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INTERNAL MEDICINE BOARD REVIEW MANUAL

Case Studies in Acute Renal Failure; Scabies: A Case Study

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Cover Illustration by Christie Grams

Chapter 1—Case Studies in Acute Renal Failure

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I. INTRODUCTION

Acute renal failure (ARF) is triggered by an extremely diverse group of etiologies. The mortality of this condition remains high (possibly as high as 80% in intensive care settings). Death often results from complications such as infection or gastrointestinal bleeding. New therapies continue to emerge, but clinicians must understand the etiologies of ARF to prevent its occurrence and to start appropriate treatment early.

Although ARF is largely a hospital-acquired phenomenon, it is important to realize that the differential diagnosis for ARF depends on whether the patient is an outpatient or an inpatient. Approximately 80% of ARF cases occur in the inpatient setting. The classic categories for ARF include prerenal, renal, and postrenal causes. This article discusses 6 of the most common presentations of renal failure and provides illustrative case studies where appropriate. A brief overview of the causes, clinical findings, laboratory findings, and treatments will accompany each case. Glomerulonephritis can present as ARF, but it will not be discussed in this article.

II. PRERENAL ACUTE RENAL FAILURE

CASE PATIENT 1 PRESENTATION

Patient 1 is a 34-year-old man who is hospitalized with nausea, vomiting, and abdominal pain of 3 days duration. He has a history of alcohol and drug abuse. His medical history is unremarkable, and he is not on any medications. Admission laboratory values reveal a serum sodium level of 152 mg/dL. His potassium is 2.8 mg/dL, chloride is 124 mg/dL, and bicarbonate is 14 mg/dL. Blood urea nitrogen (BUN) is 96 mg/dL, and serum creatinine is 3.7 mg/dL. Blood glucose is 756 mg/dL. Serum calcium is 7.4 mg/dL, and his leukocyte count is 8000/mm^3. Amylase is 256 U/dL (normal, 0–140 U/dL), and lipase is 400 U/L (normal < 140 U/L). Urinalysis reveals hyaline casts, glucosuria, and ketonuria; no blood, protein, leukocytes, or other casts are seen in the urine. The patient is hydrated vigorously. He is diagnosed with diabetic ketoacidosis and acute pancreatitis; he is treated appropriately. A contrast computed tomography (CT) scan reveals prominent ascites throughout the abdomen involving the perirenal spaces, transverse mesocolon, and colonic gutters. The pancreas is edematous, and fatty stranding can be seen. The ileum and sigmoid colon are thickened. A left pleural effusion is present.

- **What is the apparent cause of patient 1's ARF?**
  - A) Prerenal secondary to decreased circulatory volume
  - B) Direct renal toxicity
  - C) Obstructive uropathy
  - D) Diabetic nephropathy

DISCUSSION

The correct answer is A. The category of prerenal ARF has many causes (**Table 1**). Azotemia results from decreased renal blood flow when the kidneys sense a decrease in effective circulatory volume, whether from systemic causes (such as hypoalbuminemic state) or from local causes (such as bilateral renal artery stenosis). As renal blood flow decreases, the glomerular filtration rate (GFR) decreases accordingly. This patient had 3 of the main causes of decreased effective circulatory volume: vomiting, osmotic diuresis, and third spacing. Third-space fluid losses also occur with severe burns, nephrosis, cirrhosis, or heart failure. The decrease in effective circulatory volume results in reduced perfusion to the brain and other vital organs, thereby activating the baroreceptors. Angiotensin II, norepinephrine, and antidiuretic hormone concentrations increase, resulting in vasoconstriction. Sodium and water reabsorption increase. The kidneys depend on this mechanism of increasing arteriolar resistance to maintain adequate glomerular filtration.

- **Which of the following should NOT be part of the differential diagnosis when assessing a patient who may have prerenal ARF?**
  A) Toxicity from nonsteroidal anti-inflammatory drugs (NSAIDs) and angiotensin-converting enzyme (ACE) inhibitors
  B) Congestive heart failure (CHF)
  C) Cirrhosis
  D) Toxicity from acyclovir

DISCUSSION

The correct answer is D. Although acyclovir is a medication that may adversely affect kidney function by intratubular precipitation, it is not a cause of prerenal ARF. On the other hand, the kidneys sense low circulating volume in patients with CHF; cirrhosis causes third-space fluid loss. As a result, both conditions lead to a lower glomerular filtration. Medications (eg, NSAIDs, ACE inhibitors, and diuretics) also can contribute to prerenal ARF in susceptible patients by lowering the GFR.

Medications and Prerenal ARF

NSAIDs and ACE inhibitors are 2 important classes of medications that interfere with intrarenal physiology and result in a decreased GFR. Prostaglandin-mediated afferent arteriole dilation and angiotensin II–mediated efferent arteriole constriction are used to maximize glomerular filtration pressure. ACE inhibitors, by blocking production of angiotensin II, inhibit the efferent arteriole from constricting and thus decrease GFR. The renal dysfunction is usually reversible after discontinuation of the ACE inhibitor.[1] ACE inhibitors can be used in patients with mild renal dysfunction as long as they are followed carefully by a physician, but this class of drugs works best in patients without renal dysfunction.[2]

NSAIDs also can lead to decreased GFR, but they do so by cyclooxygenase (COX) inhibition. This mechanism decreases the prostaglandin-mediated afferent arteriolar tension, which results in suboptimal glomerular filtration pressure and decreased GFR. If NSAIDs are not stopped in a timely manner, the renal insult can progress to ischemic tubular necrosis. The 2 isoforms of cyclooxygenase are well described. COX-1 is a regulatory enzyme present in the gastrointestinal tract, kidney, and vasculature. COX-2 production is stimulated primarily by inflammation but is also normally present in small amounts in the kidney. The nonselective NSAIDs may cause gastric side effects; however, the selective COX-2 inhibitors, which are primarily used to curb inflammation, are useful because they typically cause fewer gastric side effects. In the normal kidney, glomerular filtration is not significantly decreased by COX-2 inhibitors. However, caution must be exercised when used in patients with baseline renal insufficiency, dehydration, CHF, or other prerenal states because the COX-2 inhibitors may cause renal impairment.[3] ACE inhibitors and NSAIDs are often successfully used in patients with heart and liver disease. They should always be used with caution in patients with tenuous hemodynamics.

Table 1. Causes of Prerenal Disease

True volume depletion
Hemorrhage
Renal losses
Gastrointestinal losses
Skin losses
Respiratory losses
Sequestration of fluid in a so-called third space (eg, in the abdomen in acute pancreatitis or in muscle after a crush injury)
Hypotension
Septic shock
Rapid reduction in blood pressure in patients with chronic severe hypertension
Edematous states*
Advanced heart failure
Advanced liver disease
Localized renal ischemia
Bilateral renal artery stenosis or unilateral stenosis in a solitary kidney
Medications
ACE inhibitors, particularly in patients with bilateral renal artery stenosis
NSAIDs, particularly in patients with an underlying reduction in renal perfusion

ACE = angiotensin converting enzyme; NSAID = nonsteroidal anti-inflammatory drug.

*Most individuals with edema resulting from the nephrotic syndrome appear to have a normal effective arterial blood volume, a finding supported by the observation that plasma renin activity is not increased in these patients.

Adapted with permission from Black RM. Acute renal failure. In: Dale DC, Federman DD, editors. Scientific American Medicine. Vol. 3. New York: Scientific American; 2001: 10(Nephrology):VI:3.

- **Which of the following is not consistent with prerenal ARF?**
  A) Urine sodium < 20 mmol/L
  B) Urine osmolality > 500 mOsm/kg

Table 2. Intrinsic Causes of Acute Renal Failure with a Low Fractional Excretion of Sodium*

ATN, usually nonoliguric (occurs in about 10% of cases of ATN)
ATN superimposed on chronic prerenal disease (eg, advanced liver disease or heart disease)
Administration of radiocontrast media or release of heme pigments (hemoglobin or myoglobin)
Acute glomerulonephritis or vasculitis
Acute interstitial nephritis

ATN = acute tubular necrosis.

*Less than 1%.

Adapted with permission from Black RM. Acute renal failure. In: Dale DC, Federman DD, editors. Scientific American medicine. Vol. 3. New York: Scientific American; 2001:10(Nephrology):VI:3.

C) Urine output > 75 mL/hour
D) Hyaline casts on urinalysis

DISCUSSION

The correct answer is C. Understanding the physiology of prerenal states is a prerequisite to understanding the associated laboratory findings. The fractional excretion of sodium is typically less than 1%, although this is not a pathognomonic finding for prerenal states (**Table 2**). If reduced effective circulatory volume is the only cause of renal failure, urine sodium, therefore, is often less than 20 mmol/L. Similarly, urine acidity and concentration are usually greater than 500 mOsm/kg because the body attempts to retain as much fluid as possible. Increased urine output is not expected in this situation. Thus, oliguria is an appropriate physiologic response in this situation and does not indicate parenchymal renal damage. Finally, Tamm-Horsfall mucoprotein, which is secreted by the cells of the thick ascending limb, precipitates in an acidic environment to form the hyaline casts characteristic of the otherwise benign urine sediment. It is important to distinguish between prerenal disease and acute tubular necrosis (ATN) because the former is much more amenable to reversal with appropriate treatment. However, these 2 conditions are on a continuum and untreated prerenal disease can progress to ATN (*see* "Acute Tubular Necrosis").

Diagnosing Hypovolemia

Electrolyte abnormalities somewhat depend on the clinical situation. In the elderly dehydrated patient who has a free water deficit exceeding the sodium deficit, hypernatremia usually will be evident. When the plasma sodium is not increased in such a patient, sodium and water are simultaneously being excreted. Thus, plasma sodium is not a reliable index of volume states; it only indicates a relative excess or depletion of water. More often, prerenal disease leads to hyponatremia because antidiuretic hormone is released, which increases sympathetic neural tone. This response to decreased circulatory volume leads to preferential free water retention relative to sodium.

Clinical signs of volume depletion should be evident in hypovolemia severe enough to allow ARF to ensue. In patients able to sit and stand, evaluation of orthostatic hypotension should be documented. Orthostatic hypotension is defined as a decrement of greater than 20 mm Hg in the systolic blood pressure from supine to standing position. However, test results vary according to the patient's age and the amount of time the patient spends supine before taking the standing measurements. Therefore, this test is not always helpful in diagnosing or excluding hypovolemia. Compressing the distal phalanx and measuring the capillary refill time on release is another frequently used bedside test. Supine tachycardia is specific but not sensitive for hypovolemia.

In severe cases, such as third spacing or massive blood loss, signs of shock will be apparent (eg, cool, clammy extremities and overt hypotension) because losses exceed the body's ability to compensate by vasoconstriction. In patients who are not in overt shock, the combination of findings (eg, confusion, generalized weakness, sunken eye, nonfluent speech, and dry, furrowed tongue) is more specific for dehydration than any 1 or 2 signs alone.[4] Although helpful when added to the entire clinical picture, poor skin turgor alone is not a very good predictor of hypovolemia.

- **Which of the following causes of prerenal disease is followed by an inappropriate therapeutic approach?**
  A) Third spacing: aggressive volume replacement with crystalloid
  B) Reverse oliguria in hepatorenal syndrome: loop diuretic
  C) Low flow state in CHF: dobutamine and dopamine
  D) Gastrointestinal losses: aggressive volume replacement with crystalloid

DISCUSSION

The correct answer is B. Appropriate therapy for hepatorenal failure is described in the next section; it does not include loop diuretics. Although prerenal azotemia is not associated with renal injury in its early stages, treatment depends on the cause of the decreased effective circulatory volume. Acid-base status can be useful

for determining the etiology of prerenal ARF and for deciding which type of replacement fluid to use. Metabolic alkalosis is seen with volume contraction secondary to excess diuretic use. As euvolemia is restored, the bicarbonate level in the blood will decrease appropriately. In a volume-depleted patient with an underlying bicarbonate loss (eg, diarrhea) compounding the situation, lactate Ringer's solution may be an appropriate choice. This solution allows for the replacement of bicarbonate and prevents the low bicarbonate level from falling further as contraction alkalosis is corrected. In cardiac disease, the renal function will improve as cardiac function improves. Inotropes, such as dobutamine or milrinone, are appropriate therapy in severe CHF. Other therapies include nitrates, which help relieve preload, and antihypertensives, which allow a failing heart to pump blood against less resistance.

Hepatorenal Syndrome

Hepatorenal syndrome is characterized by ARF in the setting of advanced liver disease for which no other cause of renal failure is apparent. As is typical of prerenal states, the kidneys themselves are not damaged. Hepatorenal syndrome has a poor prognosis; the only available treatment is a liver transplant.[5] The use of a transjugular intrahepatic portosystemic shunt may improve renal function but will do so typically during the course of several months.[6] Although no treatment has been known to reverse the condition, important measures include replacing volume (to provide at least transient improvement in renal function) and starting the patient on a low-protein diet (to minimize azotemia). Other medications have been tried in hepatorenal syndrome but are beyond the scope of this review.[7]

ACUTE TUBULAR NECROSIS

ARF caused by prerenal states has been demonstrated in some studies to account for as many as 50% of the patients acquiring ARF in the hospital setting.[8] This does not include the intensive care unit (ICU) setting where the diagnosis is more often ATN from iatrogenic causes.[9] The mortality associated with ARF is much greater when occurring in the inpatient setting and is directly correlated with the degree of elevation of the serum creatinine level.[9]

Renal Ischemia

ATN is the most common cause of intrinsic ARF. The tubular cells are irreversibly damaged, and they slough off, manifesting as granular casts or "muddy brown casts" on urinalysis. The outer medulla is the portion of the kidney most susceptible to ischemic insults. When damaged, the brush border sloughs off; the debris and resultant casts obstruct the tubules and cause further damage.

The course of ATN is described by 3 phases. The initial phase is the period of insult by either hypotension or a nephrotoxic agent. Depending on the duration of the insult, the urine sodium concentration, BUN, and serum creatinine levels increase during that time. In the second (or maintenance) phase, oliguria (urine output < 500 mL/day) is a common but not universal feature. Nonoliguric renal failure has a better prognosis than its counterpart. Changing oliguric to nonoliguric renal failure by using diuretics, however, does not change the prognosis. The final phase is the diuretic phase. The tubules at this point are regenerating but still cannot concentrate urine. A post-ATN diuresis may follow, which is less obvious in patients who did not have an oliguric phase. Of the mortality from ATN, 25% reportedly occurs during the diuretic phase.[10]

- **What is the main cause of ATN other than ischemic injury?**
  - A) Medications
  - B) Systemic lupus erythematosus
  - C) Hypertension
  - D) Vasculitis

Discussion

The correct answer is A. Aminoglycoside antibiotics are a well-known cause of ATN. These drugs are filtered by the glomerulus, but the proximal tubular cells concentrate aminoglycosides intracellularly, causing damage. The serum half-life of aminoglycosides is 3 hours; however, in the proximal tubular cells, the half-life can be more than 100 hours.[1] The number of cationic groups on the molecule correlates directly with toxicity; therefore, neomycin is the most toxic with 6 amino groups, and streptomycin is the least toxic with 4 amino groups. Some of the unabsorbed aminoglycoside may bind to the negatively charged cells of the collecting tubule. This binding interferes with ADH secretion and therefore may explain the frequent nonoliguric renal failure seen with these drugs.[11] Proper drug level monitoring is helpful in preventing toxicity, although toxicity certainly occurs even with optimal serum drug levels. Although it has been suggested that once-daily dosing is less nephrotoxic than multiple daily dosing, the data are not convincing.[1] Many other agents are known to cause renal toxicity, such as platinum compounds, amphotericin B as well as other antibiotics, and heavy metals.[12,13] Risk factors for aminoglycoside nephrotoxicity include advancing

age, underlying renal disease, hypovolemia, hypokalemia, and hypomagnesemia.

- **What is the best treatment for a patient with ATN?**
  A) Supportive care
  B) Dopamine
  C) Intravenous furosemide
  D) Alkalinization of urine

Discussion

The correct answer is A. Treatment is primarily supportive. For example, if the etiology is a drug or toxin, then discontinuation of the toxic agent should allow for recovery of renal function during the course of 1 to 2 weeks. Treatment with mannitol or loop diuretics has been employed but has not definitively been proven to be beneficial. It is important to note that the conversion of an oliguric renal failure to a nonoliguric type by using diuretics does not improve outcomes.[10] Dietary protein must be kept to a minimum in the non-dialyzed patient to minimize the nitrogen balance and therefore the level of uremia. Administration of carbohydrates helps prevent protein catabolism. However, if the patient is being dialyzed, dietary protein should be increased.

III. CONTRAST-INDUCED ACUTE RENAL FAILURE

CASE PATIENT 2 PRESENTATION

Patient 2 is a 28-year-old woman who is admitted to the hospital for respiratory support. She received a bone marrow transplant, and she has been developing moderately progressive respiratory distress during the subsequent 2.5 months. She is admitted with a BUN of 20 mg/dL and a serum creatinine level of 0.7 mg/dL. She is placed on nasal cannula and is not given intravenous fluids initially because her oral intake is adequate. Chest radiographs reveal reticulonodular disease. Antibiotic coverage is added as empiric treatment for pulmonary infection as the patient requires increasing amounts of supplemental oxygen to maintain her arterial oxygenation. The antibiotic regimen consists of piperacillin/tazobactam, gentamicin, acyclovir, and amphotericin B.

After taking this regimen for 5 days without significant change in renal function, a contrast-enhanced CT is done to evaluate her pulmonary anatomy in greater detail because her oxygen requirement is still increasing. The following morning, her serum creatinine is 1.2 mg/dL. Although all nephrotoxic drugs are discontinued, the serum creatinine level peaks on the fifth day post-procedure at 5.0 mg/dL. The urine sediment reveals muddy brown casts. On urinalysis, no hemoglobinuria, proteinuria, or eosinophils are present. The patient's renal function recovers during her stay. However, she dies 6 weeks later from her pulmonary disease.

- **What is the most likely cause of patient 2's ARF?**
  A) Dehydration alone
  B) Obstruction
  C) Contrast-induced renal dysfunction
  D) Chronic graft-versus-host disease

DISCUSSION

The correct answer is C. Contrast-induced acute renal failure (CIARF) varies in its reported frequency in the biomedical literature from 2% in normal patients to 100% in some reports.[14,15] The risk increases significantly in patients with chronic renal insufficiency,[14,16] but the greatest risk appears to occur with diabetic patients.[16] Other risk factors are hypovolemia, multiple myeloma, and intra-arterial as opposed to intravenous contrast exposure. Two other purported risk factors include dehydration and concomitant treatment with nephrotoxic drugs, and patient 2 had both of them. Physicians can minimize toxicity by limiting the actual amount of contrast agent a patient receives. CIARF is reported to be the third most common form of ARF in inpatients.[17,18] Graft-versus-host disease typically does not affect the kidneys.

- **Which of the following is characteristic of CIARF?**
  A) Renal dysfunction typically manifests 5 to 7 days post-procedure
  B) Renal injury is usually irreversible
  C) Patients will become oliguric during the peak of renal dysfunction
  D) Patients will not usually develop problems with electrolytes or volume status

DISCUSSION

The correct answer is D. Typically, CIARF starts to manifest as an increase in serum creatinine levels within 1 to 2 days post-procedure. Generally, creatinine levels continue to increase, peak between 3 and 5 days, and then return to normal. Although CIARF is not a permanent renal injury, it does prolong hospital stay. Many studies have been done to evaluate preventative measures and treatment of CIARF.[16,17,19,20] Clinically, the patient does not become volume overloaded and does not develop severe electrolyte abnormalities from

CIARF alone; it is a type of nonoliguric renal failure. Another differentiating laboratory finding is the combination of a high urine osmolality and a fractional excretion of sodium (< 1%). Studies involving experimental cross-clamping of the aorta followed by administration of contrast agents show that contrast injury is caused by an ischemic effect on the renal tissues.[14] Normally, the partial pressure of oxygen is lower in the medulla of the kidney compared with the cortex. This lower pressure in addition to metabolically active renal medullary tissues may contribute to the vulnerability of the medullary thick ascending limb to contrast-induced damage. Dehydration worsens the contrast injury by contributing to ischemic damage. Low osmolar contrast agents are currently available that cause less damage to the renal tissues.[14]

MEDICAL THERAPY FOR CIARF

- **Which of the following has been shown to improve outcomes in contrast-induced renal injury?**
  - A) Theophylline
  - B) Furosemide
  - C) Atrial natriuretic peptide
  - D) 0.45% Saline

Discussion

The correct answer is D. Only saline has proven to be significantly helpful in preventing renal damage by contrast agents. A prospective, randomized study by Solomon and colleagues examined the use of 0.45% saline alone or with either mannitol or furosemide.[21] The patients were randomly assigned and the cohort mainly included (but not exclusively) patients with diabetes. All patients had preexisting renal insufficiency with a serum creatinine level more than 1.6 mg/dL. Only saline alone proved beneficial. The other groups fared worse than controls. Theophylline has been given prophylactically and shown to be beneficial for maintaining renal function in one study.[22,23] However, more data are needed before theophylline becomes standard of care. Atrial natriuretic peptide has also been tried prophylactically but with unimpressive results.

Another randomized, prospective, placebo-controlled study evaluating patients with contrast-induced renal injury showed that the use of acetylcysteine was more effective than saline alone in preventing CIARF in patients with a starting serum creatinine of approximately 2.4 mg/dL.[24] The results were significant and the relative risk of renal failure with acetylcysteine and saline prophylaxis was 0.1%. This regimen has not been tested in patients without baseline renal dysfunction.

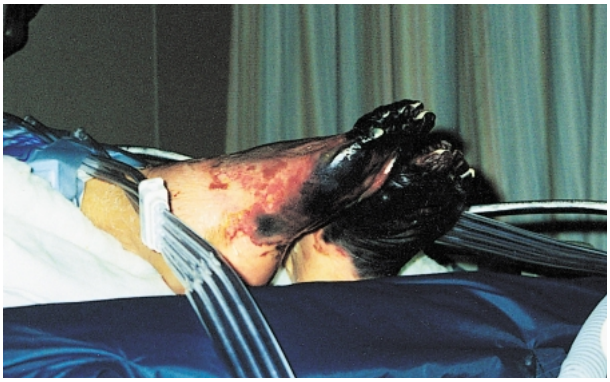

Figure 1. Dermatologic manifestation of cholesterol emboli showing bluish-black feet.

IV. ACUTE INTERSTITIAL NEPHRITIS

CASE PATIENT 3 PRESENTATION

Patient 3 is a cachectic 56-year-old man who is admitted with productive cough, upper lobe infiltrates by chest radiograph, and fever, all of which have lasted for 3 weeks. He has a history of chronic obstructive lung disease and is on meter-dose inhalers. He has been a smoker for the past 30 years. Electrolytes, complete blood counts, and renal function are normal on admission. Purified protein derivative (PPD) is placed and sputum cultures are obtained, which grow *Mycobacterium tuberculosis*. He is started on clarithromycin, rifampin, and ethambutol. Two weeks after starting therapy, his daily fevers recur. Three days later, patient 3's renal function deteriorates suddenly. His serum creatinine level increases from 1.0 to 1.5 mg/dL. During the next 3 days, the serum creatinine increases by approximately 0.2 mg/dL daily. No skin rash is present. Urinalysis reveals 5 to 8 leukocytes per high-powered field (hpf) and is positive for erythrocytes. Eosinophils are detected by Hansel stain. The patient is nonoliguric, and his fractional excretion of sodium is greater than 1%.

- **What is the most likely cause of patient 3's renal failure?**
  - A) ATN
  - B) Septic embolization to the kidney
  - C) Acute interstitial nephritis (AIN)
  - D) Cholesterol embolization
  - E) Urinary tract obstruction

DISCUSSION

The correct answer is C. AIN is a relatively common cause of ARF. Although renal biopsies are done

Table 3. Causes of Acute Interstitial Nephritis

Infections	**Drugs**
Bacterial	β-Lactam antibiotics
Streptococcus	Rifampin
Corynebacterium diphtheriae	Ethambutol
Brucella	Erythromycin
Pneumococcus	Tetracycline
Campylobacter	Acyclovir
Staphylococcus	NSAIDs
Mycobacterium tuberculosis	Diuretics
Rickettsia rickettsii	Captopril
Viral	Sulfonamides
HIV	Indinavir (Crixivan)
Epstein-Barr virus	**Other**
Paramyxovirus	Systemic lupus erythematosus
Cytomegalovirus	Idiopathic
Hantaan virus	Interstitial nephritis uveitis syndrome
Parasitic	
Toxoplasma	
Mycoplasma	
Legionella	

NSAIDs = nonsteroidal anti-inflammatory drugs.

infrequently in the typical clinical setting of ARF, they are sometimes performed in study situations. Such studies have shown that approximately 15% of renal biopsies for ARF showed AIN.[25,26] Obviously, the number of actual cases is significantly higher because not all patients with ARF have a renal biopsy.

There are many causes of AIN; a partial listing is included in **Table 3**. The 2 primary causes are infectious agents and drugs—often the drugs used to treat the infectious agents.[27] The other 2 recognized causes are collagen vascular diseases and the idiopathic group. β-Lactam antibiotics and NSAIDs are the 2 most common types of drugs associated with AIN. Methicillin is the classic model used to describe AIN, although this drug is no longer commonly used. The etiology of AIN is important to know, when possible, because the primary treatment is to remove the offending agent.

- **Which of the following is not a component of the classic presentation for AIN?**

A) Rash
B) Fever
C) Increased erythrocyte sedimentation rate (ESR)
D) Eosinophilia

DISCUSSION

The correct answer is C. Clinically, the classic triad of rash, fever, and eosinophilia is now only seen in a few patients.[25,28] This triad was most associated with methicillin in the original reports of AIN. ESR may be nonspecifically increased in a few patients with AIN, but it is not part of the classic triad.[28] AIN is a pathologic diagnosis and not a clinical syndrome. Therefore, most patients will have nonspecific complaints in the setting of rapidly declining renal function and administration of a new drug. About 50% may experience flank or abdominal pain, nausea, or anorexia.[28]

AIN occurs in the tubulointerstitial component of the kidney, which consists of the tubules, vascular structures, interstitial cells, and extracellular matrix. This comprises 80% of renal tissue. During AIN, T-lymphocytes infiltrate this tissue, mainly helper T-cells.[29] Biopsy reveals this inflammation along with other inflammatory cells. Occasionally, immune complexes will be seen in patients with underlying immune disorders. The target of the inflammation can be normal renal antigens or may involve molecular mimicry. Drug/hapten conjugates or microbial antigens stimulate the attack in most cases.

DIAGNOSIS OF AIN

On urinalysis, eosinophiluria is the diagnostic hallmark for AIN. However, this finding is seen in many other disease states (**Table 4**). The sensitivity and specificity of eosinophiluria for AIN have been reported to be 40% and 72%, respectively.[30]

Sterile pyuria is necessary to implicate AIN as the cause of increased urinary leukocyte count in the setting of ARF. Therefore, Hansel stain is useful only in cases that demonstrate more than 1 to 4 leukocyte count/hpf. Hansel stain, however, is about 5 times more sensitive in detecting eosinophils in urine than Wright stain.[31] Microscopic hematuria is more commonly seen than eosinophiluria in AIN,[27,32,33] but gross hematuria is uncommon. Proteinuria is always present but usually in sub-nephrotic ranges.[27] NSAID-induced AIN may have nephrotic range proteinuria in cases with coexisting glomerular injury. Other laboratory findings that are sometimes present include anemia, ESR more than 50 mm/hr, hyperchloremic metabolic acidosis, or hyperkalemia.

- **What is the best way to treat patient 3?**
  - A) Continue rifampin because symptoms are known to resolve over time
  - B) Remove the offending medication
  - C) Continue rifampin and dialyze until antibiotic course is completed
  - D) Administer an intravenous diuretic

Discussion

The correct answer is B. Management for AIN is either discontinuing the offending agent or treating the instigating disease process. If a patient fails to improve, renal biopsy should be done before initiating therapy with immunosuppressive drugs. Corticosteroids are most often used although this therapy has not been proven by randomized clinical trials. The recommended dose of oral prednisone is 1 mg/kg daily for a therapeutic trial of approximately 4 weeks.[25] The duration of therapy may not be effective because fibrosis is seen in AIN kidneys within 10 days to 2 weeks. If oral steroids fail, a trial of cyclophosphamide may be beneficial. If antibodies are seen in electrophoresis of the biopsy tissue, plasmapheresis may be used; however, this method of treatment is anecdotal.

PROGNOSTIC INDICATORS OF AIN

The prognosis of AIN is generally favorable. Depending on the magnitude of renal injury, most patients will recover complete renal function within 1 year. The diverse causes of AIN, however, make arriving at an overall prognosis difficult. Of the patients who have undergone renal biopsy, a diffuse interstitial infiltrate has correlated with a worse prognosis and a patchy infiltrate has a better prognosis.[25] Longer duration of ARF and older adult age at onset also are indicators of a worse prognosis.[34] Renal function typically improves rapidly in the first 6 to 8 weeks and then at a slower rate for the remainder of the first year after diagnosis. Renal function generally stabilizes thereafter. Patients with drug-induced AIN may need dialysis before improving, especially with rifampin-induced AIN.[35]

Table 4. Causes of Urine Eosinophilia

Prostatitis
Rapidly progressive glomerulonephritis
Bladder carcinoma
Renal atheroembolic disease
Postinfectious glomerulonephritis
Acute tubular necrosis
Acute pyelonephritis
Acute interstitial nephritis
Acute cystitis

CASE PATIENT 3 FOLLOW-UP

The patient is diagnosed with AIN. Rifampin is the suspected etiology, and he is switched to rifabutin. His renal function continues to worsen and eventually he needs daily dialysis for 1 week. He is discharged from the hospital, and renal function returns almost to baseline by 1 year.

V. CHOLESTEROL EMBOLIZATION TO KIDNEYS

CASE PATIENT 4 PRESENTATION

Patient 4 is a 72-year-old woman with extensive atherosclerosis. Her medical history includes a previous stroke, hypertension of 3 years duration, hyperlipidemia, and tobacco abuse. She has previously been diagnosed with an abdominal aortic aneurysm (4.7 cm × 4.8 cm) and superior mesenteric artery (SMA) stenosis (> 70%) by Doppler study. The patient's medications consist of omeprazole, simvastatin, metoprolol, and lisinopril. On admission, her electrolytes are within normal limits. Her BUN and serum creatinine are 20 mg/dL and 1.4 mg/dL, respectively.

The day after her admission to the surgical service, she has an aortoiliac bypass, a bilateral renal artery bypass, and an aortic SMA bypass. The aortic pathologic

specimen is described as being "severely atherosclerotic." She develops ARF in the postoperative period. Within 3 days, her creatinine clearance decreases by 50%. Her toes and the distal half of both feet turn bluish-black (**Figure 1**). She also develops thrombocytopenia. The nephrology service is consulted at the nadir of her renal function. Her BUN and serum creatinine increase to 80 mg/dL and 2.8 mg/dL, respectively. She has decreased urine output and has gained 10 pounds since her admission. Urinalysis shows moderate hematuria, eosinophiluria seen by Hansel stain, 1+ proteinuria by dipstick, and a few hyaline casts. Because of her intravascular hypervolemic state, she is started on continuous venovenous hemofiltration. She is continued on daily dialysis for 2 weeks without significant improvement.

- **What is the most likely cause of patient 4's renal failure?**
  - A) Intraoperative hemodynamic instability that was not reported
  - B) ATN
  - C) Septic emboli to kidneys
  - D) Cholesterol embolization to kidneys
  - E) AIN

DISCUSSION

The correct answer is D. A very important but often overlooked cause of ARF is cholesterol crystal embolization, along with other forms of atheroembolism that will not be discussed here. Analyses have been done to better delineate certain risk factors for cholesterol embolization. In one analysis of 52 patients in Italy, men were diagnosed more often than women by about 5.5:1.[36] This study and a same-size study from Brigham and Women's Hospital both showed the average age to be approximately 68 years.[36,37] Characteristics of the typical patients experiencing cholesterol embolization include history of smoking in 90% to 100% of patients,[36,37] hypertension, and known vascular disease. Rarely, cholesterol embolization can occur in younger patients, spontaneously, or in a person without previously identified risk factors.[38]

The emboli are cholesterol crystals, and therefore, occur in patients with severely atherosclerotic vessels, specifically the aorta. Typically, a vascular procedure is the initiator of this cascade. Although angiography is the most common cause, abdominal aortic aneurysm repair, aorto-iliac, and aortofemoral bypass are other frequent causes. The turbulence of the blood flow after incisions or cross-clamping of the large, diseased vessel causes pieces of the soft, loose material to dislodge and embolize to the smaller vasculature in the kidney, leading to infarction. Other likely procedures to cause atheroembolism are intraaortic balloon pumps and angioplasty. Warfarin and heparin also have been implicated in this process because they prevent a thrombus from forming over an ulceration in a vessel and allow debris from the ulceration to freely flow distally.[36] Anticoagulating a patient with cholesterol embolization to the kidney may make the problem worse and is a relative contraindication. For similar reasons, thrombolysis may also cause cholesterol embolization.[36,39] The left kidney is slightly more prone to insult because of the short, straight path from the abdominal aorta to the kidney, analogous to the straight path down the right bronchus in aspiration.

- **What other signs in patient 4 support the diagnosis of cholesterol embolization?**
  - A) Black or blue toes or involvement of soles
  - B) Hematemesis or gastro-occult positive
  - C) Flank pain
  - D) Livedo reticularis
  - E) All of the above are possible signs of cholesterol embolization

DISCUSSION

The correct answer is E. Clinically, patients with cholesterol embolization can present with signs indicative of emboli to any organ system. For example, emboli to the skin may cause necrosis or livedo reticularis,[40] and emboli to the gastrointestinal tract may cause vomiting, hematemesis, abdominal pain, or pancreatitis.[36] Sudden onset of acute flank pain is another warning sign. The acute loss of renal function typically starts between 2 and 5 weeks post-procedure but commonly manifests immediately after the procedure and then progressively declines at a slower rate. Urinalysis may show varying degrees of proteinuria but rarely shows eosinophils with Hansel stain. The urine is most likely to be nonspecifically abnormal. Other laboratory data include transient eosinophilia and hypocomplementemia,[41] leukocytosis, thrombocytopenia, and anemia.[36] The spectrum of renal involvement is variable. When abdominal aortic aneurysm repairs were first being performed in the 1950s, mortality was high and renal atheroembolism was the most common cause.[42] Today, some patients may only be mildly impaired; however, many will progress to dialysis.[36] Approximately 35% to 45% of patients with cholesterol embolization will require dialysis, and of those patients, very few are able to regain and maintain long-term renal function.[36,37]

Diagnosis and Treatment of Cholesterol Embolization

Biopsy of affected tissues is the antemortem and postmortem procedure for definitive diagnosis of

atheroembolism. With its variable presentation, a high degree of vigilance for patients in the proper setting is necessary for diagnosis. In 3 case reports, hydroxy methylglutaryl coenzyme A (HMG CoA) reductase inhibitors have been anecdotally shown to reverse this form of renal damage.[43] Conclusions are based on the correlation of administration of a statin drug and the return of renal function in one patient. In one report, pentoxifylline was beneficial.[44] Although encouraging, large randomized trials are needed before these medications become the standard of care. Steroid use has been associated with very high mortality.[36]

Decreased mortality has only been demonstrated by providing proper supportive care and medical interventions.[45] The 3 major causes of death in these patients are repeated cholesterol emboli, heart failure, and cachexia. The management of these patients should include discontinuation of all anticoagulation, management of volume overload with either diuretics or dialysis, and provision of adequate nutritional support. Patients with such management have improved survival rates. Also, rapid management of fluid balance, nutrition, and hypertension in critically ill patients results in better outcomes.[45] In a relatively recent study of 67 patients with cholesterol embolization, the 1-year mortality rate was only 24%.[45] Incidentally, the investigators performed hemodialysis in the study patients with minimal or no anticoagulation. Cholesterol embolization remains a devastating disease process. With the exception of the study by Belenfant and colleagues,[45] 1-year mortality has ranged from 64% to 87%.[36,46]

VI. INTRARENAL AND POSTRENAL OBSTRUCTION

CASE PATIENT 5 PRESENTATION

Patient 5 is a 45-year-old woman who is admitted with acute respiratory distress. No renal dysfunction is present on admission, and she has no pertinent medical history. The previous week, she had been given antibiotics for presumed bronchitis but did not improve on that therapy. Her sick contacts include 2 nieces with chicken pox, to which patient 5 has no previous exposure. In light of her diffuse skin lesions consistent with chicken pox and the diffuse bilateral infiltrates on chest radiograph, she is started on intravenous acyclovir to treat varicella pneumonia. On day 4 of treatment, her BUN increases from 22 to 50 mg/dL and her serum creatinine increases from 1.0 to 1.6 mg/dL. Microscopic examination of the urine reveals needle-shaped birefringent crystals.

- **What is the most likely cause of patient 5's renal failure?**
  - A) Acyclovir-induced renal toxicity
  - B) Renal failure because of varicella
  - C) Uric acid nephropathy
  - D) Prerenal ARF because of third spacing

DISCUSSION

The correct answer is A. Renal obstruction is an important cause of postrenal ARF and is often induced by medications (eg, acyclovir). Postrenal ARF has its own classification scheme based on the location of the obstruction (**Table 5**). Normal urine output, oliguria, or anuria may be observed, depending on the cause. Patient 5 is a previously healthy woman who now has varicella pneumonia. She has no identifiable reason to have third-space fluid. Finally, varicella does not cause renal failure.

INTRINSIC OBSTRUCTIVE RENAL FAILURE

Obstruction can be intrinsic to the urinary tract. Intrarenal obstruction is often medication induced (eg, sulfadiazine, ritonavir, sulfamethoxazole, methotrexate, or acyclovir), as can be seen with patient 5.[47] Uric acid nephropathy is identified by characteristic crystals in the urine. Uric acid crystals are rhombic or rosette-shaped as opposed to the needle-shaped crystals seen when acyclovir precipitates in the tubules. Tubular obstruction and subsequent renal hypoxia/damage are also caused by paraproteins in patients with multiple myeloma or by precipitation of pigmented substances in those with rhabdomyolysis.[48] Volume depletion is a risk factor for renal injury by these substances. ARF associated with hyperuricemia is rare outside the setting of a malignancy or tumor lysis syndrome.[49] Administration of a xanthine oxidase inhibitor, such as allopurinol, will help decrease the rate of catabolism and the uric acid load on the kidneys.

Ethylene glycol intoxication may occur. Alcohol dehydrogenase in the liver initiates the conversion of ethylene glycol to oxalate. The oxalate crystals occlude the renal tubules and result in ARF. The needle-shaped birefringent calcium oxalate monohydrate crystals or the octahedral envelope-shaped calcium oxalate dihydrate crystals can be viewed by light microscopy. These patients are often dialyzed. Fomepizole is a relatively new drug that inhibits alcohol dehydrogenase and has demonstrated good results thus far in the treatment of ethylene glycol intoxication.[50]

Massive ingestion of vitamin C can cause intrarenal obstruction because vitamin C is converted to oxalate as well. Cases have been reported in which people taking large amounts of vitamin C, to self-medicate respiratory

Table 5. Common Causes of Obstructive Uropathy by Age and Level of Obstruction

Obstruction	Infants and Children	Adults
Urethra or bladder neck	Meatal stenosis	Urethral stricture (male)
	Phimosis	Benign prostatic hypertrophy
	Urethral valves (male)	
Bladder	Neurogenic bladder	Neurogenic bladder
	Calculus (Southeast Asia)	Blood clot
	Blood clot	Carcinoma of the bladder
		Foreign body
		Calculus
Ureter	Stricture (congenital)	Calculus (male predominance)
	Ureterocele	Blood clot
	Megaureter	Renal papilla
	Blood clot	Stricture—tuberculosis, radiation
	Retroperitoneal tumor	Vesicoureteral reflux (mainly females)
	Vesicoureteral reflux (mainly females)	Carcinoma of the prostate
		Retroperitoneal tumor
		Retroperitoneal fibrosis
		Pelvic neoplasm—carcinoma of the cervix
		Pregnancy, uterine prolapse
		Inflammatory bowel disease
		Abdominal aortic aneurysm
		Surgical ligation
		Carcinoma of the ureter
Ureteropelvic junction and renal pelvis	Congenital stricture	Calculus
	Aberrant renal artery	Blood clot
	Blood clot	Renal papillary tissue
		Aberrant renal artery
		Fibrous band

Adapted with permission from Sehrier RW, Gottschalk CW, editors. Diseases of the kidney. Boston: Little, Brown & Co.; 1997:709.

tract infections or through alternative therapists, have induced massive ARF.[51]

Rhabdomyolysis is seen in crush injuries, cocaine use, after seizures, with prolonged immobilization, or by any of several infectious agents.[52] The injured muscle releases heme and myoglobin. These substances cause most of their damage indirectly by inducing renal vasoconstriction, production of free radicals, and cast formation that obstructs the flow of urine. Injured muscle can cause extravasation of fluid to the injured area thereby compounding renal injury by decreasing extracellular volume. Treatment of rhabdomyolysis includes intravenous hydration and alkalinization of the urine until the acute phase is resolved. Alkalinization is important because the crystals are more soluble in an alkaline environment and are less likely to obstruct the renal tubules. Treating the underlying disorder or removing the offending medication is the preferred management for this type of renal injury. Fluid resuscitation is the most important recommended measure, along with alkalinizing the urine for treating rhabdomyolysis and urate nephropathy.

EXTRINSIC OBSTRUCTIVE RENAL FAILURE

- **Which of the following is not a cause of extrinsic obstructive uropathy producing renal failure?**
  A) Pregnancy
  B) Obesity
  C) Prostatic hyperplasia

D) Retroperitoneal fibrosis
E) Kidney stones

Discussion

The correct answer is B. Extrinsic obstruction can cause renal failure. This type of compression is most often caused by pregnancy in women of childbearing age. In older men, the most common cause is prostatic hyperplasia. Therefore, in the older man presenting with community-acquired ARF, a urinary catheter must be placed initially to check residual volume and to rule out distal urinary tract obstruction. Other notable causes of extrinsic compression leading to postrenal ARF include prostatic carcinoma, retroperitoneal fibrosis, or other impinging tumors. Retroperitoneal fibrosis (RPF) is more often seen in men than women. It is associated with methysergide, malignancy, β-blocker therapy, and abdominal aortic aneurysms. Back pain, flank pain, and nonspecific abdominal pain are commonly reported symptoms in patients with RPF.[53] Patients diagnosed with RPF are most commonly in their sixties or fifties, in that order. CT scan is the diagnostic procedure of choice for RPF, although magnetic resonance imaging is sensitive as well. Surgical treatment options include debulking or uterine stenting. Medical options for management include steroids or steroid-sparing agents (ie, azathioprine, mycophenolate mofetil, or tamoxifen).[53]

Kidney stones are most often seen in adult males. ARF will only ensue if bilateral stones are present or if the patient has only one kidney. Intermittent colicky pain coming in waves is the classic presentation for kidney stones. Increased serum or urine calcium levels and urinary tract infection with urea-splitting organisms, such as *Proteus mirabilis,* are risk factors. Plain abdominal film is an appropriate starting point in diagnosis, depending on the suspected etiology. Although approximately 80% of kidney stones are radiopaque, the abdominal film sensitivity is only around 50% and the specificity is about 70%.[54] Intravenous pyelography (IVP) has a specificity of 92% to 94% and a sensitivity on average of 70%.[54] The drawbacks of IVP are the possibility of missing stones that are not radiopaque and/or too small to create a filling defect and the potential nephrotoxicity associated with the contrast in a potentially dehydrated patient. The non-contrast helical CT scan has the best sensitivity at 95% to 100%, with similar specificity; it is now the imaging study of choice.[54] Additionally, other information about the collecting system and potential pathology outside the urinary tract are provided when using helical CT.

- **What findings in patient 5 would lead you to pursue a workup of nephrolithiasis instead of acyclovir toxicity?**

A) Acute colicky pain
B) Hydronephrosis
C) Crystals in the urine
D) Normal abdominal radiograph

Discussion

The correct answer is A. Clinically, obstruction of the urinary tract presents as colicky flank pain because, in contrast to the abdominal viscera, the urinary tract is very well innervated. Physiologically, GFR declines rapidly after onset of complete obstruction. The afferent arteriole will dilate in an attempt to increase renal blood flow. With laboratory analysis, the BUN:creatinine ratio is very valuable for the diagnosis of postrenal obstruction. The BUN is disproportionately increased because of increased absorption from fluid that remains in the bladder due to stasis. The creatinine is absorbed more slowly so the BUN:creatinine ratio is typically increased to more than 15:1 to 20:1.[48] Although the creatinine also is increased in extracellular contraction, the serum value is greater in obstruction (ie, usually > 2.5 mg/dL). In acute obstruction, the kidneys are not morphologically changed; therefore, hydronephrosis may not be seen on ultrasound. However, emergency urology consultation is warranted when an acutely obstructed patient presents with anuria or other signs of complete obstruction or sepsis. If the obstruction is relieved within 7 days of onset, complete recovery of renal function is common.

VII. GUIDELINES FOR MANAGEMENT OF OBSTRUCTIVE ACUTE RENAL FAILURE

Because of the heterogeneity of causes and treatments, it is essential to determine the cause of ARF. The exclusion of prerenal or postrenal ARF is important at the outset. Often, the treatments are readily available and inexpensive (eg, saline or mechanical relief of obstruction). If an intrinsic cause is suspected and the etiology is not apparent, renal biopsy can be helpful for elucidating glomerular damage. A recent study evaluating the effect of renal biopsy on management of such patients showed 75% of cases had different management based on the results of the biopsy.[55] As mentioned earlier, biopsy is recommended whenever immunosuppressive or otherwise toxic medications are being considered as treatment.

Dopamine is an agent that is often recommended and thought to be effective in reversing ARF or improving urine output in oliguric patients. Although dopamine clearly exerts a diuretic effect, it has not been shown in clinical trials to change GFR or patient outcomes.[56] At

best, one trial showed a slight increase in diuresis, but this effect only lasted 48 hours.[57] Presumably, initial low-dose infusion of dopamine has primarily vasodilatory effects on the kidney. After prolonged, continuous infusion in patients with renal impairment, the serum level of dopamine is above the optimal range for deriving renal benefit, and only side effects are seen.

Other agents (including calcium channel blockers and atrial natriuretic peptides) have shown some benefit, although additional studies are needed before these agents can be recommended.[56] Mannitol has been shown to prevent ischemic damage in transplanted kidneys; however, it does not seem to prevent ischemic or toxic damage in native kidneys.[56] In fact, high-dose mannitol appears to precipitate ARF; thus, internists may want to avoid using it.[58]

Renal replacement therapy is a topic worthy of a dedicated discussion. Dialysis is indicated when hyperkalemia, metabolic acidosis, fluid overload, or symptomatic uremia with encephalopathy become apparent. Dialysis allows for tighter control of fluid and for metabolic control in critically ill patients and is advantageous from a nutritional standpoint.[56]

Studies have been done to evaluate different variables in patients with ARF to determine prognostic value. The results of the analyses have been conflicting. Age, hospitalization prior to ICU admission, sepsis, oliguria, and other factors have been evaluated for predictive value, but none has been consistently shown to be predictive of increased mortality.[59] Severity of illness has been most convincingly shown to be predictive of outcome, but the relevance of this fact in clinical practice is dubious.[59]

VIII. SUMMARY POINTS

- The etiologies of acute renal failure (ARF) are numerous and, therefore, are best categorized into prerenal, renal, and postrenal etiologies when evaluating patients.
- ARF caused by prerenal states accounts for about 50% of hospital-acquired ARF. Prerenal ARF can be caused by volume depletion, hypotension, edematous states, and localized renal ischemia. In the intensive care unit, the diagnosis is more often acute tubular necrosis from iatrogenic causes.
- The mortality associated with ARF is much greater when occurring in the inpatient setting and is associated with the degree of elevation of the serum creatinine level, degree of comorbidity, and lack of aggressive management of the patient's critical condition.
- In a patient presenting from the community with ARF, obstruction and prerenal causes must first be evaluated because they are the most likely causes in such patients.
- Contrast-induced acute renal failure (CIARF) is an important iatrogenic cause of ARF. Patients at high risk must be adequately hydrated before and after contrast administration.
- Eosinophiluria is the hallmark for acute interstitial nephritis. Other signs may include increased erythrocyte sedimentation rate (ESR), nonspecific abdominal or flank pain, nausea, or anorexia. The classic triad of rash, fever, and eosinophilia is rarely seen anymore.
- Cholesterol embolization is an often overlooked cause of renal failure. In patients with acute renal insufficiency who have recently had aortic manipulation or aortic catheterization procedures, looking for emboli to the skin and/or gastrointestinal tract as well as checking for acute flank pain can be useful confirmatory measures.
- Acute tubular necrosis is associated with a high fractional excretion of sodium; whereas, in prerenal ARF, urinalysis typically shows less than 1% fractional excretion of sodium.
- Normal urine output, oliguria, or anuria may be observed in obstructive ARF, depending on the cause.

REFERENCES

1. Choudhury D, Ahmed Z. Drug-induced nephrotoxicity. Med Clin North Am 1997;81:705–17.
2. Packer M, Lee WH, Medina N, Yushak M. Influence of renal function on the hemodynamic and clinical responses to long-term captopril therapy in severe chronic heart failure. Ann Intern Med 1986;104:147–54.
3. Swan SK, Rudy DW, Lasseter KC, et al. Effect of cyclooxygenase-2 inhibition on renal function in elderly persons receiving a low-salt diet. A randomized, controlled trial. Ann Intern Med 2000;133:1–9.
4. McGee S, Abernethy WB 3rd, Simel DL. The rational clinical examination. Is this patient hypovolemic? JAMA 1999;281:1022–9.
5. Epstein M. Hepatorenal syndrome: emerging perspectives of pathophysiology and therapy. J Am Soc Nephrol 1994;4:1735–53.
6. Ochs A, Rossle M, Haag K, et al. The transjugular intrahepatic portosystemic stent-shunt procedure for refractory ascites [published erratum appears in N Engl J Med 1995;332:1587]. N Engl J Med 1995;332:1192–7.

7. Punukollu RC, Gopalswamy N. The hepatorenal syndrome. Med Clin North Am 1990;74:933–43.
8. Shusterman N, Strom BL, Murray TG, et al. Risk factors and outcome of hospital acquired-acute renal failure. Clinical epidemiologic study. Am J Med 1987;83:65–71.
9. al-Khafaji A, Corwin HL. Acute renal failure and dialysis in the chronically critically ill patient. Clin Chest Med 2001; 22:165–74, ix.
10. Finn WF. Diagnosis and management of acute tubular necrosis. Med Clin North Am 1990;74:873–91.
11. Humes HD, Weinberg JM. The effect of gentamicin on antidiuretic hormone-stimulated osmotic water flow in the toad urinary bladder. J Lab Clin Med 1983;101:472–8.
12. Rose BD. Acute renal failure—prerenal disease versus acute tubular necrosis. In: Rose BD, editor. Pathophysiology of renal disease. 2nd ed. New York: McGraw-Hill; 1987:63–117.
13. Madias NE, Harrigton JT. Platinum nephrotoxicity. Am J Med 1978;65:307–14.
14. Deray G. Festschrift for Professor Claude Jacobs. Nephrotoxicity of contrast media. Nephrol Dial Transplant 1999; 14:2602–6.
15. Davidson CJ, Hlatky M, Morris KG, et al. Cardiovascular and renal toxicity of a nonionic radiographic contrast agent after cardiac catheterization. A prospective trial. Ann Intern Med 1989;110:119–24.
16. Townsend RR, Cohen DL, Katholi R, et al. Safety of intravenous gadolinium (Gd-BOPTA) infusion in patients with renal insufficiency. Am J Kidney Dis 2000;36:1207–12.
17. Kumik BR, Allgren RL, Genter FC, et al. Prospective study of atrial natriuretic peptide for the prevention of radiocontrast-induced nephropathy. Am J Kidney Dis 1998;31:674–80.
18. Nash K, Hafee ZA, Abrinko P, Hou S. Hospital acquired acute renal failure. J Am Soc Nephrol 1996;7:1376 [abstract].
19. Lehnert T, Keller E, Gondolf K, et al. Effect of haemodialysis after contrast medium administration in patients with renal insufficiency. Nephrol Dial Transplant 1998;13: 358–62.
20. Taylor AJ, Hotchkiss D, Morse RW, McCabe J. PREPARED: Preparation for Angiography in Renal Dysfunction: a randomized trial of inpatient versus outpatient hydration protocols for cardiac catheterization in mild-to-moderate renal dysfunction. Chest 1998;114:1570–4.
21. Solomon R, Werner C, Mann D, et al. Effects of saline, mannitol, and furosemide to prevent acute decreases in renal function induced by radiocontrast agents. N Engl J Med 1994;331:1416–20.
22. Katholi RE, Woods WT Jr, Taylor GJ, et al. Oxygen free radicals and contrast nephropathy. Am J Kidney Dis 1998;32:64–71.
23. Katholi RE, Taylor GJ, McCann WP, et al. Nephrotoxicity from contrast media: attenuation with theophylline. Radiology 1995;195:17–22.
24. Tepel M, van der Giet M, Schwarzfeld C, et al. Prevention of radiographic-contrast-agent-induced reductions in renal function by acetylcysteine. N Engl J Med 2000;343: 180–4.
25. Michel DM, Kelly CJ. Acute interstitial nephritis. J Am Soc Nephrol 1998;9:506–15.
26. Neilson EG. Pathogenesis and therapy of interstitial nephritis. Kidney Int 1989;35:1257–70.
27. Cameron JS. Allergic interstitial nephritis: clinical features and pathogenesis. Q J Med 1988;66:97–115.
28. Eapen SS, Hall PM. Acute tubulointerstitial nephritis. Cleve Clin J Med 1992;59:27–32.
29. Muller GA, Markovic-Lipkovski J, Frank J, Rodemann HP. The role of interstitial cells in the progression of renal diseases. J Am Soc Nephrol 1992;2(10 Suppl):S198–205.
30. Ruffing KA, Hoppes P, Blend D, et al. Eosinophils in urine revisited. Clin Nephrol 1994;41:163–6.
31. Nolan CR 3rd, Anger MS, Kelleher SP. Eosinophiluria—a new method of detection and definition of the clinical spectrum. N Engl J Med 1986;315:1516–9.
32. Linton AL, Clark WF, Driedger AA, et al. Acute interstitial nephritis due to drugs: review of the literature with a report of nine cases. Ann Intern Med 1980;93:735–41.
33. Sigala JF, Biava CG, Hulter HN. Red blood cell casts in acute interstitial nephritis. Arch Intern Med 1978;138: 1419–21.
34. Kida H, Abe T, Tomosugi N, et al. Prediction of the long-term outcome in acute interstitial nephritis. Clin Nephrol 1984;22:55–60.
35. Kelly CJ, Neilson EG. Tubulointerstitial diseases. In: Brenner BB, Rector FC, editors. Brenner and Rector's the kidney. 5th ed. Philadelphia: Saunders; 1996:1655–79.
36. Scolari F, Tardanico R, Zani R, et al. Cholesterol crystal embolism: a recognizable cause of renal disease. Am J Kidney Dis 2000;36:1089–109.
37. Thadhani RI, Camargo CA Jr, Xavier RJ, et al. Atheroembolic renal failure after invasive procedures. Natural history based on 52 histologically proven cases. Medicine 1995;74:350–8.
38. Domanovits H, Paulis M, Nikfardjam M, et al. Acute renal infarction: clinical characteristics of 17 patients. Medicine 1999;78:386–94.
39. Pirson Y, Honhon B, Cosyns JP, van Ypersele C. Cholesterol embolism in a renal graft after treatment with streptokinase. Br Med J 1988;296:394–5.
40. Falanga V, Fine MJ, Kapoor WN. The cutaneous manifestations of cholesterol crystal embolization. Arch Dermatol 1986;122:1194–8.

41. Lye WC, Cheah JS, Sinniah R. Renal cholesterol embolic disease. Case report and review of the literature. Am J Nephrol 1993;13:489–93.
42. Kassirer JP. Atheroembolic renal disease. N Engl J Med 1969;280:812–8.
43. Woolfson RG, Lachmann H. Improvement in renal cholesterol emboli syndrome after simvastatin. Lancet 1998; 351:1331–2.
44. Carr ME Jr, Sanders K, Todd WM. Pain relief and clinical improvement temporally related to the use of pentoxifylline in a patient with documented cholesterol emboli—a case report. Angiology 1994;65–9.
45. Belenfant X, Meyrier A, Jacquot C. Supportive treatment improves survival in multivisceral cholesterol crystal embolism. Am J Kidney Dis 1999;33:840–50.
46. Fine MJ, Kapoor W, Falanga V. Cholesterol crystal embolization: a review of 221 cases in the English literature. Angiology 1987;38:769–84.
47. Perazella MA. Crystal-induced acute renal failure. Am J Med 1999;106:459–65.
48. Martinez-Maldonado M, Kumjian DA. Acute renal failure due to urinary tract obstruction. Med Clin North Am 1990;74:919–31.
49. Conger JD. Acute uric acid nephropathy. Med Clin North Am 1990;74:859–71.
50. Sivilotti ML, Burns MJ, McMartin KE, Brent J. Toxicokinetics of ethylene glycol during fomepizole therapy: implications for management. For the Methylpyrazole for Toxic Alcohols Study Group. Ann Emerg Med 2000;36:114–25.
51. Mashour S, Turner JF Jr, Merrell R. Acute renal failure, oxalosis, and vitamin C supplementation: a case report and review of the literature. Chest 2000;118:561–3.
52. Visweswaran P, Guntupalli J. Rhabdomyolysis. Crit Care Clin 1999;15:415–28, ix–x.
53. Koep L, Zuidema GD. The clinical significance of retroperitoneal fibrosis. Surgery 1977;81:250–7.
54. Portis AJ, Sundaram CP. Diagnosis and initial management of kidney stones. Am Fam Physician 2001;63:1329–38.
55. Richards NT, Darby S, Howie AJ, et al. Knowledge of renal histology alters patient management in over 40% of cases. Nephrol Dial Transplant 1994;9:1255–9.
56. Thadani R, Pascual M, Bonventre JV. Acute renal failure. N Engl J Med 1996;334:1448–60.
57. Ichai C, Passeron C, Carles M, et al. Prolonged low-dose dopamine infusion induces a transient improvement in renal function in hemodynamically stable, critically ill patients: a single-blind, prospective, controlled study. Crit Care Med 2000;28:1329–35.
58. Visweswaran P, Massin EK, DuBose TD Jr. Mannitol-induced acute renal failure. J Am Soc Nephrol 1997;8: 1028–33.
59. Brivet FG, Kleinknecht DJ, Loirat P, Landais PJ. Acute renal failure in intensive care units—causes, outcome, and prognostic factors of hospital mortality: a prospective, multicenter study. French Study Group on Acute Renal Failure. Crit Care Med 1996;24:192–8.

Chapter 2—Scabies: A Case Study

David R. Adams, MD

I. INTRODUCTION

Scabies is a contagious dermatitis caused by infestation with the *Sarcoptes scabiei* mite. The dermatitis is caused by a delayed cutaneous hypersensitivity reaction to the mite.[1–6] This condition typically presents with generalized severe, persistent pruritus that can be distressing to patients and is often their reason for seeking care. Mites are usually spread by skin-to-skin contact, although the organism can live on inanimate objects such as clothing or furniture for up to a few days. Because skin findings are variable, a diagnosis of scabies is easily missed. The condition may persist for years if undiagnosed.

II. CASE PATIENT 6

Patient 6 is a 74-year-old obese man with stable diabetes, hypertension, and hypercholesterolemia who presents to his internist before his next scheduled appointment with what he calls "the worst itch of my life." Examination reveals that patient 6 has dry skin and hemosiderin deposits on his lower legs. Faint red papules with a few excoriations are found on his abdomen and arms. Patient 6 reports that his itching started about 6 weeks ago and is worse at bedtime. Three months before the onset of itching, he was started on atorvastatin for elevated cholesterol. No other pertinent changes in medications or health history are noted. About 1 month before the rash began, patient 6 stayed with his son's family in New York for 1 week.

The physician discontinues atorvastatin for patient 6 and schedules a follow-up examination. At follow-up, patient 6 reports worsened itching despite the discontinuation of atorvastatin and the use of over-the-counter treatments. During this visit, the rash is noted to involve his penis, and more extensive involvement is noted on his torso and extremities. A dermatologic consultation is ordered.

Patient 6 and his wife both present to the dermatologist at their wits' end. The patient says he has never had such persistent itching, and his wife is now experiencing similar symptoms. Skin examination reveals similar findings observed by his internist with the exception of one linear "burrow" and a few small papules on patient 6's right hand and wrist (**Figure 2**). A careful scraping sample is taken using mineral oil. Microscopic examination of this scraping reveals a single moving *S. scabiei* mite, oval eggs, and mite feces (**Figure 3**).

- **What are the most notable features of patient 6's history and physical examination?**
- **What is involved in a differential diagnosis of scabies?**

DISCUSSION

History, Physical Examination, and Diagnosis

Patient 6's history is most pertinent for the "worst itch of his life." Important aspects of patient 6's history are (1) the fact that his itching and rash did not resolve after discontinuation of his anticholesterol medication, which can cause such symptoms, and (2) his stay with his son's family, where the scabies infestation was most likely acquired. Anyone can be affected by scabies, but the condition is most commonly seen in patients with HIV and in those who are elderly, immunosuppressed, or institutionalized. Itching often occurs after 1 month of infestation, when a delayed immune response to mite antigen occurs. Household members often acquire scabies, as did patient 6's wife. Associated pruritus is often worse at bedtime and can interfere with or prevent sleep.[1–6]

In cases of scabies, skin examination ranges from no apparent rash to generalized erythroderma. Excoriations are often noted from intense itching. Secondary impetiginization can occur and, rarely, cellulitis or bacteremia can complicate an infestation. When patient 6 first presented to his physician, he appeared to have itching out of proportion with his initial rash, an indicator of potential scabies. Gradually, his rash has become more extensive (**Figure 4**). Patient 6 does have stasis dermatitis on his lower extremities, but this rash has no relation to the scabies infestation. The papular eruption on his penis is another clue that suggests scabies, and the single burrow on his wrist is the most diagnostic finding from the skin examination. Scabies mites are often found between fingers, on wrists or feet, near the axilla or antecubital fossa, around the belt-line or umbilicus, around nipples in

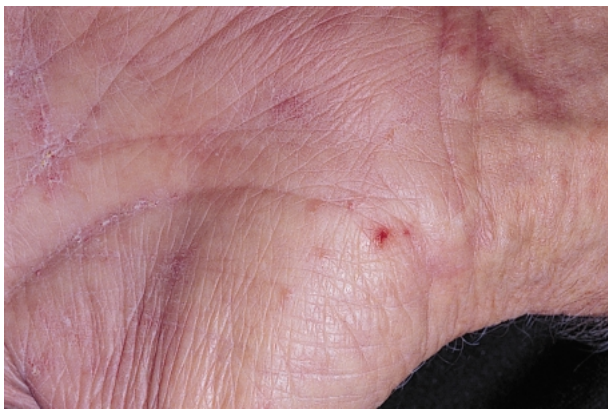

Figure 2. Scabies burrow and papules on patient 6's right hand and wrist.

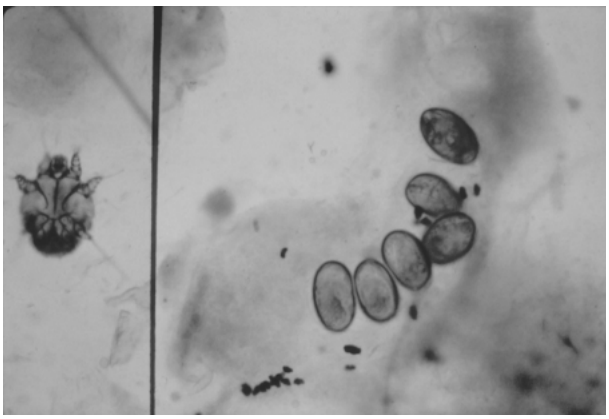

Figure 3. Microscopic examination of scabies preparation from patient 6's hand (see Figure 2), which reveals mite, eggs, and feces.

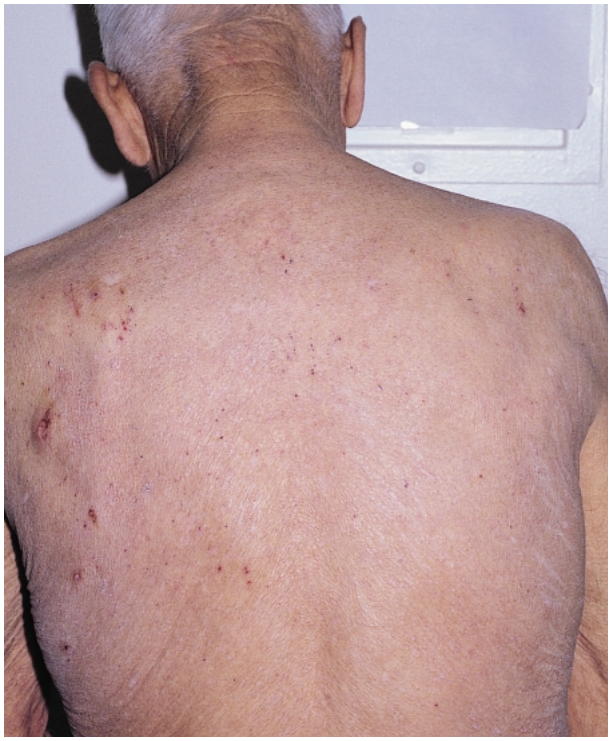

Figure 4. Scabies infection in patient 6 before treatment.

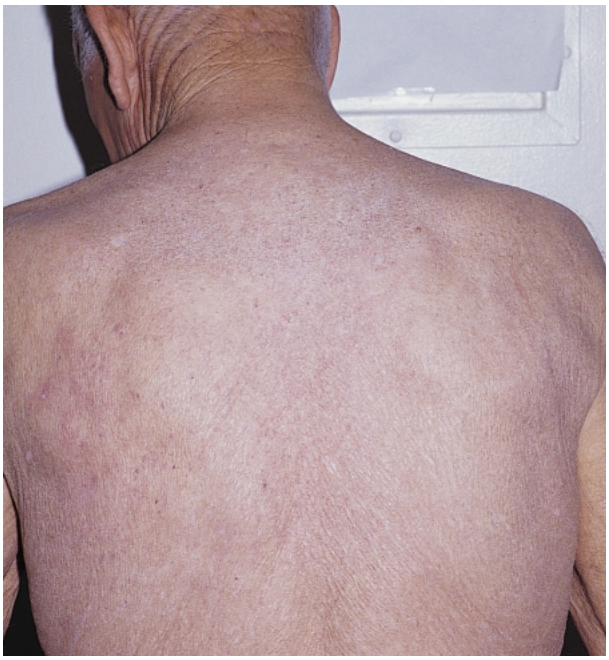

Figure 5. Patient 6's torso 1 month after treatment with permethrin 5% cream. Note that the scabies infection has resolved.

women, and on the penis in men.[1–3] Mites also hide under jewelry (eg, rings and watchbands) and can be found under fingernails from scratching. In crusted or "Norwegian" scabies, large areas of the body, including the face, can be affected and have a very crusted appearance, harboring many live mites. This type of scabies can also occur in patients with HIV as well as in elderly and institutionalized patients.

Differential diagnosis of scabies includes drug reaction, atopic dermatitis, neurotic excoriations, pruritus secondary to systemic disease, impetigo, contact dermatitis, and other similar conditions.[5] In patient 6's case, a definitive diagnosis was made by scraping the papule at the end of the burrow with a #15 blade and mineral oil and applying the specimen to a glass slide. Microscopic examination revealed the live adult mite. Sometimes, mite parts are seen under a microscope, as are oval mite eggs and feces (scybala).

III. TREATMENT

- **What are the best treatment options for scabies?**

The most effective treatment is permethrin 5% cream (Elimite), applied to the entire body from the neck down at bedtime and washed off in the morning; this formulation is available only by prescription.[1–3,6–8] This indication is approved by the Food and Drug Administration (FDA). All household members should be treated simultaneously; repeated therapy is often recommended after 1 week. Recently worn clothing, bed linens, and towels should be washed and machine dried after treatment. Of note, transient burning and stinging can occur from permethrin application.

Lindane 1% (Kwell) lotion can also be used for scabies, with overnight application similar to permethrin.[1–3,5,6] However, lindane has been reported to cause neurologic toxicity and is not recommended for infants, children, pregnant or nursing women, or patients with seizure disorders. Compounded precipitated sulfur 6% to 10% ointment, applied nightly for 3 nights, has been used and is considered safe and effective for infants, pregnant women, or lactating women.[1–3] However, this preparation is messy and staining, and the odor is bothersome. Oral ivermectin, although not approved for scabies by the FDA, is reportedly effective against Norwegian scabies when the agent is used as a single dose of 200 µg/kg (two 6-mg tablets for an adult weighing 60 kg).[1–3] Ivermectin can be repeated weekly for 2 to 3 total doses.

Antihistamines, such as diphenhydramine or hydroxyzine, can be given at bedtime to ease itching and to help patients sleep. Medium-potency topical corticosteroids (eg, triamcinolone) can be used after scabies treatment until itching resolves, which can be up to 1 month after treatment.[5]

At 1-month follow-up, after permethrin therapy is completed, patient 6 is free of itching. Only xerosis is noted on skin examination (**Figure 5**).

IV. INDICATIONS FOR REFERRAL TO A DERMATOLOGIST

Internists can often treat patients with scabies. However, a referral to a dermatologist is suggested when any of the following conditions are present.

(1) Unexplained pruritus that is unresponsive to usual therapy

(2) Persistent rash in a patient without a chronic skin condition

(3) Suspected scabies despite negative scabies preparation and/or lack of response to usual treatments

V. SUMMARY POINTS

- Scabies dermatitis is caused by a delayed cutaneous hypersensitivity reaction to the *Sarcoptes scabiei* mite. Often, symptomatic itching develops several weeks to 1 month after infestation. Manifestations range from minimal or no rash to an extensive red, papular rash with excoriations, secondary infection, and extensive crusting.
- Transmission of scabies is usually through close human-to-human contact.
- Diagnosis is often difficult, and some scabies cases may go undiagnosed for years. Hints of possible scabies infestation include location of rash (wrists, between fingers, waistline, male genitalia, around nipples in females but usually not on the scalp and face except in Norwegian scabies), a history of itching in multiple family members, and contact with another person with scabies.
- When checking for scabies, examine the patient carefully for burrows. A scraping with mineral oil can reveal a mite, eggs, or feces.
- If a patient is diagnosed with scabies, treat all members of that patient's household with an overnight application of permethrin 5% cream (Elimite). Repeat therapy in 1 week. All recently worn clothing, bed linens, and towels should be thoroughly washed and dried.

BOARD REVIEW QUESTIONS

Choose the single best answer for each question.

1. **Diagnosing scabies can be difficult. Which of the following is NOT a clue to diagnosis?**
   A) History of the patient seeing and feeling insects on the skin
   B) Location of itching and rash
   C) Discovery of burrows
   D) Itching in multiple family members

2. **Treatment for scabies can include all of the following EXCEPT:**
   A) Applying permethrin cream
   B) Vigorously scrubbing the skin

C) Taking antihistamines for itching
D) Washing clothing

ANSWERS

1. A 2. B

REFERENCES

1. Brown TJ, Yen-Moore A, Tyring SK. An overview of sexually transmitted diseases. Part II [published erratum appears in J Am Acad Dermatol 2000;421(1 Pt 1):148]. J Am Acad Dermatol 1999;41(5 Pt 1):661–77.
2. Chosidow O. Scabies and pediculosis. Lancet 2000;355: 819–26.
3. Burkhart CG, Burkhart CN, Burkhart KM. An epidemiologic and therapeutic reassessment of scabies. Cutis 2000; 65:233–40.
4. Lookingbill DP, Marks JG Jr. Principles of dermatology. 3rd ed. Philadelphia: WB Saunders; 2000.
5. Fitzpatrick TB, Johnson RA, Wolff K, et al. Color atlas and synopsis of clinical dermatology: common and serious diseases. 3rd ed. New York: McGraw Hill; 1997.
6. Sams WM Jr, Lynch PJ, editors. Principles and practice of dermatology. 2nd ed. New York: Churchill Livingstone; 1996.
7. Taplin D, Meinking TL. Pyrethrins and pyrethroids in dermatology. Arch Dermatol 1990;126:213–21.
8. Taplin D, Porcelain SL, Meinking TL, et al. Community control of scabies: a model based on use of permethrin cream. Lancet 1991;337:1016–8.