REVIEW ARTICLE

CURRENT CONCEPTS

Normotensive Ischemic Acute Renal Failure

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Acute renal failure is defined as a rapid decrease in the glomerular filtration rate, occurring over a period of minutes to days. Because the rate of production of metabolic waste exceeds the rate of renal excretion in this circumstance, serum concentrations of markers of renal function, such as urea and creatinine, rise. The causes of acute renal failure are classically divided into three categories: prerenal, postrenal (or obstructive), and intrinsic. Prerenal azotemia is considered a functional response to renal hypoperfusion, in which renal structure and microstructure are preserved. Postrenal azotemia — obstruction of the urinary tract — is initially accompanied by few microscopical changes (early hydronephrosis, with enlargement of the pelvic cavity and minimal distention or blunting of the renal papilla) or none. In contrast, intrinsic renal azotemia is due to parenchymal injury of the blood vessels, glomeruli, tubules, or interstitium. In prerenal and postrenal azotemia, complete recovery may be seen 1 to 2 days after relief of the offending lesion, provided that normal perfusion or urinary outflow is reestablished before structural changes occur.

A research focus group organized by the American Society of Nephrology recently recommended that the term "acute kidney injury" replace the term "acute renal failure."[1] However, the group left the actual definition of acute kidney injury to be determined in the future. Thus, whether acute kidney injury refers only to acute tubular necrosis or includes prerenal and postrenal azotemia and parenchymal diseases such as acute glomerulonephritis remains unclear. Most clinicians still use the term acute renal failure as defined above.

The two forms of ischemic acute renal failure, prerenal azotemia and acute tubular necrosis, account for more than half the cases of renal failure seen in hospitalized patients and are familiar to most clinicians.[2-4] Yet in many patients with acute renal failure, the contribution of ischemia is initially unrecognized. Patients with ischemic acute renal failure typically have low systemic perfusion, sometimes caused by volume depletion, although their blood pressure may not fall dramatically but instead may remain within the normal range (in an adult, systolic blood pressure >90 to 100 mm Hg). In such cases, in the absence of frank hypotension, the clinician may speculate that an unobserved drop in blood pressure must have caused the renal failure. Although this scenario cannot be ruled out, other causative mechanisms can usually be identified. This type of ischemic acute renal failure (termed normotensive, because the patient's blood pressure is — at least temporarily — within the normal range) can occur as a result of several processes, most of which involve increased renal susceptibility to modest reductions in perfusion pressure. Fortunately, the factors that lead to ischemic renal failure in patients with apparently normal blood pressure are discernible in most instances. Recognition of these factors allows the physician to make an early diagnosis and facilitates the interventions that can help to reestablish normal renal hemodynamics.

The importance of addressing even mild renal failure is illustrated by a recent study showing that hospitalized patients with a modest increase in the serum

creatinine level (0.3 to 0.4 mg per deciliter [26.5 to 35.4 μmol per liter]) have a 70% greater risk of death than persons without any increase.[5] This article reviews the renal response to ischemia, notes the risk factors for the development of normotensive ischemic acute renal failure, and discusses the diagnosis of this condition.

RENAL RESPONSE TO ISCHEMIA

The salient feature of the renal response to a drop in perfusion pressure is autoregulation — maintenance of normal blood flow and glomerular filtration rate, even with mean arterial pressure as low as 80 mm Hg (Fig. 1).[6] Each of the million or so glomeruli per kidney has an afferent (incoming) and an efferent (outgoing) arteriole, and pressure within the glomerular capillaries is affected by the resistances in these two arterioles as they respond to a variety of vasoconstrictor and vasodilatory factors, including a myogenic stretch reflex in the afferent arteriole. Autoregulation during a decrease in renal-artery pressure derives mainly from a drop in afferent glomerular arteriolar resistance, mediated in large part by prostaglandins (Fig. 2A and 2B). This drop in afferent resistance sustains glomerular capillary pressure, the driving force of filtration. Glomerular capillary pressure is also partly supported by an increase in efferent glomerular arteriolar resistance, mediated largely by angiotensin II.[7-9]

As renal perfusion pressure drops below the autoregulatory range, endogenous vasoconstrictors increase afferent arteriolar resistance. This reduces glomerular capillary pressure and the glomerular filtration rate, resulting in functional prerenal azotemia.[7,9,10] The postglomerular capillary bed, which perfuses the tubules, has diminished blood flow and pressure, but the tubules remain intact. However, increasing severity and duration of ischemia may cause structural tubular injury, further impairing renal function. Sloughed tubular epithelial cells and brush-border–membrane debris form casts that obstruct tubules, and experimental data indicate that glomerular filtrate leaks from the tubular lumen across denuded tubular walls into capillaries and the circulation (a phenomenon called back-leak).[3,9-11] In addition, impaired sodium reabsorption by injured tubular epithelial cells increases the sodium concentration in the tubular lumen. The increased intratubular sodium concentration polymerizes

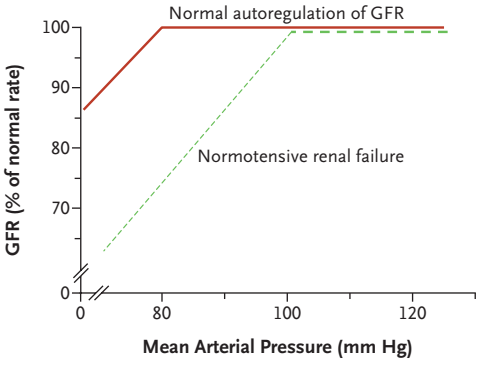

Figure 1. Normal and Impaired Autoregulation of the Glomerular Filtration Rate during Reduction of Mean Arterial Pressure.

In normal autoregulation, the glomerular filtration rate (GFR) is maintained until the mean arterial pressure falls below 80 mm Hg. However, in patients with impaired autoregulation, the GFR falls below normal values while the mean arterial pressure remains within the normal range, resulting in normotensive ischemic acute renal failure.

Tamm–Horsfall protein, which is normally secreted by the loop of Henle, forming a gel and contributing to cast formation.[10,12]

The mechanism whereby ischemia and oxygen depletion injure tubular cells starts with ATP depletion, which activates a number of critical alterations in metabolism (Fig. 3).[13,14] Cytoskeletal disruption leads to loss of brush-border microvilli and cell junctions and to mislocation of integrins and sodium–potassium ATPase from the basal surface to the apical surface. As a result, brush-border membranes and cells slough and may obstruct tubules downstream. ATP depletion also activates harmful proteases and phospholipases, which, with reperfusion, cause oxidant injury to tubular cells. Similar damage occurs in endothelial cells of the peritubular capillaries, especially in the outer medulla, which is marginally oxygenated under normal circumstances. This oxidant injury, together with a shift in the balance of vasoactive substances toward vasoconstrictors such as endothelin, results in vasoconstriction, congestion, hypoperfusion, and expression of adhesion molecules.[14] The expression of adhesion molecules, in turn, initiates leukocyte infiltration, augmented by proinflammatory and chemotactic cytokines generated by ischemic tubular cells. These leukocytes obstruct the microcirculation and release cytotoxic cytokines, reac-

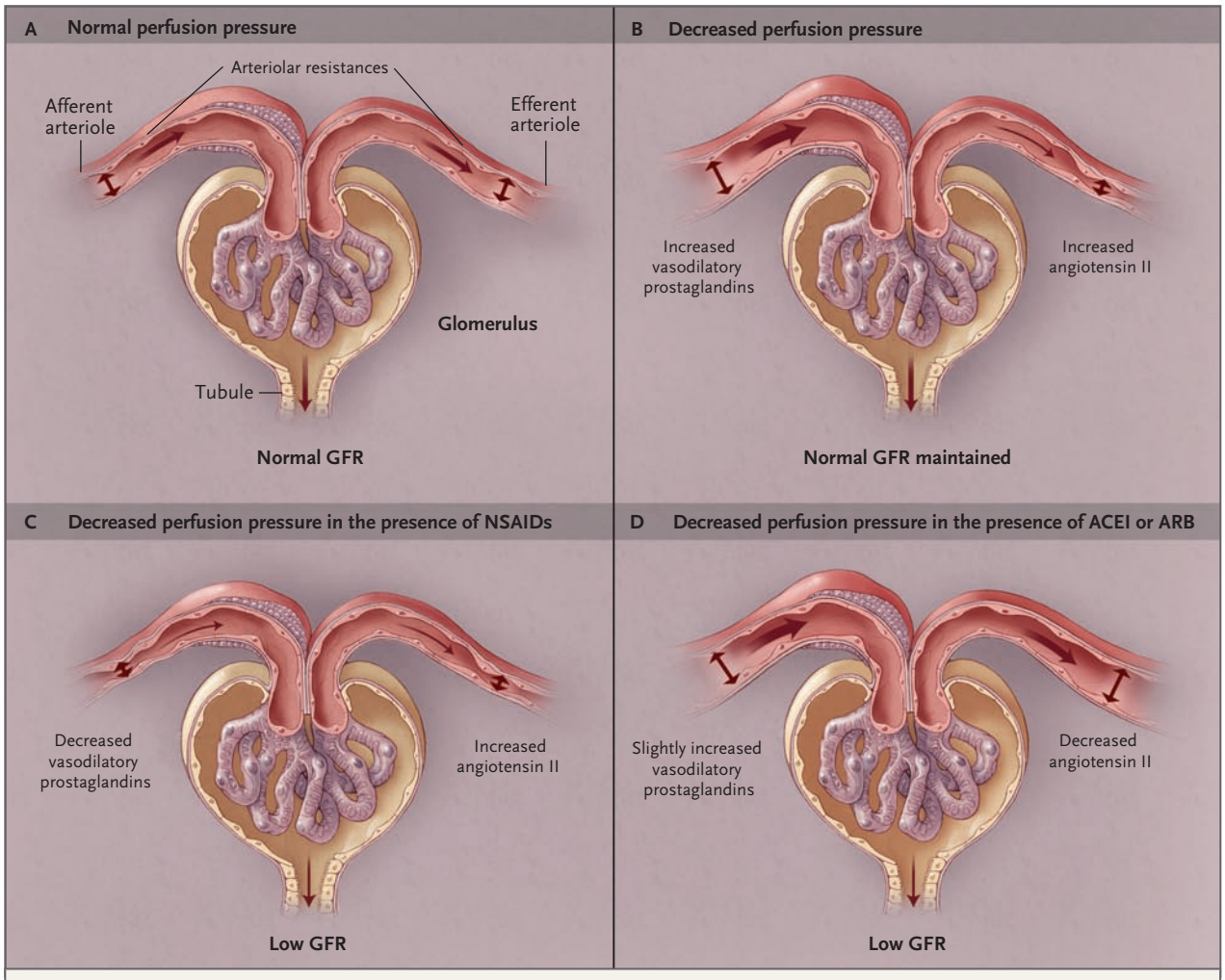

Figure 2. Intrarenal Mechanisms for Autoregulation of the Glomerular Filtration Rate under Decreased Perfusion Pressure and Reduction of the Glomerular Filtration Rate by Drugs.

Panel A shows normal conditions and a normal glomerular filtration rate (GFR). Panel B shows reduced perfusion pressure within the autoregulatory range. Normal glomerular capillary pressure is maintained by afferent vasodilatation and efferent vasoconstriction. Panel C shows reduced perfusion pressure with a nonsteroidal antiinflammatory drug (NSAID). Loss of vasodilatory prostaglandins increases afferent resistance; this causes the glomerular capillary pressure to drop below normal values and the GFR to decrease. Panel D shows reduced perfusion pressure with an angiotensin-converting–enzyme inhibitor (ACEI) or an angiotensin-receptor blocker (ARB). Loss of angiotensin II action reduces efferent resistance; this causes the glomerular capillary pressure to drop below normal values and the GFR to decrease.

tive oxygen species, and proteolytic enzymes, which damage the tubular cells.[14]

This tubular damage is commonly known as acute tubular necrosis. The term is misleading, however, because only some tubular cells are necrotic; most are viable (either healthy or reversibly injured), and some are apoptotic (i.e., undergoing an orderly programmed death). "Ischemic acute kidney" and "acute tubular injury" have been proposed as better terms[14]; neither of these newer terms is in common use.

FACTORS INCREASING RENAL SUSCEPTIBILITY TO ISCHEMIA

The kidneys are most vulnerable to moderate hypoperfusion when autoregulation is impaired (Fig. 1), which occurs most often when afferent arteriolar resistance does not decrease appropriately or even increases (Table 1). This phenomenon may be seen in elderly patients or in patients with atherosclerosis, hypertension, or chronic renal failure, in whom hyalinosis and myointimal hyperplasia cause

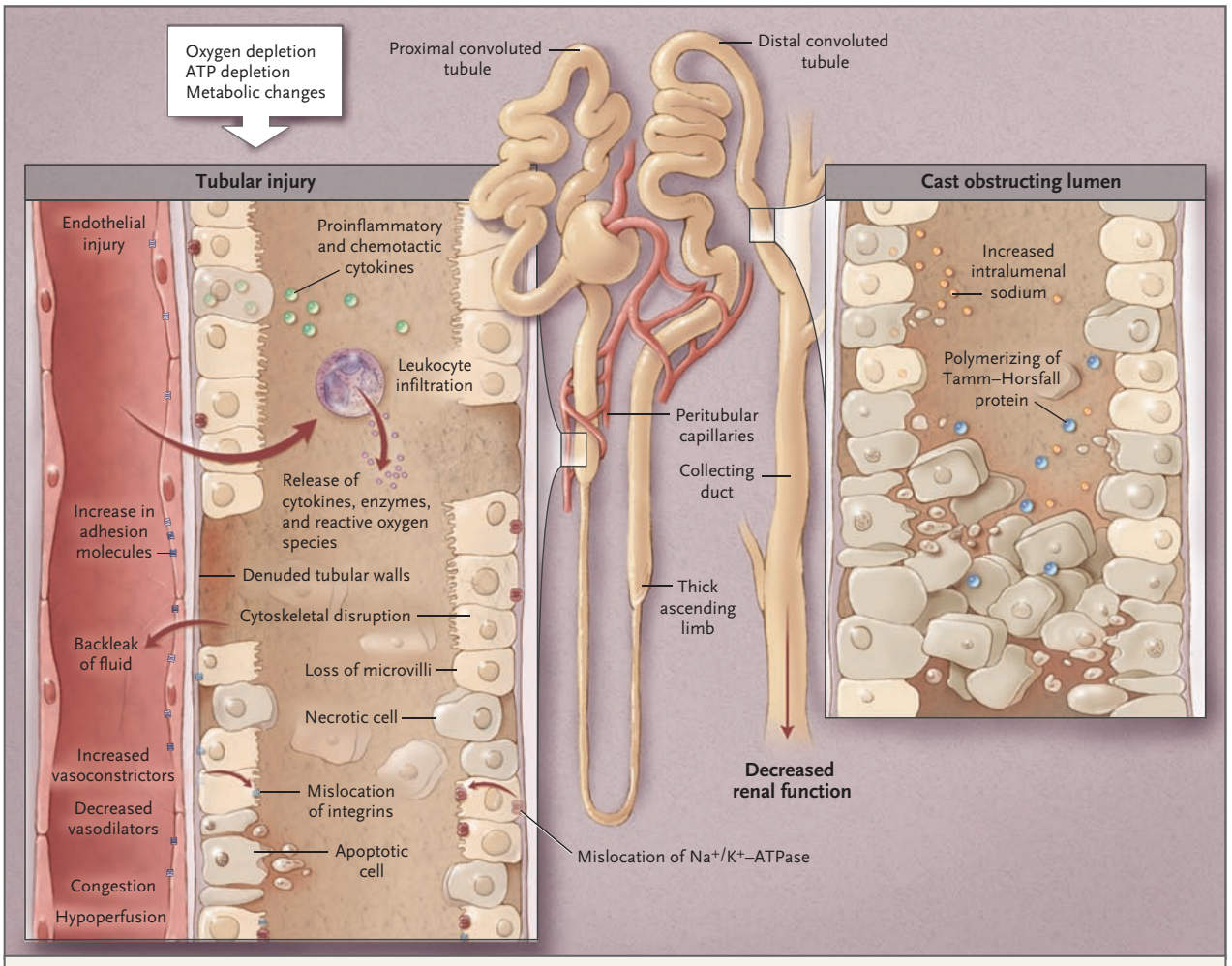

Figure 3. Pathophysiological Mechanisms of Ischemic Acute Tubular Necrosis.

Tubular injury is a direct consequence of metabolic pathways activated by ischemia but is potentiated by inflammation and microvascular compromise. The inset shows shedding of epithelial cells and denudation of the basement membrane in the proximal tubule, with backleak of filtrate (inset, left) and obstruction by sloughed cells in the distal tubule (inset, right).

structural narrowing of the arterioles.[7,9,15] Increased susceptibility to renal ischemia may also occur in malignant hypertension because of intimal thickening and fibrinoid necrosis of the small arteries and arterioles.[16] In addition, in chronic kidney disease, afferent arterioles in the functioning glomeruli become dilated, which increases their filtration rate (hyperfiltration). Although an increased glomerular filtration rate per nephron compensates for the loss of nephrons, the inability to vasodilate further markedly impairs the kidney's ability to autoregulate the glomerular filtration rate in low-perfusion states.[17]

Failure of afferent resistance to decrease can also occur when a patient is receiving nonsteroidal antiinflammatory drugs (NSAIDs) or cyclooxygenase-2 (COX-2) inhibitors, which reduce the synthesis of vasodilatory prostaglandins in the kidneys (Fig. 2C).[16,18-20] When this occurs, angiotensin II, norepinephrine, and other vasoconstrictors released in low-perfusion states may act on the afferent arterioles unopposed, further decreasing glomerular capillary pressure. In other situations, sepsis,[21,22] hypercalcemia,[23,24] severe liver failure,[25,26] calcineurin inhibitors,[27] and radiocontrast agents[28] can act through various vasoconstrictor mediators to increase afferent arteriolar resistance. In addition, sepsis and contrast agents may have direct toxic effects on the tubules.[21,28] Decreased renal perfusion may also cause an ex-

Table 1. Factors Increasing Susceptibility to Renal Hypoperfusion.

Failure to decrease arteriolar resistance
Structural changes in renal arterioles and small arteries
Old age
Atherosclerosis
Chronic hypertension
Chronic kidney disease
Malignant or accelerated hypertension
Reduction in vasodilatory prostaglandins
Nonsteroidal antiinflammatory drugs
Cyclooxygenase-2 inhibitors
Afferent glomerular arteriolar vasoconstriction
Sepsis
Hypercalcemia
Hepatorenal syndrome
Cyclosporine or tacrolimus
Radiocontrast agents
Failure to increase efferent arteriolar resistance
Angiotensin-converting–enzyme inhibitors
Angiotensin-receptor blockers
Renal-artery stenosis

Table 2. Causes of Low-Perfusion States.

Hypovolemic causes
Fluid loss to the third space
Tissue damage (e.g., pancreatitis)
Hypoalbuminemia (e.g., the nephrotic syndrome)
Bowel obstruction
Blood loss
Fluid loss to the outside
Gastrointestinal causes
Renal causes (e.g., diuretics, adrenal insufficiency, hypercalcemia)
Dermal causes (e.g., burns, sweating)
Cardiovascular causes (congestive heart failure)
Myocardial causes (e.g., infarction, cardiomyopathy)
Pericardial causes (e.g., tamponade)
Pulmonary vascular causes (e.g., embolism)
Arrhythmia
Valvular disease
Distributive causes (reduced vascular resistance)
Sepsis
Hepatorenal syndrome
Overdose of drugs (e.g., barbiturates)
Vasodilators (e.g., nitrates, antihypertensive agents)
Local renal hypoperfusion
Renal-artery stenosis (atherosclerosis or fibromuscular hyperplasia)
Malignant hypertension

aggerated drop in the glomerular filtration rate — for example, when angiotensin II does not raise efferent resistance in patients who are receiving angiotensin-receptor blockers or angiotensin-converting–enzyme (ACE) inhibitors (Fig. 2D).[15,16,29-31]

Narrowing of the main renal arteries due to atherosclerosis can increase susceptibility to renal ischemia. In the case of unilateral renal-artery stenosis, the contralateral, normally perfused kidney maintains the glomerular filtration rate; however, renal failure may occur if renal-artery stenosis in a solitary kidney or in both kidneys is greater than 70% of the lumen.[16] Renovascular insufficiency affecting the total renal mass may not reduce poststenotic perfusion pressure enough to impair glomerular filtration, but lowering blood pressure with antihypertensive therapy can worsen ischemia and reduce renal function.[32]

LOW-PERFUSION STATES IN NORMOTENSIVE RENAL FAILURE

The cause of classic ischemic acute renal failure is hypovolemic, cardiogenic, or distributive shock, with systolic blood pressure typically dropping below 90 mm Hg. Normotensive renal failure usually involves milder degrees of these low-perfusion processes (Table 2), but azotemia occurs because of factors that increase renal susceptibility to ischemia, as described above (Table 1).

A less common mechanism for normotensive renal failure is severe hypoperfusion in the presence of increased levels of vasoconstrictive substances that limit the drop in blood pressure but that may occasionally increase the measured blood pressure. Hypoperfusion may be systemic; for example, in acute myocardial infarction or acute pulmonary edema, low cardiac output may be accompanied by stable or even elevated blood pressure mediated by sympathetic discharge.[33,34] Hypercalcemia may increase afferent glomerular arteriolar resistance, as mentioned above, and may lead to marked hypovolemia because it may increase renal fluid losses. Hypercalcemia may simultaneously cause systemic vasoconstriction, which may paradoxically maintain or increase blood pressure.[23,24]

Conversely, the severe hypoperfusion may be local: in renal-artery stenosis, the poststenotic drop in blood pressure causes intrarenal ischemia

but is accompanied by hypertension from hypervolemia or renin release into the circulation. Small-vessel disease in malignant hypertension similarly leads to renal ischemia with increased renin secretion, which worsens the hypertension.

DIAGNOSIS OF NORMOTENSIVE ISCHEMIC ACUTE RENAL FAILURE

Common conditions in which normotensive ischemic acute renal failure may develop include hypertension, chronic kidney disease, and old age, all of which are associated with narrowing and blunted vasodilatory capacity of renal vessels. Other conditions include cirrhosis, infection, myocardial infarction, and congestive heart failure, as well as decreased intake of food, which can reduce renal perfusion. In addition, diuretics reduce extracellular volume, which can compromise cardiac output, and medications such as ACE inhibitors and NSAIDs interfere with autoregulation. In classic ischemic acute renal failure, when a patient goes into shock, the physician should be vigilant in looking for a decrease in urinary output and an increase in the serum creatinine concentration. In the normotensive variant, when the urinary output decreases or the creatinine concentration increases, the clinician should look for the presence of a low-perfusion state that may not have been readily apparent. On the first day during which the creatinine concentration increases, the blood pressure is usually noted to be below its usual level. In persons who have underlying hypertension, blood pressure decreases from high to normal (e.g., a drop in systolic blood pressure from 160 to 118 mm Hg). Since patients are normotensive when renal failure occurs, the decrease in blood pressure may be overlooked. Frequently the patient's usual blood pressure is not recorded alongside current blood pressures; the usual blood pressure must be ascertained from medical records and compared with the blood pressures when the serum creatinine concentration began to rise. In patients with hypovolemia, blood pressure must often be measured in the upright position to confirm the degree and orthostatic nature of the decline in blood pressure.

The cause of the decline in blood pressure may not be apparent. The following two scenarios are not uncommon. In the first, a patient has what turns out to be early sepsis but at the onset does not have fever or any localizing symptoms. Such patients usually have one or more of the following signs or symptoms: hypothermia, confusion, cool extremities, leukocytosis, "bandemia" (an elevated level of band forms of white cells), leukopenia, or unexplained lactic acidosis. Especially in patients with relative hypotension and acute renal failure, any of these clinical pictures should lead the clinician to search for an occult infection, using physical examination, imaging, and microbiologic studies.

Alternatively, a patient in stable condition who is receiving diuretics for hypertension or congestive heart failure may have anorexia and stop eating for some reason or may otherwise have decreased salt intake. Progressive negative sodium balance results in volume depletion and a downward drift in blood pressure. Patients may not be aware of decreases in oral intake or may not volunteer the information spontaneously. Thus, the clinician needs to question the patient, family, and caregivers about recent weight loss or changes in diet.

In addition to watching for low-perfusion states, clinicians should try to identify susceptibility factors for renal ischemia (Table 1). Because normotensive renal failure is multifactorial, several low-perfusion states and susceptibility factors may be present. It is important to ask about the patient's use of over-the-counter NSAIDs that might change renal perfusion and to obtain a measurement of the serum calcium concentration, corrected for any degree of hypoalbuminemia that is present. Sepsis, hypercalcemia, and the hepatorenal syndrome may all cause both low-perfusion states and increased afferent arteriolar resistance.[21-26]

Susceptibility factors may sometimes result in ischemic acute renal failure in the absence of a low-perfusion state. In these cases, the factors result in severe enough renal vasoconstriction to cause a critical reduction in renal perfusion. Examples are radiocontrast agents given to patients with chronic renal failure[28] and cyclosporine, tacrolimus,[27] NSAIDs,[35] or COX-2 inhibitors[36] given in high or supratherapeutic doses.

Patients with malignant hypertension, renal-artery stenosis in a solitary kidney, or bilateral renal-artery stenosis have severe hypertension on presentation but also have compromised renal perfusion. As high blood pressure is controlled, renal function may worsen because of a critical drop in glomerular capillary pressure.[16,30-32]

Once low-perfusion states and susceptibility factors are recognized, a tentative diagnosis of normotensive renal failure can be made, supported by laboratory findings and a response to therapy.

LABORATORY FINDINGS

Low-perfusion states trigger the body's water- and sodium-conserving mechanisms. Thus, by the time glomerular capillary pressure and glomerular filtration rate drop, the renal tubule is reabsorbing more water and sodium, which also increases passive reabsorption of urea. There is experimental evidence that this increase in reabsorption is facilitated by increased expression of urea transporters in the collecting duct, mediated by high plasma vasopressin concentrations.[37] As a result of these changes, the specific gravity of the urine often increases to 1.015 or higher, while urinary sodium and urea excretion decrease (urinary sodium, <20 mmol per liter; fractional excretion of sodium, <1%; and fractional excretion of urea, <35%), and the ratio of blood urea nitrogen to creatinine rises from the usual value of 10:1 to 20:1 or higher.[3,9,10,38] These laboratory findings strongly suggest the presence of renal hypoperfusion, even with a blood pressure in the normal range.

If further ischemia causes acute tubular necrosis, the injured tubules are no longer able to increase reabsorption of water, sodium, and urea. The specific gravity of the urine becomes isosthenuric, similar to plasma, and urinary sodium and fractional excretion of sodium and urea increase to more than 20 mmol per liter, greater than 1%, and greater than 35%, respectively, while the ratio of blood urea nitrogen to creatinine falls back to 10:1.[3,9,10,38] The urinary sediment will show sloughed renal tubular epithelial cells and debris-filled, muddy-brown, granular casts. Although these elements are easily recognized by the nephrologist examining the urinary sediment, clinical laboratories may fail to identify them.[39] Laboratory personnel may not distinguish these pigmented casts from other granular casts and may not examine a sufficient number of fields on the slide to find them. Furthermore, the dipstick often shows no red cells, white cells, or proteinuria, so the clinical laboratory may not examine the sediment as part of the urinalysis. Many patients appear to be "between" prerenal azotemia and acute tubular necrosis because of mixed findings — for example, a ratio of blood urea nitrogen to creatinine of 25:1 and urinary sodium excretion of 15 mmol per liter, suggesting prerenal azotemia, but with renal tubular epithelial cells in the urinary sediment, a finding that is consistent with acute tubular necrosis.

THERAPY AND RESPONSE

Low-perfusion states and risk factors for renal ischemia are often treatable and thus should be identified and dealt with promptly. If possible, blood pressure that is on the lower end of the normal range should be increased by correction of any hypovolemia and by dose reduction or discontinuation of antihypertensive medication and other medications that may lower blood pressure (e.g., narcotics). The patient should be evaluated for occult infection, and any such infection should be treated. If acute tubular necrosis has not yet occurred, effective therapy can reverse the increase in the creatinine concentration within 24 to 48 hours. Improvement may even occur if only one of the causes is reversed — for example, stopping treatment with NSAIDs may be beneficial in a patient with severe cardiomyopathy. However, if acute tubular necrosis has occurred, several days are usually required before improvement is seen, even after the underlying causes have been treated. If the cause of acute renal failure is not apparent or if the patient's condition does not improve, consultation with a nephrologist may help to ensure complete assessment and appropriate management.[40,41]

There are a number of considerations in treating patients with ischemic acute tubular necrosis. Since these persons are highly susceptible to recurrent renal damage, volume depletion, and hypotension, administration of NSAIDs and nephrotoxic drugs, unnecessary anesthesia, surgery, and radiocontrast medium should be avoided.[41] However, critical surgical, imaging, and percutaneous procedures, such as transluminal coronary angioplasty in patients with acute myocardial infarction, should not be withheld or delayed if clinically important harm might result. Prophylactic measures, such as administration of *N*-acetylcysteine, hydration, and low volumes of iso-osmolol contrast agents, may reduce the risk of nephropathy induced by contrast medium.[42] Doses of renally excreted drugs need to be adjusted for kidney failure and their plasma concentrations

monitored. Fluid, electrolyte, and acid–base balance must be maintained, and volume overload and hyperkalemia avoided. In certain cases, sodium bicarbonate intravenous solutions (150 mmol of sodium bicarbonate added to 1 liter of a 5% dextrose solution in water) can be used for volume resuscitation, rather than sodium chloride, to mitigate acidosis from uremia or diarrhea. Furosemide and low-dose dopamine have long been used to treat acute renal failure, but there is no evidence of their effectiveness.[41,43,44] Similarly, atrial natriuretic peptide and mannitol do not appear to ameliorate acute renal failure.[41]

Adequate nutrition should be provided; malnutrition is associated with increased complications and death in patients with acute renal failure.[41,45] Such patients frequently have accelerated protein breakdown and increased caloric needs, especially if they are critically ill or receiving renal-replacement therapy (hemodialysis). In general, daily intake should include 25 to 30 kcal per kilogram of body weight; catabolic patients should receive up to 1.5 g of protein per kilogram daily. Enteral nutrition with food or formula designed for renal failure is preferred over parenteral nutrition, when possible, because it maintains the integrity of the gut, requires less fluid intake, and is less expensive.[41,45,46] Advice from a dietitian or a nutrition consultant may be helpful. Although intake of potassium and phosphate is typically restricted because of impaired renal excretion, hypokalemia and hypophosphatemia due to cell uptake or external losses can occur, and supplements may be required.

Indications for intermittent or continuous renal-replacement therapy are florid uremic symptoms, volume overload, hyperkalemia, and metabolic acidosis that cannot be managed by conservative means. How severe these problems need to be before treatment is initiated is controversial. Arguments in favor of starting renal-replacement therapy early may be based on the desire to avoid the dangerous metabolic, fluid, and electrolyte derangements of uremia[47]; arguments in favor of withholding renal-replacement therapy until definite indications are present are based on the risk of hemorrhage during vascular access, hypotension and arrhythmia during dialysis, and possible dialysis-induced recurrent renal injury or delayed renal recovery.[48] Existing data on the timing of renal-replacement therapy are inadequate to provide clear guidance.[47,49] Unfortunately, many patients with normotensive renal failure have important complicating factors, such as old age, sepsis, and heart disease, and progression to frank shock and death is not unusual.

CONCLUSIONS

An acute increase in the serum creatinine concentration is usually due to renal ischemia. If the patient does not have frank hypotension, normotensive ischemic acute renal failure must be considered. A drop in systolic blood pressure to the low-normal range (100 to 115 mm Hg) must not be overlooked. Many cases can be treated quickly by replacing volume, treating infection, or stopping medications such as NSAIDs, diuretics, and antihypertensive agents, especially ACE inhibitors or angiotensin-receptor blockers.

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