

Highlights from *ACP Journal Club*

MODS assay accurate but expensive in detecting TB

The microscopic-observation drug-susceptibility (MODS) assay proved a faster and more accurate way of detecting tuberculosis (TB) in a recent study of almost 2,000 patients.

In the study by Moore and colleagues, which was reported in the Oct. 12, 2006, issue of *The New England Journal of Medicine*, 1,980 patients 18 years or older presenting at hospitals and clinics in Lima, Peru, provided two sputum samples each. The samples were analyzed using the MODS assay, the automated mycobacterial culture or the Lowenstein-Jensen culture.

Overall, 10.7% of the samples tested positive for TB. The MODS assay had a sensitivity of 97.8%, compared with 89% for automated mycobacterial culture and 84% for Lowenstein-Jensen culture. In addition, the MODS assay was faster in identifying drug-resistant strains (7 days to positive test compared with 13 and 26 days, respectively).

Currently, sputum microscopy is the primary method for diagnosing TB in developing countries, where 95% of cases occur, said *ACP Journal Club* reviewer Oommen John, MD, of the Leprosy Mission Trust India in New Delhi. However, this method is slower than MODS assay and detects only half of the cases.

While the MODS assay has the potential to reduce transmission, there are some concerns, said Dr. John. Developing countries often cannot afford the sophisticated labs needed to safely perform MODS culture.

These countries also often do not have adequate infection control and biohazardous waste disposal methods, which are particularly important with MODS because the potential exposure time for health care workers is greater than with other methods that do not use microscopic culture techniques.

Further research is needed on using the MODS assay in resource-limited countries, said Dr. John, because physicians in these areas often rely on empirical treatment rather than lab diagnosis.

Star ratings: IM/Referred Care/Hospitalists, 6/7 stars.

Etoricoxib poses similar risks as diclofenac in arthritis

A recent study found that using the cyclooxygenase-2 (COX-2) inhibitor etoricoxib did not increase the incidence of major cardiovascular events compared with using the nonsteroidal anti-inflammatory drug (NSAID) diclofenac in patients with osteoarthritis or rheumatoid arthritis.

In the trial by Cannon and colleagues, which was reported in the Nov. 18, 2006, issue of *Lancet*, 34,701 patients with osteoarthritis or rheumatoid arthritis received either 60 or 90 mg of etoricoxib daily, 75 mg of diclofenac twice daily or 50 mg of diclofenac three times per day. The cardiovascular event rate per 100 patient-years was similar in all groups. The incidence of major gastrointestinal problems was higher in the diclofenac group.

COX-2 inhibitors were initially thought of as superior to traditional NSAIDs because they were less likely to cause gastrointestinal bleeding, noted *ACP Journal Club* reviewer Michael Denman, MD, of Northwick Park Hospital in Harrow, England. However, some studies subsequently showed that patients who received COX-2 inhibitors had higher incidences of myocardial infarction and cerebral thrombosis.

This study suggests that COX-2 inhibitors are as safe as NSAIDs. However, Dr. Denman advised against changing practice because the study compared a single COX-2 inhibitor with a single NSAID, and outcomes might vary among drugs in both classes.

In addition, the study did not account for the fact that rheumatoid arthritis is a risk factor for cardiovascular disease and that some patients in the study were taking corticosteroids.

As a result, physicians should continue to assess patients on an individual basis, said Dr. Denman. Future research should look at risk factors in susceptible patients rather than large heterogeneous groups, he suggested.

Star ratings: IM/Referred Care/Hospitalists, 6/7 stars.

Key Points

Case 1:

- Patients with chronic kidney disease have increased risk for acute renal failure because of their use of osmotic agents such as dextran 40, mannitol and sucrose-containing preparations of intravenous immune globulin.

Case 2:

- Antiretroviral therapy and plasmapheresis are indicated for patients with HIV infection and thrombotic thrombocytopenic purpura.

Case 3:

- Angiotensin-converting enzyme inhibitor therapy is warranted in patients with stage III and stage IV chronic kidney disease unless the creatinine level rises more than 30% after initiation of therapy.
- Once-daily dosing of ACE inhibitors can decrease the risk for hyperkalemia.

Case 4:

- Calcific uremic arteriopathy typically presents with painful violaceous nodules on the trunk, proximal extremities and buttocks.

patient demonstrated a more than 100% increase in the creatinine level, which should raise suspicion for bilateral renal artery stenosis or advanced intrarenal small-vessel disease.

The glomerular filtration rate (GFR) in patients with bilateral renal artery stenosis is maintained to a great extent by an angiotensin II-induced vasoconstriction at the efferent arteriole. Both ACE inhibitors and angiotensin-receptor blockers cause loss of efferent arteriolar vasoconstriction with a resultant decrease in the glomerular capillary pressure and GFR.

This patient's urine sediment is not sufficiently active to warrant a renal biopsy.

Discontinuation of enalapril would be favored over a dose reduction because of this patient's marked decline in GFR and the risk for subsequent ischemic renal injury. Magnetic

resonance angiography of the renal arteries would document the status of the renal arteries after discontinuing enalapril. However, percutaneous angioplasty for renal artery stenosis generally is reserved for patients who remain hypertensive despite aggressive pharmacologic therapy. Prospective randomized clinical trials have yet to definitively establish indications for intervening to preserve renal function or decrease cardiovascular complications. Losartan, an angiotensin-receptor antagonist, would be as likely as enalapril to cause a decrease in GFR.

Case 4

Correct answer: C.

The location and clinical presentation of this patient's lesions are most characteristic of calcific uremic arteriopathy, often termed "calciophylaxis." These lesions typically present as painful violaceous nodules on the trunk, proximal extremities and buttocks. Risk factors for development of this syndrome include use of warfarin, vitamin D analogues and calcium-based phosphate binders; an elevated calcium-phosphorus product; protein S or C deficiency; obesity; and female sex.

Calcinosis cutis presents with painless calcified subcutaneous nodules that do not ulcerate. Necrobiosis lipoidica diabetorum usually is asymptomatic, and the lesions associated with this condition typically appear as oval to irregularly shaped plaques on the shins of patients with diabetes. Venous stasis ulcers are shallow, red-based ulcers typically located medially in the lower leg. Warfarin-induced skin necrosis typically occurs early in the course of warfarin therapy, and lesions associated with this condition present as erythematous macules but progress to ulcers within hours.

The role of parathyroid hormone in the pathogenesis of calcific uremic arteriopathy remains uncertain. Therapy for this condition includes avoidance of vitamin D analogues and calcium-based phosphate binders, control of the phosphorus level with non-calcium-based phosphate binders, aggressive wound care and treatment of secondary infection. Parathyroidectomy is reserved for affected patients whose serum calcium and phosphorous levels cannot be controlled with phosphate binders and other medical interventions such as cinacalcet. ■

Answers and commentary

Case 1

Correct answer: A.

This patient has osmotic tubular injury due to dextran 40 use. This condition can present as oliguric or nonoliguric acute renal failure and also has been reported in patients treated with mannitol or sucrose-containing preparations of intravenous immune globulin. Patients with pre-existing renal insufficiency are at increased risk for developing this disorder. There are no clearly defined diagnostic urinary or laboratory findings associated with this condition, and renal biopsy is needed for definitive diagnosis.

Treatment of osmotic tubular injury generally is supportive, but patients with oliguria and sustained increases in plasma osmolality may benefit from plasma exchange to remove retained dextran 40 and thereby limit further renal injury.

This patient's urinary sediment findings show no muddy brown casts to support a diagnosis of acute tubular necrosis. The absence of hypotension and tachycardia on physical examination and during the surgery is not consistent with prerenal azotemia. Long-term ACE inhibitor therapy is unlikely to cause acute renal failure. Thrombotic microangiopathy is unlikely in the absence of thrombocytopenia and hemolytic anemia. However, because of this patient's recent use of clopidogrel therapy, this diagnosis should be considered. Preliminary evidence shows that IgG inhibitors of the von Willebrand factor–cleaving protease ADAMTS13 mediate clopidogrel-induced thrombotic thrombocytopenic purpura.

Case 2

Correct answer: C.

The most appropriate next step in this patient's management is plasmapheresis and antiretroviral therapy. This patient presents with the classic pentad of thrombocytopenia, anemia, neurologic symptoms, renal dysfunction and fever characteristic of thrombotic thrombocytopenic purpura. The peripheral blood smear shows schistocytes that indicate an underlying thrombotic microangiopathy.

A deficiency or decreased activity of the von Willebrand factor–cleaving protease ADAMTS13 plays an important role in the pathogenesis of thrombotic thrombocytopenic purpura–hemolytic uremic syndrome.

Decreased cleavage of large multimers of von Willebrand factor by ADAMTS13 synthesized in endothelial cells leads to the persistence of unusually large multimers of von Willebrand factor, which results in platelet activation and endocapillary thrombosis.

Decreased ADAMTS13 activity has been demonstrated in patients with HIV infection who have thrombotic thrombocytopenic purpura, possibly because endothelial production of ADAMTS13 by HIV-infected endothelial cells is decreased or because these patients produce an IgG inhibitor of ADAMTS13 activity.

Plasmapheresis has been shown to effectively ameliorate thrombotic thrombocytopenic purpura in this setting, and highly active antiretroviral therapy reduces the incidence of relapses. If plasmapheresis is not available, infusions of cryoprecipitate-free fresh frozen plasma may be helpful until plasma exchange can be performed. However, this intervention is not the preferred initial therapy.

Infusions of cryoprecipitate are contraindicated in this setting, because this fraction of plasma is enriched with von Willebrand factor. Platelet transfusions may worsen renal and neurologic complications and therefore generally are avoided. Renal biopsy is indicated for selected patients with atypical features in whom the diagnosis remains uncertain when thrombocytopenia is not a limiting factor; however, a clinical diagnosis can be established in this patient. Oral corticosteroids may be beneficial but are insufficient as the sole intervention.

Case 3

Correct answer: D.

This patient most likely has ACE inhibitor–induced prerenal acute renal failure. Therefore, the most appropriate initial step in this patient's management is discontinuing enalapril.

Generally, an increase in the creatinine level up to 30% is acceptable after initiation of ACE inhibitors or angiotensin-receptor blockers. A recent study demonstrated that continued ACE inhibitor therapy was associated with sustained renoprotective benefit in patients with stage III and IV chronic kidney disease. Therefore, continuation of ACE inhibitor therapy in patients with chronic kidney disease is indicated when possible. Once-daily administration of lower doses of these agents is initially indicated, as is measurement of the potassium and creatinine levels 7 to 10 days after initiation of therapy and then every 2 to 3 months. However, this

level, 129 mEq/L (129 mmol/L); potassium level, 3.2 mEq/L (3.2 mmol/L); chloride level, 88 mEq/L (88 mmol/L); bicarbonate level, 30 mEq/L (30 mmol/L); lactate dehydrogenase level, 7483 U/L (124.74 μ kat/L); and urinalysis results of 1+ leukocyte esterase, 1+ protein, trace blood and 5 to 10 dysmorphic erythrocytes per high-power field.

A peripheral blood smear is shown on the preceding page.

Which of the following is the most appropriate next step in this patient's management?

- A. Cryoprecipitate infusions
- B. Renal biopsy
- C. Plasmapheresis and antiretroviral therapy
- D. Oral corticosteroids

Case 3

A 60-year-old man with a 10-year history of hypertension is hospitalized for shortness of breath. Two weeks before admission, he developed headache and dyspnea on exertion. Medications include metoprolol and hydrochlorothiazide.

Physical examination on admission reveals a blood pressure of 180/120 mm Hg. Laboratory studies at that time showed a potassium level of 4.2 mEq/L (4.2 mmol/L) and a creatinine level of 1.5 mg/dL (132.63 μ mol/L).

Over the next 2 weeks, the blood pressure gradually normalizes after enalapril, 5 mg once daily, and amlodipine, 5 mg once daily, are added to his regimen. On follow-up examination, his blood pressure is 132/76 mm Hg.

Funduscopy examination shows arteriolar tortuosity. The PMI is laterally displaced. Cardiac examination reveals a right femoral systolic bruit. Distal pulses are 1+ bilaterally, and there is no peripheral edema.

Laboratory findings are as follows: blood urea nitrogen level, 45 mg/dL (16.07 mmol/L); creatinine level, 3.5 mg/dL (309.47 μ mol/L); sodium level, 140 mEq/L (140 mmol/L); potassium level, 5.1 mEq/L (5.1 mmol/L); chloride level, 105 mEq/L (105 mmol/L); bicarbonate level, 20 mEq/L (20 mmol/L); and urinalysis results of trace protein and several hyaline casts per high-power field.

Which of the following is the most appropriate initial step in this patient's management?

- A. Perform renal biopsy
- B. Decrease the enalapril dose to 2.5 mg/d
- C. Perform magnetic resonance angiography of the renal arteries
- D. Discontinue enalapril
- E. Switch enalapril to losartan

Case 4

A 49-year-old woman with end-stage renal disease is evaluated for painful ulcers involving both legs. Approximately 6 months ago, she noted nodular lesions on the right thigh and then the left. These lesions became progressively more painful and developed into ulcerative lesions over several months. She also has type 2 diabetes mellitus, atrial fibrillation and hypertension.

The patient has been maintained on long-term in-center hemodialysis for the past 6 years. Medications are warfarin; aspirin, 81 mg/d; enalapril; metoprolol; atorvastatin; calcium carbonate; calcitriol; and erythropoietin.

On physical examination, pulse rate is 86 beats/min and irregular and blood pressure is 140/90 mm Hg. She is obese. There are necrotic ulcers covering most of the thighs bilaterally.

Cardiac examination shows an irregularly irregular rhythm. The lungs are clear to auscultation. Abdominal examination is unremarkable. There is no peripheral edema.

Laboratory findings are as follows: hemoglobin level, 11.6 g/dL (7.2 mmol/L); leukocyte count, 15,000 cells/ μ L (15×10^9 cells/L); platelet count, 326,000 cells/ μ L (326×10^9 cells/L); international normalized ratio, 2.6; sodium level, 136 mEq/L (136 mmol/L); potassium level, 5.3 mEq/L (5.3 mmol/L); chloride level, 105 mEq/L (105 mmol/L); bicarbonate level, 19 mEq/L (19 mmol/L); calcium level, 10.1 mg/dL (2.52 mmol/L); and phosphorus level, 8.8 mg/dL (2.84 mmol/L).

Which one of the following is the most likely diagnosis?

- A. Calcinosi cutis
- B. Necrobiosis lipoidica diabetorum
- C. Calcific uremic arteriolopathy
- D. Venous stasis ulcers
- E. Warfarin-induced skin necrosis

Test yourself: Acute renal failure

The following four cases and commentary deal with evaluation of acute renal failure. They are excerpted from ACP's Medical Knowledge Self-Assessment Program (MKSAP14). For the correct answers, turn to page 18.

Case 1

A 62-year-old woman with type 2 diabetes mellitus, cerebrovascular disease and chronic kidney disease develops nonoliguric acute renal failure after a left femoral–popliteal bypass. During the surgery, intra- or postoperative hypotension did not develop. Preoperatively, she began cefazolin therapy for wound prophylaxis.

For the first 48 hours postoperatively, she received hydration with dextran 40, followed by normal saline (0.45%). Over the first 3 days of hospitalization, her creatinine level increased to 5.4 mg/dL (477.47 $\mu\text{mol/L}$); her creatinine level had been between 1.6 mg/dL (141.47 $\mu\text{mol/L}$) and 1.8 mg/dL (159.16 $\mu\text{mol/L}$) over the past year. Regular medications are ramipril; atenolol; and clopidogrel, which was discontinued 5 days preoperatively and has not been reinitiated.

On physical examination, temperature is 36.7 °C (98.1 °F), pulse rate is 86 beats/min and blood pressure is 132/80 mm Hg. Cardiac examination is unremarkable except for a murmur of aortic sclerosis. The lungs are clear to auscultation. There is trace pretibial edema bilaterally. The operative site shows no erythema or drainage.

Complete blood count is normal without peripheral eosinophilia. C3 and C4 levels are normal. Urinalysis shows 1+ protein, many monomorphic erythrocytes and no cellular casts. Ultrasound shows symmetric echogenic kidneys without hydronephrosis.

Which of the following is the most likely diagnosis?

- A. Osmotic tubular injury
- B. Ischemic tubular epithelial cell injury
- C. Angiotensin-converting enzyme (ACE) inhibitor–induced acute renal failure
- D. Thrombotic microangiopathy

Case 2

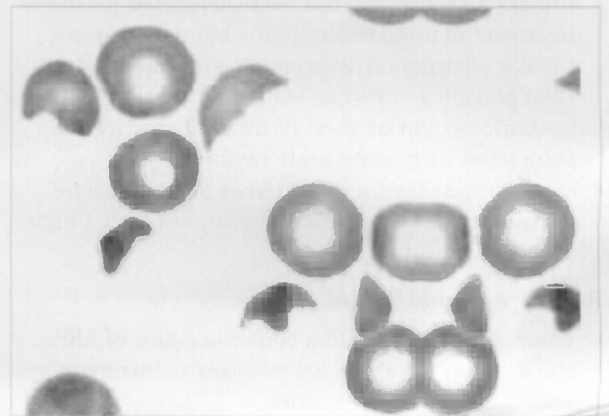
A 38-year-old man with advanced AIDS is hospitalized for respiratory distress, fever and hypoxemia. Community-acquired pneumonia is diagnosed, and the patient initially improves after initiation of levofloxacin therapy.

Over the next 2 weeks, his creatinine level progressively increases from 0.8 mg/dL (70.74 $\mu\text{mol/L}$) to 3.7 mg/dL (327.15 $\mu\text{mol/L}$). Over the past 3 days, his urine output has decreased to 500 mL/24 h. He has previously been treated for pulmonary tuberculosis and polysubstance abuse.

On physical examination, temperature is 37.8 °C (100.1 °F), pulse rate is 110 beats/min and blood pressure is 110/60 mm Hg. He is thin and in mild respiratory distress. There are scattered petechiae and ecchymoses across his skin, and he has spontaneous gingival bleeding.

Pulmonary examination reveals crackles at the right base. The PMI is laterally displaced. The abdomen is soft without organomegaly. There is no edema. On neurologic examination, he is lethargic and able to answer only simple questions.

Laboratory findings are as follows: hemoglobin level, 7.6 g/dL (76 g/L); leukocyte count, 9400 cells/ μL (9.4×10^9 cells/L); platelet count, 18,000 cells/ μL (18×10^9 cells/L); blood urea nitrogen level, 75 mg/dL (26.78 mmol/L); creatinine level, 3.5 mg/dL (309.47 $\mu\text{mol/L}$); sodium



Key points

Acute prerenal failure

- Numerous medications, iodinated contrast agents, and hypercalcemia may reduce glomerular capillary pressure through afferent arteriolar vasoconstriction.
- Abdominal compartment syndrome is a form of prerenal ARF that develops in patients with an expanded extracellular fluid volume after massive fluid resuscitation.
- Surgical or percutaneous decompression of the abdomen usually causes a prompt return of renal function in patients with abdominal compartment syndrome.
- Treatment of prerenal azotemia in patients with true volume depletion consists of restoring the extracellular fluid volume to normal with isotonic saline.
- Management of patients with functional prerenal failure should focus on reversing the underlying cause.
- Medications suspected of decreasing the glomerular capillary pressure should be discontinued in functional prerenal ARF.

Acute postrenal failure

- The presence of hydronephrosis is 90% sensitive and specific for obstruction but may not be evident in patients with concurrent volume depletion or retroperitoneal fibrosis.
- Urinary tract obstruction is most common in men with prostatic hypertrophy or cancer and in patients with intra-abdominal and pelvic malignancies.
- The clinical presentation of urinary tract obstruction may vary from anuria to polyuria alternating with oliguria.
- Methotrexate, intravenous acyclovir, sulfadiazine and indinavir may cause obstruction of the renal tubule.
- Allopurinol prophylaxis has significantly decreased the incidence of urate nephropathy after induction of cancer chemotherapy.
- Early intervention with hemodialysis is indicated for ARF associated with tumor lysis syndrome.
- Urinary alkalization has been advocated for the treatment of urate nephropathy but may worsen tubular obstruction by promoting formation of calcium phosphate crystals within the renal tubules.
- Rasburicase can be used to treat hyperuricemia associated with acute urate nephropathy.
- Rasburicase may be indicated as a prophylactic measure in patients with malignancies with a high proliferation rate.

Acute intrarenal failure

- Therapeutic agents are a common cause of ARF, and account for up to 30% of cases of intrarenal ARF in hospitalized patients.

- Ischemic tubular injury is the most common form of intrinsic renal injury in critically ill patients.
- Initial treatment of established ischemic tubular injury includes prevention of further renal parenchymal injury; correction of the inciting event, when possible; maintenance of fluid and electrolyte balance; and tight glycemic control.
- Aminoglycoside antibiotics are the most common cause of medication-induced renal failure.
- In aminoglycoside-induced acute tubular injury, cumulative uptake of the causative agent by the proximal tubular cells appears to be more important than trough levels in the development of nephrotoxicity.
- Aminoglycosides have been shown to exhibit less nephrotoxicity and equivalent efficacy when administered in higher doses on a once-daily basis.
- To prevent radiocontrast nephropathy, routine simultaneous renal arteriography in patients undergoing cardiac catheterization is discouraged.
- Volume expansion with isotonic saline or sodium bicarbonate is the most effective means of preventing radiocontrast nephropathy.
- An elevated serum creatine kinase level and heme positivity on urine dipstick in the absence of erythrocytes on microscopic analysis of the urine suggest rhabdomyolysis.
- The risk for renal failure increases when the serum creatine kinase level exceeds 5000 U/L.
- Expansion of the extracellular fluid volume with isotonic saline is the most effective measure to limit nephrotoxicity in rhabdomyolysis.
- Interstitial nephritis associated with NSAIDs and cyclooxygenase-2 inhibitors responds only minimally to corticosteroids.

Established acute renal failure

- Judicious fluid resuscitation and avoidance of further ischemic or nephrotoxic insults remain the mainstay of ARF therapy.
- Modifying drug dosing according to the degree of renal impairment and frequent monitoring of drug levels are indicated for patients with ARF.
- Indications for dialysis in patients with ARF include diuretic-resistant fluid overload, hyperkalemia, acidosis and uremic complications.
- Dialysis for ARF increasingly is initiated earlier, particularly in oliguric, critically ill patients.
- Stable patients with ARF expected to recover renal function within several days may benefit from restriction of fluids, sodium, potassium, phosphorus and protein to avoid the need for dialysis.

Adapted from ACP's Medical Knowledge Self-Assessment Program (MKSAP 14).