of regulatory capacity is an important characteristic of acute renal failure, it fails to address the prerenal causes of decreased glomerular filtration rate. Acute renal failure is a common entity with approximately five percent of all hospitalized patients developing acute renal failure. However, in the hospital setting such as the critical care unit, that percentage may grow to as much as 20%.[1] When a patient develops ARF, the possibility for fatality increases approximately 8 times. Infection is the most common cause of death in patients with ARF, with cardiorespiratory complications being the second most common.[2] Because of the high percentage of patients that develop ARF and the increase in mortality that results, it is crucial to create a logical approach for early diagnosis as well as treatment for these patients.

Recognition of a patient with ARF is by recognizing an increase in the blood urea nitrogen and/or the serum creatinine concentration. To be detectable from the limits of normal by a simple blood test, such as serum creatinine, this accumulation in serum creatinine usually implies a least a 50% decrease in the glomerular filtration rate. However, if acute renal failure is superimposed on a pre-existing renal insufficiency such as chronic renal failure, detectable rises in serum creatinine require smaller decrements in the glomerular filtration rate. For example, an increase in serum creatinine from 5mg/dL to 6mg/dL in a patient with chronic renal failure results in a 15% decrease in the glomerular filtration rate. A decrease in urine output has commonly been associated with the presence of acute renal failure. However, it has been determined that not all patients with acute renal failure are oligouric, and therefore the presence of urinary flow rates of greater than 30 mL/h does not exclude the presence of acute renal failure.[1] Although an increase in the blood urea nitrogen and/or the serum creatinine concentration are the primary ways in which ARF presents itself. It may also present itself as other clinical manifestations such as, abnormal mental status or gastrointestinal symptoms, or as other laboratory manifestations such as, anemia or hyperkalemia. Diagnosis of acute renal failure is critical in order to decrease morbidity and mortality of patients that are suffering from the disorder. Visualization of the kidneys in acute renal failure allows for the differentiation from chronic renal failure. In chronic renal failure, the kidneys will usually be small bilaterally and contracted. Visualization also allows for the diagnosis of obstructive uropathy and the ability to estimate the patency of renal vessels.

CAUSES

Acute renal failure can be due to a decrease in renal profusion, known as prerenal azotemia. This is a decrease in glomerular filtration rate resulting from renal hypoperfusion that is immediately reversed with the restoration of renal blood flow, and is not associated with structural damage to the kidney. It can also be due to intrinsic renal failure, which is a decrease in glomerular filtration rate resulting from renal hypoperfusion or a nephrotoxin, not immediately reversed upon discontinuation of the cause. It is also associated with tubule cell damage. Acute renal failure can also be a result of interstitial inflammation, which is known as acute interstitial nephritis. Another cause of ARF is acute glomerulonephritis or vasculitis, which is a decrease in GFR resulting from glomerular or vessel inflammation. Acute renovascular disease can also cause ARF as a result of obstruction of the renal artery or vein in a single functioning kidney or with bilateral kidney disease. An additional cause of ARF is obstructive uropathy, which is a decrease in glomerular filtration rate due to obstruction in the urinary collecting system. This is also known as postrenal azotemia. Urine formation begins with glomerular ultrafiltration of blood delivered to the kidneys, proceeds through tubular processing of the ultrafiltrate by secretion and absorption, and ends by excretion of urine through the ureters, bladder, and urethra.

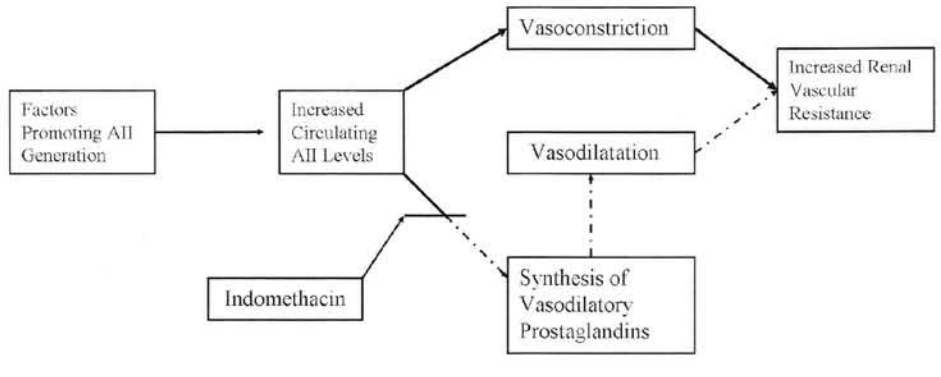
A combination of hypotension, hypovolemia, and diminished renal perfusion is the most common cause of acute azotemia in the hospitalized patient.[3] Prerenal azotemia is the cause of approximately 40 to 80% of the cases of acute renal failure. If treated appropriately,

prerenal azotemia is reversible. However, if left untreated, prolong renal hypoperfusion can lead to ischemic acute tubular necrosis with significant increase in morbidity and mortality. Circulating blood is critical to the perfusion of vital organs, depletion of extracellular volume triggers compensatory systemic and renal changes. The systemic responses include activation of the autonomic nervous system, renin-angiotensin system, and antidiuretic hormone release with the results of peripheral vasoconstriction, stimulation of thirst, and a decrease in sweat electrolyte content. The renal response occurs in different phases. The early changes are increased tubule reabsorption of sodium and water, mediated mostly by nerves and hormones. The decrease in urine flow that results produces a drop in urea clearance, with the consequence being a disproportionate increase of urea in the blood. However, more advanced hypovolemia will overcome renal autoregulation of blood flow and glomerular filtration rate, first with a decrease in renal blood flow associated with its redistribution from the cortex to the medulla. Subsequently, the glomerular filtration rate maintained by autoregulation and controlled by a balance between angiotensin II, prostaglandins, and renal neural activity, will decline. Therefore, the consequences are a decreased glomerular filtration rate with enhanced fluid reabsorption.[4] When performing a physical examination on a patient with acute renal failure, it is important to pay close attention to blood pressure, pulse rate, jugular venous pressure, cardiac function, skin turgor, and mucous membranes.

Acute intrinsic renal failure can be caused by renal hypoperfusion, nephrotoxins either exogenous or endogenous, and frequently a combination of hypoperfusion and nephrotoxins. Hypoperfusion is the most frequently recognized single insult leading to acute intrinsic renal failure in the setting of trauma, surgery, hemorrhage, or dehydration.[5] Mild hypoperfusion seen in volume depletion causes the syndrome of prerenal azotemia with mild decrease in glomerular filtration rate. It will also lead to a more pronounced decrease in urea clearance and tubule reabsorption of sodium and water, resulting in the production of small amounts of concentrated urine. This small amount of urine is low in sodium, with a high ratio of urine to plasma creatinine and low fractional excretion of sodium. The fractional excretion of sodium (FeNa) is defined as the clearance of sodium by the kidney (U_{Na}*V/P_{Na}) expressed as a percentage of glomerular filtration rate. Therefore: FeNa(%)= U_{Na}/P_{Na} / U_{Cr}/P_{Cr} x 100. In prerenal azotemia, the combination of high tubule resorption and therefore a high U_{Cr} and a low U_{Na}, will produce a low FeNa of less then one percent.[4]

Renal hypoperfusion as a result of an increased ratio of renal to systemic vascular resistance, is derived from functional renal vasoconstriction, systemic vasodilation, or a combination of both. Renal vasoconstriction may be neuromediated, hormone-mediated, or caused by exogenous or endogenous toxins. Neuromediated vasoconstriction is often caused by large doses of

Fig 1. Effects of Indomethacin on Increased Levels of Circulating Angiotensin II*



* Adapted from Brezis and Rosen, et al

Figure 1.

alpha-adrenergic agonists such as norepinephrine. Stimulation of the renal nerves produces vasoconstriction, mediated via alpha receptors. Hormone mediated renal vasoconstriction has been associated with prostaglandin synthesis inhibitors and angiotensin I converting enzyme inhibitors such as Captopril. Inhibitors of prostaglandin synthesis such as salicylates, proprionic acid derivatives (ibuprofen), and indoleacetic acid derivatives (indomethacin) have been shown to produce a rapid decrease in renal blood flow and glomerular filtration rate in patients with reduced effective arterial blood volume or renovascular disease such as CHF, hypoalbuminemia, sepsis, or pre-existing renal disease. Prostaglandins produce vasodilation which induces an important protective compensatory vasodilation in the setting of renal hypoperfusion, when activation of the renin-angiotensin system alone would threaten the kidney with further vasoconstriction (Figure 1). Captopril has been reported to produce a severe deterioration in renal function with renal artery stenosis. It is thought that at the low perfusion pressure associated with renovascular disease, glomerular filtration rate depends on a balance between efferent and afferent arteriolar resistances regulated by the renin-angiotensin system.[4] Captopril prevents the conversion of angiotensin I to angiotensin II, leading to decreased levels of angiotensin II. Angiotensin II increases the glomerular filtration rate by causing constriction of the efferent arteriole. Its absence decreases the glomerular filtration rate, and thus causing acute renal failure.

Nephrotoxic injury can also lead to renal vasoconstriction as well as direct parenchymal toxicity. Because of its natural function of waste excretion, the kidney is exposed to high concentrations of blood-borne substances. Thus, the renal tubule cells are often the first target of direct toxicity for a wide variety of drugs, heavy metals, and solvents. Nephrotoxic acute renal failure is usually reversible and preventable if the offending material is identified and avoided. A general principle applicable to nephrotoxic injury is that the severity of the injury is strongly related not only to the concentration of the toxin and the duration of exposure, but all the predisposing factors that are different in all hosts. Each individual is affected by nephrotoxic insults differently. Exogenous toxins are composed of a large variety of chemicals, ranging from antibiotics to recreational drugs (Table 1). An example of exogenous nephrotoxins are a group of antibiotics called aminoglycosides. Aminoglycosides have nephrotoxicity as a major adverse effect. ARF complicates 10-26% of therapeutic courses of gentamicin, amikacin, and tobramycin.[6] Aminoglycoside-induced ARF is usually nonoligouric, the urinary output being an unreliable marker of renal function. ARF is not clinically evident within 5-10 days of the drugs administration.[7] Aminoglycosides differ in their ability to cause nephrotoxicity, neomycin being the most and streptomycin being the least nephrotoxic.[8] The mechanism of toxicity seems to be due to the accumulation of the antibiotic by the renal parenchyma, primarily the renal cortex. In sufficient concentrations, aminoglycosides inhibit phospholipase A2, and therefore reduce the formation of prostaglandins by limiting the availability of the arachidonic acid precursor. Although exogenous nephrotoxins are common and do exist, endogenous nephrotoxins also exist, and must be considered. The most frequent causes of rhabdomyolysis and myoglobinuria are alcohol abuse, muscle

Table 1

CAUSES OF EXOGENOUS TOXIC ACUTE RENAL FAILURE*

Antibiotics
- Aminoglycosides
- Quinolones
- Cephalosporins
- Tetracyclines
- Bacitracin

Contrast Media
- Iopanoic acid
- Diatrizoate

Chemotherapeutic Agents
- Methotrexate
- Nitrosureas
- Mitomycin
- Interleukin-2

Organic Solvents
- Aromatic hydrocarbons
- Halogenated hydrocarbons

Poisons
- Insecticides
- Herbicides
- Yellow oleander

Recreational Drugs
- Heroin
- Amphetamines

* Adapted from Brezis and Rosen, et al.

compression, seizures, drugs, and infections.[9] Muscle pain and dark brown urine without red blood cells are important diagnostic clues, but elevations of creatinine phosphokinase and myoglobin are more sensitive. The mechanism of myoglobin nephrotoxicity is unclear, but both hemoglobin and myoglobin enhance vasoconstriction by inhibiting the production of endothelial relaxing factor. So it is quite clear that there a wide variety of causes of acute renal failure that can be attributed to prerenal and intrarenal causes. There is also an additional cause of acute renal failure, which is postrenal azotemia.

Postrenal azotemia is the cause for approximately 10% or less of all cases of acute renal failure.[1] Because obstruction is frequently amendable to treatment, it must be considered in all patients that have deteriorating renal function. Bladder neck obstruction due to prostatic disease or denervation due to neuropathy or anticholinergic medications are common causes of postrenal azotemia and can be evaluated by suprapubic palpation and percussion for an enlarged bladder. Obstruction of the upper urinary tract is not as common, because it would entail simultaneous obstruction of both ureters or unilateral ureteric obstruction with severe disease or absence of the contralateral kidney. Causes of bilateral urinary tract obstruction include retroperitoneal fibrosis and space-occupying processes such as an abscess, surgical accident, or bilateral intraureteric occlusion. An example of a cause of intraureteric occlusion would be stones, papillary tissue, blood clots, or pus. A plain film of the abdomen may reveal retroperitoneal disease or radiopaque calculi, which compose 90% of kidney stones. If the presence of an upper urinary tract obstruction cannot be ruled out sufficiently with ultrasound, or computed tomographic scanning, evaluation of the patency of the ureters by retrograde pyelography may be required.

TREATMENTS

General treatment of acute renal failure should initially focus on correcting fluid and electrolyte balances and uremia, while the cause of the ARF is being determined. If the patient is volume depleted, they should be resuscitated with saline; however, more often the patient is in volume overload. Furosemide should be administered every six hours for the treatment of volume overload. The initial dose should be between 20 and 100 mg, and if an inadequate response occurs in one hour, the dose can be doubled. A continuous furosemide drip may be required, and the last resort is ultrafiltration via dialysis. The main electrolyte disturbances in ARF are hyperkalemia and acidosis. The aggressiveness of treatment depends on the severity of hyperkalemia. Intravenously administered calcium is cardioprotective and temporarily reverses the neuromuscular effects of hyperkalemia. Potassium can be temporarily shifted into the intracellular compartment using intravenous insulin and glucose. Potassium excretion is aided with sodium polystyrene sulfonate (Kayexalate). If this does not control the hyperkalemia that exists, dialysis should be administered. Acidosis is treated with intravenously administered sodium bicarbonate if the serum bicarbonate level is less than 15 mEq/L2. Intractable acidosis requires dialysis. Between 20 and 60% of patients require short-term dialysis, particularly when the blood urea nitrogen levels surpass 100 mg/dL. Indications for dialysis include acidosis or electrolyte disturbances that do not respond to pharmacologic therapy, fluid overload that does not respond to diuretics, and uremia.

CONCLUSION

As a podiatric physician it is rare to ever be managing a patient with acute renal failure alone. However, some of the common causes of ARF (ibuprofen, aminoglycosides) are in the treatment regimen for the patients that are seen in the office daily. Therefore, it is vital to understand the cause, the symptoms, and the treatments of acute renal failure.

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