

Acute Renal Failure in HIV-Infected Patients: A Case-Based Review

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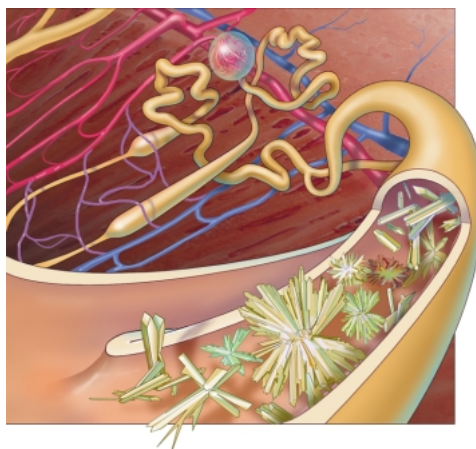
Patients infected with HIV commonly develop pathology in the kidneys. Underlying disturbances in renal function, as well as renal tubular dysfunction, predispose these patients to both hemodynamic and toxic renal injury. Some of the clinical renal syndromes that can result include HIV-associated glomerulopathies, various metabolic perturbations, and—most seriously—acute renal failure (ARF).¹⁻¹⁴

When compared with similarly matched subjects not infected with HIV, hospitalized HIV-infected patients are much more likely to develop ARF.^{1,5,12-14} Causes of ARF in these patients include prerenal azotemia, nephrotoxic and ischemic acute tubular necrosis (ATN), acute tubulointerstitial nephritis (ATIN), crystal-induced tubular injury, and obstructive uropathy (Table 1).¹⁻¹⁴ Using a case-based approach, this article will discuss these most common causes of HIV-associated ARF, reviewing their pathogenesis, risk, diagnosis, treatment, and prevention.

PRERENAL AZOTEMIA

Case 1 Presentation

Patient 1 is a 38-year-old man with AIDS who comes to the emergency department because of weakness, dizziness, and a 3-week history of abdominal discomfort and large-volume watery diarrhea. On further questioning, he also reports anorexia and low-grade fever. Vital signs include a supine blood pressure of 82/45 mm Hg and a pulse of 115 bpm; systolic blood pressure decreases to 60 mm Hg when the patient is in a sitting position. Physical examination reveals absent neck veins and poor skin turgor. The abdomen is diffusely tender, and auscultation of the abdomen reveals hyperactive bowel sounds. Urine output is only 75 mL during his first 12 hours in the emergency department. Results of laboratory testing show an increased blood urea nitrogen (BUN) level of



75 mg/dL and an increased serum creatinine level of 3.9 mg/dL; serum bicarbonate level is 7 mEq/L, suggesting metabolic acidosis. Stool specimens are positive for salmonella infection.

To treat his volume depletion and associated prerenal azotemia resulting from diarrhea, poor oral intake, and increased insensible fluid loss from fever, the patient is given fluids intravenously (0.45% saline plus sodium bicarbonate 75 mEq/L). Cipro-

floxacin also is administered intravenously to treat the enteric infection. Within 5 days of therapy, the patient's BUN level is 18 mg/dL and serum creatinine level is 1.1 mg/dL, representing a return to baseline values.

Pathogenesis of Prerenal Azotemia

The etiology of renal insufficiency in this patient is prerenal azotemia, the most common cause of ARF in HIV-infected patients.^{1,5,6,8-14} This type of hemodynamic renal failure is caused by either *true* or *effective* depletion of intravascular volume.

According to a retrospective study undertaken in the mid-1980s, true depletion of intravascular volume was the most frequent cause (38%) of ARF in HIV-infected patients.¹² True volume depletion, such as that in patient 1, often results from the gastrointestinal fluid loss associated with diarrhea and/or vomiting, 2 common symptoms of the gastrointestinal infections typically found in HIV-infected patients.^{1,5,6,8-14} Disordered renal regulation of salt and water balance also can cause or contribute to intravascular volume depletion in this group of patients. For example, hormonal disturbances (such as adrenal insufficiency and isolated

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hypoaldosteronism) and underlying tubular dysfunction in HIV-infected patients promote renal salt wasting¹⁻¹⁴ and a resultant excessive diuresis. Likewise, central or nephrogenic diabetes insipidus in these patients often causes unregulated water loss, leading to dehydration.^{1,9,10} Additionally, insensible fluid losses associated with pulmonary disturbances (eg, the lung fluid losses that occur in pneumonia) and prolonged high fevers also can deplete the intravascular space. Volume depletion resulting from these causes is further aggravated by concomitant anorexia and hypodipsia.^{1,9,10}

Effective depletion of intravascular volume is synonymous with arterial underfilling, which occurs when low- and high-pressure baroreceptors in the circulation sense inadequate arterial pressures and consequently stimulate production of systemic hormones to signal the presence of the disturbance to the appropriate organs. A patient thus can be markedly overloaded with sodium and water yet still have effective intravascular depletion (as occurs in patients with congestive heart failure, cirrhosis, and sepsis). Ultimately, however, renal perfusion is impaired.

Sepsis, commonly caused by infection with bacterial and fungal organisms, has become the leading cause of hemodynamic ARF in HIV-infected patients.¹³ In a retrospective study covering the period 1984 to 1993, investigators demonstrated that septicemia was the most common cause (52%) of renal insufficiency in AIDS patients.¹³ Prerenal azotemia resulting from sepsis develops from a combination of endotoxin-associated systemic vasodilatation, arterial hypotension, capillary leakage, and renal arteriolar vasoconstriction associated with vasopressor drug therapy.

Other established causes of effective prerenal azotemia in HIV-infected patients include hepatorenal syndrome, severe pancreatitis caused by various infections or drugs, and congestive cardiomyopathy.^{1,5,8,9,12-14} A marked reduction in renal blood flow occurs with these disease processes and results in hemodynamic acute renal insufficiency.

Management of Prerenal Azotemia

The systemic physiology underlying the various types of HIV-associated ARF differs according to etiology. Therefore, preventive and therapeutic interventions need to address the pathophysiologic basis of the underlying process. Patients with severe extrarenal losses of salt and water (because of vomiting and diarrhea) often require intravenous resuscitation with fluids, using an isotonic sodium chloride (ie, normal saline) solution. As was true in patient 1, a variant of normal saline might be required if patients have a severe metabolic acidosis

Table 1. Causes of HIV-Associated Acute Renal Failure

Prerenal

True volume depletion

Extrarenal losses

Renal losses

Effective volume depletion

Renal

Acute tubular necrosis

Glomerular disease

Vascular disease

Acute tubulointerstitial nephritis

Crystal-associated nephropathy

Postrenal

Ureterocaliceal obstruction

Bladder obstruction

Urethral obstruction

because of a diarrhea-associated loss of bicarbonate or a coexistent renal tubular acidosis. Creation of an isotonic sodium-based solution that replaces the chloride anion with an equal amount of bicarbonate (determined by the severity of metabolic acidosis) is useful. As in the case presented, the addition of 75 mEq of sodium bicarbonate to 1 L of 0.45% sodium chloride produces an isotonic solution that provides 75 mEq of bicarbonate per liter of solution. This type of solution especially benefits HIV-infected patients who possess an underlying defect in renal acidification from an acquired tubular injury.

Ultimately, treatment of the underlying causes of the gastrointestinal illness will reduce extrarenal losses and facilitate discontinuation of intravenous fluids and initiation of oral therapy with fluids. HIV-infected patients who have ongoing renal losses of salt and water will require forced oral intake of salt (eg, sodium chloride, sodium bicarbonate) and water to prevent volume depletion and dehydration. Patient education stressing the importance of drinking sufficient quantities of fluid is imperative. Moreover, patients infected with HIV should be instructed to contact their caregivers when a superimposed process, such as nausea/vomiting or diarrhea, develops. This step will allow timely intravenous administration of fluids to prevent or reduce the occurrence of prerenal azotemia.

In contrast to HIV-infected patients with true volume depletion, those with effective contraction of the intravascular space require therapies beyond fluid

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resuscitation. Hypotensive septic patients with multi-organ failure often develop severe hemodynamic ARF and have a high mortality rate.^{1,5,13} Appropriate treatment with antimicrobial agents, vasopressors (to achieve adequate blood pressure), fluid resuscitation (to optimize filling pressures), and ventilatory support (when required) is necessary to minimize the degree of renal failure. Renal replacement therapy, which can be intermittent or continuous, likewise is often required to control uremic, metabolic, and volume disturbances in these critically ill patients.^{1,13} A reduction in exposure to nephrotoxins will help reduce renal injury and facilitate recovery of renal function in patients who survive a septic process.

Patients with cirrhotic physiology require optimization of their volume status as well as appropriate treatment of ascites and peripheral edema. Large-volume paracentesis with albumin infusion or judicious administration of diuretics safely reduces volume overload in many of these patients. Therapy with a vasopressin analogue, avoidance of all nephrotoxins (especially nonsteroidal anti-inflammatory drugs and aminoglycosides), and provision of colloid to maintain adequate filling pressures also can benefit these patients. Crystalloid therapy alone will serve only to promote further volume overload and perpetuate prerenal azotemia.

Patients who develop hepatorenal syndrome have a very high mortality rate and will recover from renal failure only if the underlying liver process is reversible. In the same light, patients with an HIV-associated cardiomyopathy require treatment that will improve underlying cardiac performance. Appropriate measures include intravenous administration of inotropic agents, afterload reduction, and diuretic therapy. Medications can improve cardiac output and renal perfusion, thus correcting the underlying prerenal azotemia. To maximize cardiac performance in patients with a cardiomyopathy, a cautious trial of angiotensin-converting enzyme (ACE) inhibitors is warranted. However, in some patients, worsening ARF can develop, necessitating discontinuation of the medication. Unfortunately, this adverse hemodynamic response is not uncommon and often signals serious cardiac impairment. In patients intolerant of ACE inhibitors, therapy with hydralazine and nitrates might improve cardiac output without impairing the efferent arteriolar response to reduced renal blood flow.

Finally, severe pancreatitis can be associated with massive sequestration ("third-spacing") of fluids. In this setting, hypotension and prerenal azotemia develop. Correction of the underlying cause of pancreatitis (eg, discontinuation of the offending medications,

relief of the biliary or pancreatic duct disease) and aggressive intravenous therapy with fluids will reduce the severity and duration of ARF in affected patients. Fortunately, renal function often returns to baseline if the underlying pancreatic process is corrected and adequate fluid resuscitation is achieved.

NEPHROTOXIC ACUTE TUBULAR NECROSIS

Case 2 Presentation

Patient 2 is a 26-year-old woman who has AIDS and multidrug-resistant, cytomegalovirus-associated retinitis. She undergoes laboratory testing while in the third month of therapy with intravenously administered cidofovir (5 mg/kg body weight per week for 2 weeks followed by 5 mg/kg every other week, with intravenous administration of normal saline before drug administration) and probenecid (pre- and postcidofovir). Results show clearly impaired renal function parameters compared with baseline values (BUN level of 99 mg/dL and serum creatinine level of 8.1 mg/dL); renal function does not improve over the next few weeks despite discontinuation of the cidofovir. The patient is oliguric, producing only 175 mL of urine per 24 hours. Results of urinalysis also show the presence of glycosuria, low-grade proteinuria (protein level, 1100 mg/24 hours), and proximal renal tubular acidosis, indicating a proximal renal tubular nephrotoxic injury. A diagnosis of severe, irreversible ARF secondary to cidofovir-induced ATN is made. Peritoneal dialysis is initiated as renal replacement therapy.

Etiology of Nephrotoxic ATN

Medication-induced ATN is a common cause of ARF in hospitalized HIV-infected patients. Because of the varied opportunistic and nosocomial infections that these patients develop, therapy with a variety of nephrotoxic drugs often is required.^{1,5,6,8,12-14} In patient 2's case, cidofovir was the only medication suitable to treat her multidrug-resistant, cytomegalovirus-associated retinitis. Unfortunately, the patient developed dose-dependent, severe nephrotoxicity as a consequence of the vision-saving therapy.

HIV-infected patients are at increased risk for drug-induced ATN by virtue of their attendant volume-depleted state.^{1,5,8,9,12-14} By necessity, however, known nephrotoxins frequently are administered to patients infected with HIV to treat multidrug-resistant infections. In the 1980s, for example, pentamidine and amphotericin B were used frequently to treat *Pneumocystis carinii* pneumonia and cryptococcal infections, respectively, in HIV-infected patients,¹² although both drugs were known for their direct toxicity to renal tubular cells.

Approximately 25% of HIV-infected patients receiving treatment courses with pentamidine develop reversible renal failure.¹⁵ In the presence of other risk factors such as volume depletion and underlying renal disease, pentamidine may cause ARF in as many as 95% of patients receiving the drug.¹⁵ Amphotericin B infusion acutely decreases renal blood flow and induces ischemic injury by way of afferent arteriolar vasoconstriction.¹⁶ In addition, this antifungal agent directly disrupts renal tubular membranes in a dose-dependent fashion.¹⁶

Other drugs associated with ATN that are frequently administered to HIV-infected patients include aminoglycoside antibiotics and diagnostic imaging agents.^{1,5,8,12–14} Aminoglycosides induce intracellular injury and cell death following their uptake into proximal tubular cells. Radiocontrast agents with both high and low concentrations of osmotically active particles cause ARF in patients with underlying renal insufficiency and volume depletion through hemodynamic insult and direct tubular toxicity. The antiviral agents foscarnet and cidofovir and the protease inhibitor ritonavir also are associated with acute renal impairment from direct tubular injury.^{1,5,8,12–14} Rao and Friedman reported that many of these nephrotoxic medications, used alone or in combination, accounted for approximately 23% of cases of ARF in HIV-infected patients.¹³ Additionally, ATN caused by use of nonsteroidal anti-inflammatory drugs and rhabdomyolysis caused by trauma and use of heroin or crack cocaine also contributed to the cases of ARF reported in this study.¹³

Prevention of Nephrotoxic ATN

Knowledge of those medications that are nephrotoxic, as well as modulation of risk factors that predispose HIV-infected patients to the development of renal insufficiency, is key to prevention of nephrotoxic ATN. As noted previously, volume depletion from both renal and extrarenal etiologies is frequently encountered in HIV-infected patients.^{1–14} Therefore, it is imperative that a patient's volume status be optimized prior to—or at least concurrently with—the initiation of any drug with nephrotoxic potential.

Avoidance of nephrotoxic exposures is preferable if other reasonable diagnostic or therapeutic choices exist. Ultrasonography, computed tomography (CT) scanning without contrast, and magnetic resonance imaging are examples of imaging studies that spare renal exposure to potentially harmful material; they can be used in place of diagnostic studies that depend on intravenously administered contrast agents. However, treatment with a nonnephrotoxic agent should be pursued only if it is

considered optimal and effective therapy for the patient. In patients who absolutely require therapy with a nephrotoxic substance, the dosage must be adjusted, depending on the degree of renal and liver impairment already present, and drug levels monitored. It is also paramount that combinations of potentially nephrotoxic medications be avoided.

Management of Nephrotoxic ATN

The development of ARF in HIV-infected patients receiving drug therapy should prompt withdrawal of the responsible drug or drugs, unless there is no other option for therapy. Volume status should be optimized to limit superimposed ischemic renal injury, which would only prolong renal insufficiency. Other nephrotoxic substances also should be avoided. Renal replacement therapy might be required to correct uremic, metabolic, and volume perturbations in patients with severe and ongoing renal injury.^{1,5,13} All caregivers for such patients should recognize that the underlying illness and hemodynamic status, rather than merely the presence of HIV infection, can influence renal recovery and mortality.^{1,5,13} As a result, both aggressive dialytic intervention and meticulous supportive measures should be pursued in HIV-infected patients with nephrotoxic ATN.^{1,5,13}

ACUTE TUBULOINTERSTITIAL NEPHRITIS

Case 3 Presentation

Patient 3 is a 41-year-old woman infected with HIV who is admitted to the hospital because of severe dyspnea, dry cough, and fever. A chest radiograph reveals bilateral interstitial infiltrates. A diagnosis of *Pneumocystis carinii* pneumonia is made, and intravenous administration of high-dose trimethoprim-sulfamethoxazole (TMP-SMX) is initiated. After 6 days of therapy, the patient develops eosinophilia (9% eosinophils on leukocyte differential), pyuria (25 to 30 leukocytes per high-power field on analysis of urine sediment), renal insufficiency (BUN level of 68 mg/dL and serum creatinine level of 4.3 mg/dL), and a morbilliform rash on her trunk. Renal ultrasonography shows large, echogenic kidneys without evidence of hydronephrosis. The patient, who is oliguric, refuses to undergo a renal biopsy to determine the cause of her ARF. After therapy with TMP-SMX is discontinued, a gallium scan with delayed imaging reveals markedly positive uptake in both kidneys. Renal function improves to baseline values, and other abnormal findings resolve over the next week, supporting a likely diagnosis of ATIN.

Etiology of ATIN

ATIN should always be considered a possible cause of ARF when certain medications are prescribed to HIV-infected patients (Table 2). In a series published in 1991, ATIN resulting from administration of TMP-SMX accounted for 9% of ARF cases in HIV-infected patients.¹² A histologic diagnosis consistent with ATIN was found in 13% of HIV-infected patients with renal insufficiency at autopsy.⁸ Another study also noted that ATIN caused by drugs such as TMP-SMX, allopurinol, rifampin, and phenytoin contributed to ARF in a significant number of HIV-infected patients.¹³ It is noteworthy that the incidence (9% to 13%) of ATIN reported in HIV-infected patients is higher than the 1% to 3% incidence noted in the general population.¹⁷⁻²⁰ As other new medications are manufactured for HIV infection, it is possible that these agents also might cause allergic interstitial nephritis in patients to whom they are given.

Diagnosis of ATIN

The presence of ATIN might not be recognized in HIV-infected patients who have onset of fever, rash, and eosinophilia.¹⁷⁻²² The development of this classic triad of findings is extremely variable and more often determined by both the class of drug (occurring more commonly with β -lactam antibiotics) and the host response to the offending medication.¹⁷⁻²² More frequently, ATIN is recognized when ARF develops after administration of a suspicious drug.¹⁷⁻²² Consequently, clinicians should remain vigilant to detect any adverse reactions to medications in order to facilitate rapid recognition and treatment of ATIN in patients infected with HIV. Unfortunately, identification of the actual offending agent can be difficult in these patients, who are typically prescribed many potentially causative drugs.

Results of urinalysis and analysis of urine sediment can help in the diagnosis of ATIN by revealing low-grade proteinuria, renal tubular cells, erythrocytes, and leukocytes, as well as the occasional cellular cast. Eosinophiluria, which is sometimes present in patients with ATIN, is not helpful diagnostically because this finding is neither sensitive nor specific for ATIN.¹⁷⁻²² Large, echogenic kidneys, as seen in patient 3, are often present on ultrasonography in patients with ATIN.¹⁷⁻²³ However, this finding is not diagnostic and is only useful to exclude obstruction as the etiology of ARF.

Gallium scanning also has been reported to provide important information in the evaluation of suspected ATIN.^{17-20,24} Although this test, which is considered positive if gallium uptake by the kidney persists for 48 to 72 hours, is not specific for the diagnosis of

Table 2. Medications Associated with Acute Tubulointerstitial Nephritis in HIV-Infected Patients

β -Lactam antibiotics
Sulfonamides
Histamine (H ₂)-receptor blockers
Quinolones
Allopurinol
Phenytoin
Nonsteroidal anti-inflammatory drugs
Indinavir
Other drugs

ATIN, it appears to be relatively sensitive in the work-up of ATIN.^{17,24} As was the case with patient 3, gallium scanning is best suited for patients who refuse or who are unable to undergo renal biopsy. Renal biopsy remains the gold standard of testing to conclusively diagnose ATIN.¹⁷⁻²² Light microscopic evaluation of a biopsy specimen often reveals either patchy or diffuse infiltration of the interstitium with lymphocytes, plasma cells, and eosinophils.¹⁷⁻²²

Interstitial edema (an early finding) or interstitial fibrosis also occurs with ATIN. In severe cases of ATIN, tubulitis or invasion of the tubular cells by lymphocytes also can be present.¹⁷⁻²² In general, the glomeruli and blood vessels are spared and appear normal.¹⁷⁻²²

Management of ATIN

Avoidance of therapy with certain medications in patients with known allergies can reduce the occurrence of ATIN. Optimal treatment of ATIN requires early recognition of the disorder and prompt discontinuation of the culprit medication.¹⁷⁻²² Early diagnosis is key to preventing the occurrence of interstitial fibrosis (which can occur as early as 2 weeks after drug exposure) and irreversible renal dysfunction.¹⁷⁻²² If renal function does not improve within a few days to a week following drug discontinuation, a short course of orally administered corticosteroids (eg, prednisone 1 mg/kg for 2 weeks, with gradual tapering of the drug) is appropriate to suppress tubulointerstitial inflammation.¹⁷⁻²² However, this recommendation has not been substantiated by any prospective, controlled studies and is based on anecdotal success documented in case reports and small case series.¹⁷⁻²² Moreover, the possible detrimental effect of such immunosuppressive corticosteroids in some HIV-infected patients with severe, life-threatening infections must be considered.

Fortunately, the majority of HIV-infected patients who develop ATIN will recover normal renal function. End-stage renal disease does occur in patients with severe renal insufficiency, especially when the entity is recognized late and widespread interstitial fibrosis has developed.^{17–20} Some patients will require temporary renal replacement therapy, whereas others might need long-term treatment with dialysis.^{17–20}

CRYSTAL-INDUCED NEPHROPATHY

Case 4 Presentation

Patient 4 is a 29-year-old man with HIV infection who has a high viral load and a low CD4 cell count on laboratory evaluation. The protease inhibitor indinavir is added to his antiretroviral regimen. Six months later, the patient has sterile pyuria and a new elevation in his BUN level (to 56 mg/dL) and serum creatinine level (to 2.1 mg/dL). Urine output is within normal limits (1.8 L/24 hours). Renal ultrasound reveals normal bilateral kidney size and normal echogenicity without hydronephrosis. The patient undergoes renal biopsy for diagnosis. Light microscopy of biopsy tissue reveals the presence of aggregates of crystals admixed with cells forming casts within the cortical and medullary collecting tubular lumens. Electron microscopy confirms the presence of the crystals. Indinavir-associated crystal nephropathy is diagnosed. The medication is discontinued, and intravenous fluids are administered. Over the next week, renal function returns to baseline values. Indinavir therapy is restarted, and the patient is instructed to drink at least 2 L of fluid daily. Renal function remains intact over the next several months of observation.

Pathogenesis of Crystal-Induced Nephropathy

The deposition of insoluble crystals in the kidney can cause ARF in HIV-infected patients.^{1,5,8,14,25,26} This process, termed *crystal-induced nephropathy*, typically is associated with mild azotemia. However, severe ARF can develop in the presence of risk factors that increase intratubular crystal precipitation (**Table 3**).^{1,5,8,14,25,26} For example, HIV-infected patients who have an AIDS-associated lymphoma produce excessive amounts of uric acid during cell death.^{1,5,26,27} Spontaneous or chemotherapy-induced lysis of tumor cells is associated with the release of intracellular purines that are converted to uric acid in the systemic circulation.^{1,5,26,27} This process results in a large burden of uric acid to be filtered and secreted by the kidney, resulting in massive hyperuricosuria. As a result, uric acid crystals are precipitated out and deposit in the tubular lumens of the distal nephron, causing intrarenal obstruction.^{1,5,13,26,27}

True or effective intravascular volume depletion, as well as acidic urine (pH less than 5.5), increases the risk for crystal deposition.^{1,5,26,27}

A number of medications taken by HIV-infected patients also are associated with crystal-induced nephropathy.^{1,5,8,25,26} Sulfadiazine, acyclovir, indinavir, and foscarnet are all therapeutic agents reported to cause intrarenal crystal deposition.^{1,5,8,25,26} As occurs with uric acid, these substances precipitate more fully within tubular lumens in the setting of volume depletion and low urinary flow rates.

Acidic urine further increases precipitation of sulfadiazine in the kidney.^{1,5,8,25,26} Hypoalbuminemia and renal insufficiency are associated with higher plasma and urinary concentrations of free sulfonamide, resulting in a further risk for tubular deposition of sulfa crystals.^{25,26} Patients treated with sulfadiazine who have any of these associated findings can develop back, flank, or abdominal discomfort and well as oliguric ARF.^{25,26} Examination of urine sediment from such patients typically reveals crystals that have been described as needle-shaped, rosettes, and “shocks of wheat.”^{1,5,8,25,26} Renal ultrasound studies in these patients can reveal sulfa-based uroliths and other calculous material sludging in the renal calices that appear as layered clusters of echogenic material.^{1,5,8,25,26}

Rapid intravenous infusion of acyclovir also can produce obstructive intratubular crystals in the distal nephron.^{1,5,8,25,26} Excessive doses of acyclovir given to patients with underlying renal insufficiency and volume depletion increase intrarenal precipitation of crystals.^{25,26} Although patients are typically asymptomatic during drug administration, nausea, vomiting, and flank or abdominal pain can develop within 1 to 2 days of acyclovir administration.^{25,26} Acyclovir crystals, either free or engulfed by leukocytes, appear as needle shapes admixed with other cellular material in the urine sediment.^{25,26} Inspection of the sediment with a polarizing microscope reveals positively birefringent crystals.^{25,26}

Treatment of HIV-infected patients with indinavir also has been associated with nephrolithiasis and crystal-induced ARF.^{1,25,26,28} This medication is very insoluble at a physiologic pH and will precipitate in tubular lumens, especially in patients with low urinary flow rates.^{25,26,28} Dysuria, flank or back pain, or gross hematuria can herald indinavir crystalluria or calculus formation.^{25,26,28} In general, however, most patients are asymptomatic. Renal insufficiency or abnormal results on urinalysis usually provide the only evidence of crystal-related renal injury.^{25,26,28} Analysis of urine sediment reveals a variety of crystal shapes (eg, fan shapes, plate-like rectangles, and starburst forms).^{25,26,28}

Alkalinization of a urine specimen increases the visibility of crystals under the microscope. Once halted (until the crystal-induced ARF resolves), indinavir therapy can be successfully reinstated in 75% of patients, as long as they are able to drink 2 to 3 L of fluid daily.

The antiviral agent foscarnet also causes ARF because of intrarenal crystal deposition in the kidney.^{1,25,26} In contrast to the manufactured form of foscarnet-sodium salt, formation of the less soluble foscarnet-calcium salt leads to early precipitation of crystals in the glomerular capillaries and subsequently in tubular lumens. This crystal deposition in both glomerular capillaries and tubular lumens distinguishes foscarnet from previously described medications, which deposit crystals in tubular lumens only. Renal insufficiency from crystal precipitation is more likely to develop in the setting of volume contraction, rapid intravenous infusion of the drug, or underlying renal impairment.^{25,26} Patients are typically asymptomatic during the course of foscarnet-induced nephrotoxicity. Cylindruria, hematuria, and proteinuria of varying degrees are found on urinalysis.^{1,25,26} Evidence of crystalluria, however, is strikingly absent in the urine.

Management of Crystal-Induced Nephropathy

Induction of high urinary flow rates, which can decrease the urinary concentration of various substances, is the key to prevention of these forms of crystal-associated nephropathy.^{1,25–28} High urinary flows wash away crystals and any obstructing intratubular casts that have already formed. Allopurinol therapy will reduce the level of serum uric acid and prevent massive hyperuricosuria in patients with bulky lymphoma.^{1,26,27} Appropriate drug dosing with sulfadiazine, foscarnet, and acyclovir in HIV-infected patients who have underlying renal dysfunction is also crucial.^{1,25,26} Slower and more prolonged infusions of acyclovir and foscarnet also can reduce the likelihood of patients' developing renal impairment.^{25,26} Alkalinization of the urine (to a pH greater than 7.0 or even 7.5) with either intravenously or orally administered sodium bicarbonate will solubilize both uric acid and sulfadiazine and further decrease intratubular precipitation.^{25,26} Acidification is not advised in patients receiving indinavir. Discontinuation of the responsible medications usually results in recovery of renal function.^{1,25,26,28}

OBSTRUCTIVE UROPATHY

Case 5 Presentation

A 36-year-old man with advanced AIDS is admitted to the hospital because of a 10-day history of nausea, anorexia, and reduced urine output. Evaluation reveals

Table 3. Etiology of HIV-Associated Crystal Nephropathy

Crystal Type	Risk Factors
Uric acid	Volume depletion Acidic urine (pH < 5.5)
Sulfadiazine	Volume depletion Acidic urine (pH < 5.5) Renal insufficiency
Acyclovir	Volume depletion Renal insufficiency Rapid intravenous infusion
Indinavir	Volume depletion Alkaline urine (pH > 5)
Foscarnet	Volume depletion Renal insufficiency Rapid intravenous infusion

acute renal failure, with a BUN level of 91 mg/dL and a serum creatinine level of 5.6 mg/dL. Urine output is 45 mL/24 hours. Renal ultrasonography shows bilateral hydronephrosis with marked pelvocaliceal dilatation. A CT scan reveals hydronephrosis and bulky retroperitoneal lymphadenopathy. After a failed attempt at retrograde ureteral stent placement, bilateral percutaneous nephrostomy tubes are placed, resulting in successful drainage of urine. Renal function returns to near baseline values (BUN level of 28 mg/dL and serum creatinine level of 1.9 mg/dL) over the next 10 days. Results of a lymph node biopsy are consistent with B-cell lymphoma. The patient subsequently begins chemotherapy for the tumor.

Etiology of Urinary Obstruction

Obstruction of the urinary system is a rare but noteworthy cause of ARF in patients infected with HIV. A number of unusual causes of obstruction have been described in these patients.^{1,5,6,12–14,25,26,29–34} Some reported causes of urinary obstruction in AIDS patients include pelvic and/or ureteral obstruction from fungus balls and blood clots.^{1,5} Extrarenal compression of the ureters by retroperitoneal lymph nodes enlarged by infiltrating lymphoma, as occurred in patient 5, also can lead to obstructive uropathy and ARF in these patients.^{1,5,28} Other types of tumors, certain infections, and fibrosis in the retroperitoneum similarly can obstruct urinary flow.^{1,5,28} Structural (fungus balls, blood clots, calculi) or functional (neuropathic) abnormalities of the bladder also can obstruct urinary flow and cause renal

insufficiency. Severe urethritis and blood clots within the urethra may induce anuria and renal failure.

However, the most common cause of obstruction in HIV-infected patients is the development of calculi from a few of the therapeutic drugs typically administered to them.^{1,5,29-34} Such lithogenic medications include the antibiotic sulfadiazine and the protease inhibitor indinavir.³⁰⁻³⁴ Urinary obstruction from drug-associated calculi has been noted with both agents.³⁰⁻³⁴ Symptomatic nephrolithiasis, characterized by classic renal colic with hematuria and dysuria, also occurs.³⁰⁻³⁴

Diagnosis of Urinary Obstruction

ARF resulting from obstruction of the urinary system is usually asymptomatic, but patients can manifest symptoms of the underlying disease process causing the urinary obstruction. Some patients also describe vague flank, back, or loin pain in addition to noting changes in their patterns of urination. Complete urinary obstruction is signaled by anuria, whereas oliguria alternating with polyuria heralds partial obstruction. Hematuria, manifested either microscopically or as frank blood clots, can develop in some patients. Examination of urine sediment can demonstrate pyuria, crystal forms, renal tubular epithelial cells, or bland urine, depending on the underlying obstructive etiology.^{1,5,29-34} Diagnosis of obstruction is rapidly and reliably achieved with renal ultrasonography; this modality sometimes can provide insight into the causative agent (eg, calculus, blood clot). A CT scan typically provides more precise information about the underlying etiology of obstruction. This imaging technique visualizes retroperitoneal structures, obstructing calculi, and other diseases of the urinary system more precisely than does ultrasonography. The case of patient 5 is an example of the diagnostic superiority of CT scan versus ultrasonography in the evaluation of the retroperitoneum.

Management of Urinary Obstruction

Prevention of obstruction caused by sulfadiazine and indinavir calculi is possible. Volume expansion, to at least 2 to 3 L daily, will induce high urinary flow rates, decrease urinary concentrations of the calculus-forming substances, and thus diminish calculus formation from these 2 drugs.^{25,26,28,30-34} Urine alkalinization (to a pH greater than 7.0 or even 7.5) will also reduce precipitation of sulfadiazine crystals.^{24,25,27,29,30} Acidification of the urine to solubilize indinavir is difficult to achieve, potentially dangerous, and therefore not advisable.³¹⁻³⁴ Ultimately, the cause of obstruction will determine its treatment.

In the case of patient 5, percutaneous nephrostomy tube placement was able to divert the urine and bypass the obstruction. This technique will also allow treatment of ureterocaliceal fungus balls with amphotericin B and blood clots with saline lavage. In addition to removal of uroliths by standard urologic techniques, sulfadiazine calculi can be dissolved by lavage with 5% bicarbonate solution.^{25,26} Ureteral stent placement will bypass an obstruction caused by ureteral calculi and might also treat obstructive retroperitoneal disease. Catheter placement in the bladder will correct obstruction at the level of the bladder and urethra. Complete obstruction is often associated with a postobstructive diuresis after relief of the obstructing process, a fact that should be kept in mind. Therefore, patients' hemodynamic status and fluid management must be closely monitored.

CONCLUSION

HIV-infected patients develop acute renal insufficiency from various causes. The most frequent cause of ARF in these patients is prerenal azotemia, resulting from intravascular volume losses and septic processes. Nephrotoxic ATN is the second most common cause of renal injury in patients infected with HIV. In addition, medications administered to these patients often cause nephrotoxic ARF through a variety of mechanisms. Direct tubular injury, allergic interstitial nephritis, and intrarenal crystal deposition are common renal insults in HIV-infected patients. Finally, urinary obstruction is a rare cause of renal impairment in these patients. Fungal infections, tumors, or treatment with calculus-forming medications also can lead to obstruction.

When possible, prevention of ARF in HIV-infected patients should be attempted. Appropriate steps include optimization of volume status, avoidance of nephrotoxin administration, and rapid recognition of patients at risk for renal insufficiency. Heightened awareness of allergic drug reactions often can preserve renal function. Crystal deposition from tumor lysis and sulfadiazine therapy can be avoided with alkalinization of the urine. Relief of obstructive processes will rapidly correct postrenal azotemia. Most importantly, clinicians caring for HIV-infected patients should pursue aggressive therapy in these patients because their recovery from ARF is not different from that observed in subjects not infected with HIV. **HP**

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