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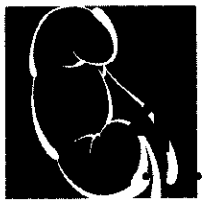


Roger A. Rodby
C. William Wester

A previously healthy 27-year-old man came to the emergency room with a change in mental status and hyperthermia. The patient works in a foundry, and at quitting time he was found slumped over by a fellow worker.

In the emergency room, the physical examination revealed an obtunded patient with a temperature of 106°F, BP 70/50 mm Hg, P 48 bpm, RR 14/min. The lungs revealed bibasilar crackles, and the cardiovascular examination revealed bradycardia with occasional pauses; no pericardial rub was appreciated. The abdominal examination was unremarkable. The neurologic examination revealed a Glasgow Coma Scale of 8; no cranial nerve or focal motor and/or sensory deficits were elicited.

The patient received intravenous 50% dextrose, naloxone, and thiamine without improvement in his mental status. The initial arterial blood gas demonstrated a pH of 7.16, Pco_2 28 mm Hg, Po_2 40 mm Hg, and O_2 saturation of 76% on room air. The patient was intubated.

QUESTION 1 In an attempt to ascertain the underlying diagnosis for this patient's change in mental status, the laboratory analysis revealed a sodium of 150 mEq/L, potassium 6.9 mEq/L, chloride 114 mEq/L, bicarbonate 8 mEq/L, BUN 20 mg/dl, and serum creatinine of 4.8 mg/dl. The remainder of his laboratory data was remarkable for a serum calcium of 7.1 mg/dl, phosphorus 7.2 mg/dl, serum aspartate aminotransferase (SGOT) 420 U/L, lactate dehydrogenase (LDH) of 160 U/L, uric acid of 9.4 mg/dl, serum creatine kinase (CPK) of 55,000 U/L, and serum lactic acid (lactate) of 16.0 mmoles/L. The complete blood count (CBC) revealed a hemoglobin of 12.1 g/dl, white blood cell count of $7,600 \times 10^9$/L (with normal differential), and platelet count of $75,000 \times 10^9$/L. The urinalysis revealed 4+ blood and 30 mg/dl protein on dipstick with microscopic evaluation revealing 0-5 RBC/HPF. Multiple pigmented casts were visualized. The urinary chemistries demonstrated a sodium of 37 mEq/L and a creatinine of 74 mg/dl. What diagnosis is suggested by these labs and what are the potential ramifications of this disease process?

Acute renal failure (ARF) is a clinical syndrome of diverse etiologies characterized by an acute deterioration in renal function often, but not invariably, associated with oliguria. Any acute reduction in glomerular filtration will result in the accumulation of nitrogenous wastes (azotemia) that defines this syndrome.

Depending on the disease process and its reversibility, ARF may last anywhere from a few days to many weeks. If recovery is delayed, dialysis may be necessary until renal function recovers. When renal function is lost (either acutely [ARF], or chronically [CRF]), the body becomes a "closed system," unable to excrete fluid, electrolytes, and toxins. As a result these substances are retained, and changes in the composition of the body's intracellular and extracellular fluid occur. Potassium retention leads to hyperkalemia, which has deleterious effects on the heart. Hydrogen ion retention produces a metabolic acidosis. Sodium retention leads to edema, hypertension, and pulmonary congestion. Water retention causes hyponatremia. The inability to excrete the by-products of protein metabolism leads to accumulation of urea in the blood: azotemia. Urea, and other nitrogen-containing breakdown products produced as a

result of protein catabolism, in high concentrations, produce a number of symptoms referred to as the uremic syndrome, including nausea, vomiting, pruritus, pericarditis, lethargy, coma.

Because there are causes of hyperkalemia, hyponatremia, and metabolic acidosis other than ARF, the clinical diagnosis of ARF rests on increases in the plasma levels of two final products of protein and muscle metabolism that are eliminated by the kidney through glomerular filtration: urea and creatinine. The blood urea nitrogen (BUN) is easily measured and is used as a determination of the level of protein breakdown products in the blood. Its level correlates fairly well with the level of the severity of the clinical syndrome of uremia. Creatinine is measured because it is freely filtered, neither reabsorbed nor secreted (for all practical purposes), and is produced on a constant basis, therefore serving as a measure of GFR. Depending on the severity of the reduction in GFR and the muscle mass of the patient, the serum creatinine increases by 0.5 to 2.0 mg/dl/day in patients with ARF (typical increase is approximately 1 mg/dl/day). Muscle injury will result in an increase in creatinine production, and the serum creatinine may rise at a faster rate (2 to 4 mg/dl/day). Urea accumulation rates vary considerably depending on the protein catabolic rate but average 10 to 20 mg/dl/day. ARF is often oliguric (<400 ml/day of urine). Nonoliguric ARF is usually associated with less injury and a less severe reduction in GFR. Its prognosis is better than oliguric ARF because of the propensity for an earlier recovery and because hypervolemia and hyperkalemia are less common.

QUESTION 2 How do you categorize the types of ARF? What are the major differential diagnoses for each type?

The disease processes that cause ARF can be separated into 3 major categories:

1. Prerenal ARF: A decrease in glomerular filtration rate (GFR) secondary to inadequate renal plasma flow to functionally and structurally intact kidneys
2. Intrinsic ARF: A decrease in GFR secondary to diseases of the renal parenchyma
3. Postrenal ARF: A decrease in GFR secondary to obstruction to the outflow of urine

The understanding of ARF depends upon an understanding of the factors that produce normal glomerular filtration. There are 4 major steps involved in the urinary elimination of nitrogenous waste:

1. Delivery of plasma to the glomerular capillaries via an adequate renal blood flow
2. Formation of a filtrate of the plasma through the glomerulus
3. Normal tubular handling of the ultrafiltrate
4. Excretion of final urine through a nonobstructed urinary tract

An interruption in any of these processes may precipitate ARF. Diseases that affect step #1 are considered "prerenal ARF"; the kidney is functionally and structurally intact but cannot perform its function because of inadequate renal perfusion. The kidney accommodates in two ways to maintain GFR in these situations. First, as renal perfusion pressure decreases, renal plasma flow may be maintained via the normal autoregulatory response of arterial vasodilatation (common to all organs). As this mechanism may be inadequate to maintain sufficient renal plasma flow to avoid a decrease in GFR, a second mechanism, unique to the kidney, is available. Afferent arteriolar dilatation (prostaglandin-mediated) and efferent arteriolar constriction (angiotensin II-mediated) occur. The combination of these two microvascular hemodynamic changes increases both the glomerular capillary hydrostatic pressure and filtration fraction; where GFR = renal plasma flow × filtration fraction. This helps to maintain GFR despite the decrease in renal plasma flow that is seen in prerenal states: [lower renal plasma flow] × [greater filtration fraction] = [maintained GFR]. If renal blood flow is further compromised, these mechanisms may not be able to maintain GFR, and acute renal failure occurs. Any condition that leads to a reduction in renal blood flow may cause prerenal azotemia.

Intravascular volume depletion from any cause

may result in a reduced cardiac output, lowered renal plasma flow, and the possibility of ARF if severe enough. Given the same amount of fluid loss, fluids with higher sodium concentrations are more likely to cause a reduction of GFR than those with a lower sodium concentration since the former will represent a greater amount of extracellular (as opposed to intracellular) and therefore intravascular volume loss. This intravascular fluid loss does not have to be associated with a loss of weight if third spacing occurs as can be seen with edema, ascites, pleural effusions, burns, etc.

Any cardiac disease associated with a reduced cardiac output may impair renal perfusion and result in prerenal ARF. These conditions include valvular, pericardial, and myocardial diseases. States of peripheral vasodilatation, on the other hand, are associated with a high cardiac output state. If shunting of blood is present, renal perfusion may nevertheless be compromised and produce ARF. This may be seen in patients with severe liver failure, septic shock, or the sepsis syndrome.

Finally, systemic hemodynamics may be normal, but if vasoconstriction of the renal vascular bed is present, an impairment in renal blood flow can cause prerenal ARF. This may be seen in patients receiving cyclosporine, amphotericin B, and nonsteroidal antiinflammatory agents (NSAIAs), especially if renal blood flow is already impaired for any reason before the administration of these agents. Severe hypercalcemia may also precipitate ARF through renal vasoconstriction. Since there may be no specific signs and symptoms of primary renal vasoconstriction, the diagnosis may depend on the history of exposure to one of these predisposing factors in addition to information gained from the urinary chemistries.

The degree of GFR reduction in prerenal azotemia is usually not as severe as that seen in other forms of ARF. Oliguria is common. The BUN may rise disproportionately to the creatinine since urea reabsorption increases as a result of passive diffusion secondary to the increased sodium and water reabsorption seen in all prerenal states. As a result, the BUN:creatinine ratio often exceeds 20:1. The BUN is also affected by the protein catabolic rate, and care must be taken not to include or exclude the diagnosis of prerenal ARF on the basis of the BUN:creatinine ratio alone. The diagnosis of prerenal azotemia is often suggested by the physical examination when signs of volume depletion, heart disease, or an edematous state are present. Because the kidney itself is not responsible for the reduction in GFR, and because it interprets low renal perfusion as volume depletion, the kidney will attempt to retain both sodium and water. Therefore the chemical composition of the urine can be extremely useful in evaluating and confirming prerenal states.

Diseases that affect step #4 of glomerular filtration, diseases that cause obstruction to the outflow of urine, are classified under "postrenal ARF." Approximately 15% of all ARF is secondary to obstruction, and all patients with ARF should have this ruled out with a renal ultrasound unless another cause of ARF is immediately apparent. Obstruction may occur at any level of the urogenital tract and may be secondary to stones, tumors (intrinsic or extrinsic), an enlarged prostate, blood clots, or sloughed renal papillae. Obstruction of a single ureter will not cause ARF if two functional kidneys are present since functional reserve of a healthy contralateral kidney is enough to prevent a significant reduction in GFR. Therefore obstruction must be bilateral or distal to the urinary bladder to result in ARF. Obstruction at any site will cause ARF in the patient with a structurally or functionally solitary kidney.

Obstruction may be accompanied by (1) anuria <50 ml/day (total obstruction), (2) oliguria, (3) a normal urine output, or (4) polyuria; the latter three associated with partial obstruction. Anuria is suggestive of obstruction, but there are conditions other than obstruction that are associated with anuria. Since obstruction can be associated with the complete range of urine outputs, the urine flow rate should not be a strong factor in whether obstruction is considered in the patient with ARF. Even partial obstruction can be associated with severe reductions in GFR as the glomer-

ular capillary pressure is negated by pressure in Bowman's space. Polyuria may occur as a result of damage to the collecting duct secondary to the high intratubular pressures that accompany obstruction. In this situation the collecting duct no longer responds normally to antidiuretic hormone, and nephrogenic diabetes insipidus with large dilute urine volumes may occur. Similar damage to the distal tubule may affect potassium secretion and urine acidification, resulting in hyperkalemia and acidosis.

The renal collecting system dilates rapidly proximal to an obstruction. This can be seen with ultrasound visualization of the kidney, ureters, and bladder. Rarely, obstruction can occur without dilatation as seen if the obstruction is caused by a process that encases the kidney and ureter. This is termed *non-dilated obstruction* and must be considered in those patients at risk for ureteral encasement (e.g., abdominal carcinomatosis, prostatic or cervical cancer, lymphoma, or a history of methysergide usage [retroperitoneal fibrosis]). The clinician must maintain a high index of suspicion for these conditions because they will not be diagnosed with the usual means of evaluating for obstruction (renal ultrasound). If a non-dilated obstruction is suspected, patients require cystoscopy with retrograde pyelography to determine patency of the ureteral drainage system.

Disease processes that affect steps #2 and #3 represent injury to renal parenchyma itself and are classified under "intrinsic ARF." These include diseases of the largest (renal artery and vein) to the smallest (glomerular capillaries) blood vessels of the kidney, in addition to diseases of the renal tubules.

Arterial occlusion may result from thromboses, emboli, or dissection of the thoracic aorta or renal arteries. Renal vein involvement is usually the result of thrombosis. ARF will only occur if these processes are bilateral or if the patient has a functionally or structurally solitary kidney. Complete obstruction to renal blood flow leads to anuria. If renal infarction has occurred, patients will usually have flank pain and hematuria (if not anuric). The serum level of LDH will also increase markedly when a large amount or renal tissue has infarcted, since this enzyme is abundant in the kidney (isoenzyme 1).

There are a number of conditions that affect the smaller blood vessels of the kidney that may produce ARF. Included in this category are diseases of the capillaries of the kidney (the glomerulus). The injury may be due to an immunologic inflammatory response (glomerulonephritis and vasculitis), intravascular thrombi formation (microangiopathic syndromes), or to direct barotrauma (malignant hypertension). These disorders are suggested by an abnormal urinary sediment that includes proteinuria, RBCs ± RBC casts. If the microvascular disease is entirely preglomerular, which can occasionally be seen in some of the larger vessel vasculitides, the urinary sediment may be normal. Many of the glomerular and vasculitic diseases that are associated with ARF are associated with a systemic disease with other organ system involvement that direct the differential diagnosis. In addition there are a number of serologic tests that may be useful in the diagnosis (see Fig. 9-5-1 in Nephrology Case #5 and Table 9-6-1 in Nephrology Case #6).

Most of the glomerulopathies and vasculitides do not cause ARF unless severe, and when they do are termed rapidly progressive (RPGN). Glomerular damage in RPGN is often accompanied by crescents (crescentic GN). On the other hand, the microangiopathic syndromes are frequently associated with severe ARF. Common to the microangiopathic diseases is injury to endothelium with vascular thrombosis of the arterioles and/or glomerular capillaries. As a result, actual infarction may occur in areas of the cortex. This is termed *cortical necrosis* and may be seen in patients with the hemolytic uremic syndrome (HUS), thrombotic thrombocytopenic purpura (TTP), disseminated intravascular coagulation (DIC), and preeclampsia. Patients with cortical necrosis are often anuric. The initiating endothelial damage may be the result of an infection (HUS), or any cause of DIC (e.g., endotoxemia, amniotic fluid embolism, and retained dead fetus). The hallmark of the diagnosis of a microangiopathic process is the

presence of hemolysis associated with schistocytes on the peripheral smear, usually accompanied by thrombocytopenia. Unlike most other causes of ARF including acute tubular necrosis, recovery from cortical necrosis is often incomplete. This seems to be a result of actual loss of renal mass secondary to the patchy infarction.

Finally, the small blood vessels of the kidney may be affected by atheroemboli, small plaques of cholesterol that embolize to the kidney. This is usually seen only in patients with severe atherosclerotic disease of the aorta and large arteries, and when present, usually follows a major intravascular procedure such as arteriography. Many patients will have stigmata of peripheral embolization (e.g., blue toes and ischemic central nervous system events), which may be confused with systemic vasculitis. The reason for renal failure in this condition is not clear since only a small percentage of the renal blood vessels become occluded. Infarction is not always apparent. Other factors may be responsible. An elevated erythrocyte sedimentation rate with peripheral eosinophilia is often present and suggests that an allergic mechanism may be involved. The eye grounds are a particularly sensitive area to look for cholesterol clefts (Hollenhorst plaques). This disorder is usually nonoliguric, and the urine is benign. The diagnosis often requires a renal biopsy.

Allergic interstitial nephritis encompasses a large group of disorders that include many mechanisms. Usually though, there appears to be a reduction in GFR as a result of a reaction to a toxin, usually a drug. The hypersensitivity response to drugs is often, but not invariably, accompanied by a generalized allergic reaction consisting of fever, rash, and peripheral eosinophilia. This condition was originally described with methicillin, although a number of other drugs (e.g., antibiotics, diuretics, sulfa-containing medications), have been shown to produce a similar response. Although interstitial infiltrates and tubular cell damage is present, the reason for the acute reduction in GFR is not clear. Mechanisms similar to that in acute tubular necrosis (to follow) may be involved. Discontinuation of the responsible agent is usually all that is required to result in renal recovery, although glucocorticoids have been used in severe cases. Patients are usually nonoliguric and will often have WBCs, WBC casts, or epithelial cell casts in their urine. Other signs of tubular damage may be present and include renal tubular acidosis and glycosuria in the presence of a normal serum glucose concentration.

ARF can be seen as a result of tubular obstruction from very high filtered load of urate, usually produced as a result of massive breakdown of cells following chemotherapy for lymphoma or leukemia. Tumor lysis is more likely to occur in patients with extreme elevations in their LDH before chemotherapy. ARF may be avoided by aggressive hydration, allopurinol, and alkalinization of the urine. ARF from tubular obstruction may also be seen with precipitated filtered myeloma proteins in patients with multiple myeloma. Drugs that may cause a similar tubular obstruction include acyclovir, certain relatively insoluble sulfonamides, and methotrexate.

QUESTION 3 What is acute tubular necrosis, and what is the pathophysiologic explanation for the reduction in GFR? What are the different stages of recovery?

The final and most common cause of intrinsic ARF is referred to as acute tubular necrosis (ATN). This syndrome is characterized by an abrupt and severe reduction in GFR, usually initiated by a clearly defined event. There are two categories: postischemic and nephrotoxic.

Although the kidney may be able to maintain renal blood flow through autoregulatory mechanisms in states of impaired cardiac output, this compensatory response may not be sufficient. If a severe enough reduction in renal blood flow occurs that results in renal ischemia and tubular cell injury, the patient may develop ARF. This is the basis for postischemic ATN. Similarly, certain nephrotoxic agents can cause renal tubular cell damage and ARF: nephrotoxic ATN. Both are associated with a similar pathologic description,

clinical course, and pathophysiologic explanation for the severe reduction in GFR. In patients with ATN, the GFR is abruptly reduced from a normal level of over 100 ml/min to usually less than 5 ml/min. Reversal of the shock or removal of the nephrotoxic agent does not immediately restore the GFR.

Any situation with a severe prolonged impairment in renal perfusion may result in ischemic ATN. In addition to obvious states of shock, this includes all the causes of decreased renal perfusion mentioned in the section on prerenal ARF, when severe and prolonged.

There are a number of nephrotoxins that can cause tubular damage and nephrotoxic ATN. These include aminoglycoside antibiotics, certain heavy metals, halogenated hydrocarbons as well as many other medications and toxins. Myoglobin (released from damaged muscle) and hemoglobin (released with intravascular hemolysis) can be filtered and cause ARF when large amounts are released into the blood. By themselves they do not appear to be nephrotoxic but when accompanied by volume depletion may form intratubular casts with tubular cell damage. It is unclear if they are only toxic in settings of volume depletion or if other substances released as a result of muscle breakdown or hemolysis are responsible for the ATN. One of the more common causes of nephrotoxic ATN is iodide-containing radiocontrast. The exact mechanism for tubular cell damage in many forms of nephrotoxic ATN is yet to be determined.

There are several theories regarding the pathogenesis of the severe reduction in GFR that follows ATN, but the best understood is explained by changes in renal blood flow and glomerular hemodynamics. It appears that whatever the initiating event in the kidney, be it ischemic or nephrotoxic, decreased perfusion of the renal cortex secondary to afferent arteriolar vasoconstriction occurs. Agents that have been proposed as the mediator of this vasoconstriction include angiotensin II and adenosine. In addition, there appears to be a vasodilatation of the efferent arteriole. The combination of afferent vasoconstriction and efferent vasodilatation produces a low capillary hydrostatic pressure and filtration fraction in the glomerular capillary bed and is at least partially responsible for the severe impairment in GFR seen in ATN. This afferent and efferent arteriolar vascular tone relationship is the opposite of what is seen in prerenal states where the GFR is maximized for a given renal blood flow (high glomerular transcapillary hydrostatic pressure gradient and a maximized filtration fraction).

Pathologically, ATN is often associated with morphologic evidence of damage to the renal tubular cells. One may see atrophic changes in some cells, total destruction of other cells, and mitotic figures in some remaining viable tubular cells. It is for this reason that the lesion is referred to as *acute tubular necrosis (ATN)*. However, the morphologic abnormality is not necessarily noted in all cases and clinical examples of ATN with a profound depression of renal function with normal or relatively normal appearing renal tubular cells can be seen. This does not imply that the renal tubular cells are necessarily functioning normally. In these cases the damage is apparently not severe enough to be expressed morphologically.

The clinical course of the renal failure in ATN is usually self-limiting and often follows an oliguric, diuretic, and recovery phase. Whether the insult be ischemic or nephrotoxic, the initial phase of ARF is usually associated with a decrease in urine output. Generally, the urine volume is of the order of 10 to 20 mls per hour (oliguria), although some patients may be anuric. Because of the unresponsive nature of the lesion to attempts to reverse the condition, the urine volume does not significantly increase with the administration of agents that increase the blood volume, cardiac output, or renal plasma flow. Because of the low GFR, there is a poor response to diuretic agents. The glomerular filtration rate is usually only a few percent of normal. Eventual recovery is the rule if new tubular insults are avoided. This occurs spontaneously over a course of days to weeks. If recovery never

occurs, consideration must be made that the patient had cortical necrosis over and above ATN.

The "diuretic phase" of ATN is often the first indication that the lesion is undergoing spontaneous recovery. In this instance the patient's urine volume progressively increases. The increased urine volume reflects a slowly increasing glomerular filtration rate. The patient's urine flow may increase to 50 to 200 ml/hr. Most of this "diuresis" is an appropriate response to volume expansion and solute retention that has accompanied the acute renal failure. Although improved, the GFR may still be markedly impaired, and it is therefore not surprising that the patient's BUN and creatinine may continue to rise (although less rapidly). This stage is a good prognostic indicator of recovery from ATN. The diuretic phase of ATN slowly blends with a "recovery phase" in which the glomerular filtration rate continues to rise concomitant with a peaking of the BUN and creatinine, followed by a decline in their serum levels until they normalize. The kidney also reaches a state in which the salt and water content of the urine are determined by physiologic mechanisms. That is, the urine content reflects the patient's intake of salt and water and the need for excretion of these substances.

The great majority of patients with ATN will ultimately regain normal renal function. Hence, while the lesion is not immediately reversible by providing factors that could improve renal perfusion such as returning a patient's blood volume to normal or removal of the nephrotoxin, the kidney is capable of spontaneously reversing this abnormal state over a period of days to weeks.

There is a suggestion that the profound decrease in GFR in ATN is actually a teleologic adaption to the tubular cell damage that occurs from ischemia or nephrotoxins. The normal kidney reabsorbs over 99% of the filtered sodium. Tubular cell damage leading to only a mild decrease in this ability to reabsorb sodium would lead to massive volume depletion because the filtered load with a normal GFR is so large. The "acute renal success" theory states that the acute reduction in GFR through hemodynamic mechanisms is actually protective by decreasing the filtered load of sodium and therefore avoiding the risk of volume depletion.

In summary, ATN secondary to either an ischemic event or the administration of a nephrotoxin leads to a clinicopathologic entity characterized by:

1. A profound decrease in the flow of blood to the renal cortex
2. A profound decrease in the filtration fraction and the glomerular filtration rate
3. Renal tubular cell dysfunction, which is sometimes associated with morphologic evidence of necrosis
4. Resistance of this lesion to immediate reversal by extrarenal factors such as restoration of renal blood flow or the withdrawal of the nephrotoxin
5. A tendency to spontaneous resolution to normal function over a period of days to weeks

QUESTION 4 An abdominal ultrasound demonstrated normal-sized kidneys without evidence of obstruction. The hyperkalemia and metabolic acidosis were treated appropriately. Additional supportive measures were administered, and the patient was transferred to the medical intensive care unit in guarded condition. The patient's blood pressure improved after the administration of several liters of normal saline, but he remained oliguric and his BUN and creatinine continued to rise. What are the diagnostic steps in the evaluation of ARF?

The first step in evaluating a patient with ARF is to distinguish among prerenal, postrenal, and intrinsic renal causes. This usually starts with a renal ultrasound. A careful history must be obtained, including exposure to hemodynamic insults and nephrotoxins. Both the history and physical examination must look for evidence of prerenal states, systemic diseases, and general vascular insufficiency. Evaluation of the urine is an important tool. Proteinuria and hematuria usually accompany the glomerulonephritides and

vasculitides. Red blood cell casts are specific for glomerular inflammation (see Nephrology Case #6). A positive urine dipstick for blood in the absence of microscopic hematuria suggests the presence of hemoglobinuria or myoglobinuria. White blood cells, WBC casts, and tubular cell casts usually indicate tubulointerstitial disease (interstitial nephritis). Eosinophils in the urine suggest an allergic interstitial nephritis. Obstruction, atheroemboli, and prerenal azotemia are usually associated with a "bland" urine without significant protein, cells, or casts. This is also true of diseases of the larger renal vessels, if the glomeruli are spared inflammation. ATN will often have a urine displaying tubular cell casts, as well as numerous coarse granular casts consisting of tubular cell debris. Lastly, papillary necrosis, a diagnosis suspected in patients with diabetes mellitus, hemoglobinopathies, and chronic analgesic abuse is associated with a urine sediment containing many white blood cells in clumps or casts as well as, on occasion, an identifiable renal papilla.

The hematologic profile may be useful as well. Peripheral eosinophilia suggests allergic interstitial nephritis and atheroembolic disease. Schistocytosis suggests one of the microangiopathic diseases associated with cortical necrosis.

Urine chemical composition may be extremely helpful in determining the cause of ARF. The kidney is functionally intact in prerenal ARF, and it retains the ability to reabsorb sodium and water. Because the kidney detects volume depletion in these states, an attempt is made to preserve volume. As a result, the concentration of sodium in the urine (UNa) is usually low: <20 mEq/L. The tubular cell damage in ATN prevents this from being possible (independent of the patients volume status), and the UNa is usually >40 mEq/L. (UNa 20 to 40 are nondiagnostic.)

One of the problems with using the UNa to differentiate prerenal from intrinsic causes of ARF is that the UNa is affected by the degree of water as well as sodium reabsorption. Since water reabsorption is impaired in ATN (secondary to the loss of the osmotic gradient as a consequence of damage to tubular cells), the UNa will be reduced by dilution. This lowering of the UNa in an ATN state may make it appear to be a prerenal condition. On the other hand, increased water reabsorption in prerenal states (secondary to volume-mediated antidiuretic hormone release) can raise the UNa above 20 mEq/L, even in the face of avid sodium retention. This may make the prerenal state appear to be an ATN condition. These effects of water transport can be overcome by measuring the fractional excretion of sodium (FE_{Na}) which is a direct measure of sodium excretion. The FE_{Na} represents the percent of the filtered sodium that is excreted =

$$\frac{\text{Urine sodium (mEq/l)} \times \text{Plasma creatinine (mg/dl)}}{\text{Plasma sodium (mEq/l)} \times \text{urine creatinine (mg/dl)}} \times 100$$

This is usually <1% in prerenal states and >1% in states associated with ATN. There is essentially no overlap between the FE_{Na} associated with prerenal states (<1%) and ATN (>1%). Therefore this measurement is the most useful of the urinary indices in evaluating patients with ARF. There are a few conditions, usually not considered prerenal, that may have a low FE_{Na} if evaluated very early in their course. These include early obstruction, early pigment nephropathy (hemoglobinuria and myoglobinuria), and early radiocontrast nephropathy. The sodium avidity is probably related to a vasoconstrictive phase that occurs before tubular cell damage. A low FE_{Na} can also be seen in patients with acute glomerulonephritis since tubular flow may be impaired with tubular function remaining intact.

For all practical purposes, creatinine is neither secreted nor reabsorbed by the renal tubules. Therefore the increase in concentration of creatinine in the tubular fluid relative to plasma is directly related to the amount of H_2O reabsorbed in the renal tubules. The urine to plasma (U/P) creatinine ratio becomes a quantitative index of total water absorption by the kidneys. Water absorption is high in prerenal states, and as a result, the U/P creatinine ratio increases. A U/P creatinine >40 is usually seen only with prerenal ARF. Urinary concentration (water reabsorption) is impaired in ATN syndromes, and the U/P

creatinine will be lower than in prerenal states. ATN is usually associated with a U/P creatinine ratio <20. (Values between 20 and 40 are considered nondiagnostic.)

Urinary concentration depends upon intact tubular function. ATN is usually associated with isosthenuria, a urine osmolality equal to serum osmolality. Prerenal states usually demonstrate a urine that is concentrated compared to the serum. Urine concentration is dependent on an osmotic gradient in the renal medulla. This in turn depends on solute delivery to the loop of Henle. Because proximal reabsorption is enhanced in prerenal states, distal delivery is impaired, and solute delivery to the loop of Henle is reduced. As a result, in prerenal states, renal concentration may be less than would be otherwise expected. Therefore, overlap in urine osmolalities can be seen in patients with ATN and prerenal ARF (300 to 500 mosm/L). Still urine osmolalities >500 mosm/L are usually seen only in prerenal states.

For a summary of the diagnostic approach in dealing with ARF, refer to the algorithm displayed in Fig. 9-4-1.

QUESTION 5 For each of the pathophysiologic mechanisms of ARF, what are the correct modes of therapy?

Obstruction is usually treatable by either urologic or radiographic procedures. The degree of recovery will depend on how long the obstruction has been present. The renal failure of acute obstruction will usually totally reverse if it has not persisted longer than 1 to 2 weeks.

Patients with prerenal ARF should respond immediately to an improvement in renal circulation. Unfortunately, except for cases of pure volume depletion, most causes of an impairment in renal circulation are not immediately reversible.

Patients with ATN need time to recover. The most important factor is to try to avoid further tubular insults. This requires an attempt to maximize systemic hemodynamics, to avoid other ischemic events, and the avoidance of further nephrotoxic insults.

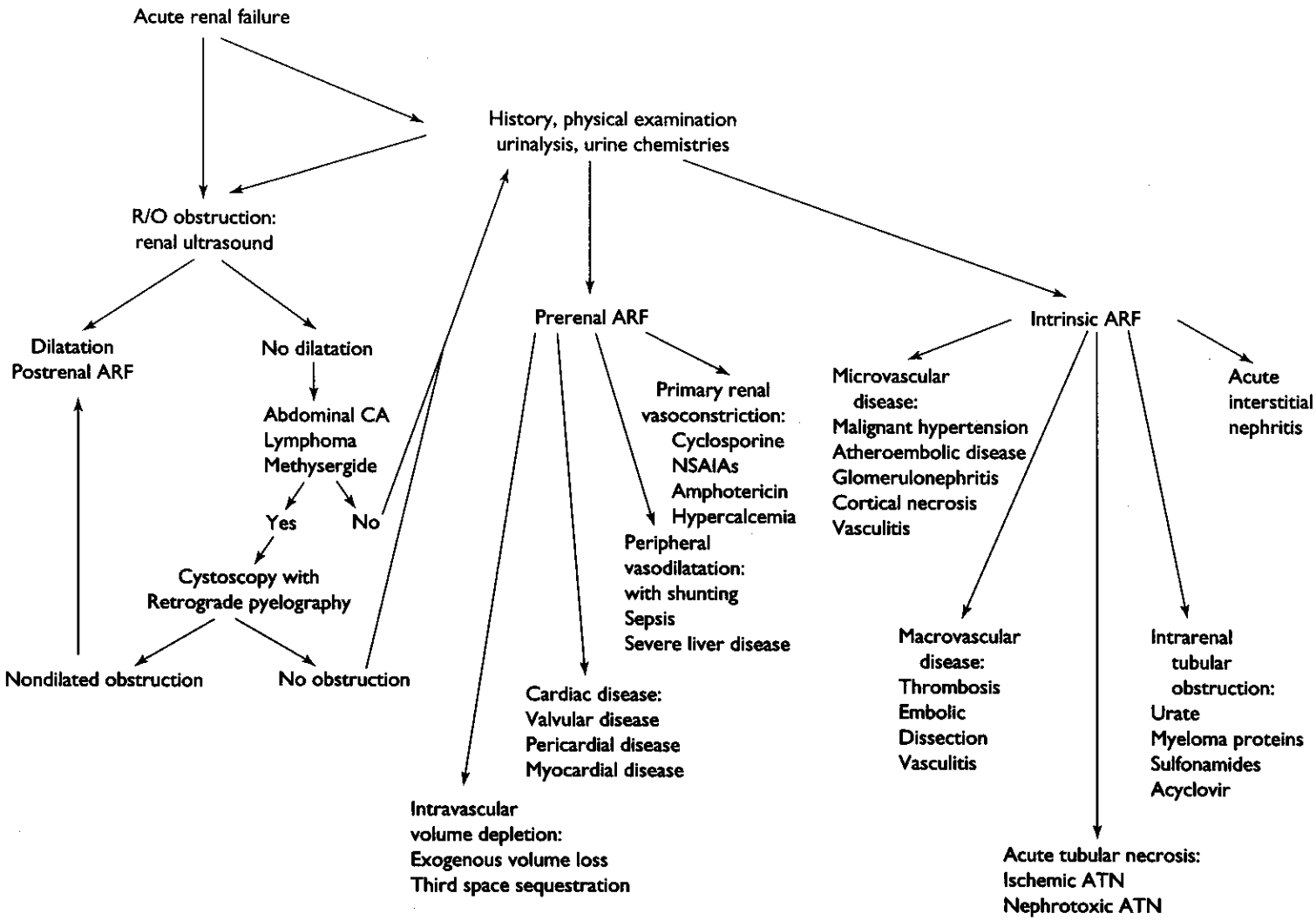
The proper management of all patients with ARF, regardless of the cause, demands close attention to many details of the patient's daily physical examination and blood chemistries. Since the body becomes a closed system, care must be taken to monitor the composition and amount of all intravenous fluids, medications, and dietary intakes. A patient with oliguric ARF may quickly and dangerously expand body fluid volume unless fluid intake is restricted. The best monitor of the adequacy of the fluid therapy is the daily clinical assessment of volume status and weights. Adequate caloric intake must be provided to the ARF patient so as to minimize endogenous catabolism.

Since infections remain the leading cause of death in ARF, constant vigilance in the maintenance of IV lines, pulmonary toilet, and avoidance of unnecessary indwelling urinary catheters is necessary. Acute gastrointestinal hemorrhage is a common comorbid factor.

Last, meticulous attention must be paid to metabolic derangements including hyperkalemia, hyponatremia, metabolic acidosis, hyperphosphatemia, and hypocalcemia. Serum electrolytes may need to be followed daily or more often. Absolute indications for dialysis include central nervous system and gastrointestinal disturbances, pericarditis, severe electrolyte abnormalities, and pulmonary congestion. The choice of dialytic method depends on the clinical situation.

CASE DISCUSSION Our patient is a young man presenting with ARF complicated by multiorgan system involvement. He suffers from many of the complications related to exertional heatstroke, which in this case caused nontraumatic rhabdomyolysis, myoglobinuria, and ARF. Rhabdomyolysis and its associated complications of hyperkalemia, hyperphosphatemia, hypocalcemia, hyperuricemia, and myoglobinuria are common findings in exertional heatstroke.

The patient was hypotensive when he presented and suggested a pure prerenal cause of his ARF. Volume resuscitation improved his systemic hemodynamics but did not improve his renal function. His



9-4-1 Approach to patient with acute renal failure based on radiographic, history, physical examination, and biochemical features.

urine chemistries suggested ATN (FE_{Na} 1.6%, U/P creatinine 15.4, urine Na 37). The diagnosis of myoglobinuric ARF is suggested by the marked rise in muscle enzymes in the presence of a dipstick indicating large amounts of blood in the urine without red blood cells on microscopic examination. In addition, the increase in creatinine out of proportion to the BUN suggests rapid muscle catabolism. This patient developed nephrotoxic ATN secondary to myoglobinuria and may have a component of ischemic ATN secondary to his transient hypotension. He will likely recover, but not until after an unpredictable period has elapsed that may require dialytic support.

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