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### On the Cover

*What's the diagnosis?* Kidney biopsy from a patient with acute kidney injury that developed in the setting of sepsis, multiple antibiotic exposure and rhabdomyolysis revealed findings consistent with myoglobinuric acute tubular injury/necrosis. The upper panel reveals acute tubular injury accompanied by intraluminal myoglobin casts. In the lower panel, immunohistochemical staining of the tubular casts is positive for myoglobin. Myoglobin is a heme pigment-containing protein released from injured muscle in the setting of traumatic or non-traumatic rhabdomyolysis. Myoglobin enters the urinary space via glomerular filtration whereupon the protein is degraded and heme pigment is released. While somewhat controversial, myoglobinuria is speculated to cause acute kidney injury through 3 possible mechanisms. These include direct tubular toxicity, tubular obstruction, and intra-renal vasoconstriction with reduced blood flow to the outer medulla. Importantly, myoglobin-associated heme pigment rarely causes kidney injury in the absence of other risk factors such as volume depletion and/or hypotension, which are associated with ischemic tubular injury and further perpetuate myoglobin cast formation. Acidic urine may also enhance toxicity by increasing cast formation, and facilitating the conversion of myoglobin to ferriheme (or hemein), which may be more nephrotoxic. Prevention of kidney injury in the setting of rhabdomyolysis with myoglobinuria includes volume repletion to correct both hypovolemia and hypotension while also preventing myoglobin cast formation by producing brisk urine flow rates. While theoretical benefits to bicarbonate-containing intravenous fluids to prevent myoglobin-induced kidney injury exist, there are limited clinical data to support this fluid over intravenous isotonic saline. In addition, metabolic alkalosis can potentially worsen hypocalcemia, which is often associated with rhabdomyolysis, and promote calcium-phosphate deposition in the kidneys. Loop diuretics do not prevent myoglobin-associated AKI, but should be utilized in patients that develop hypervolemia. Some patients may require renal replacement therapy to manage AKI, the associated metabolic abnormalities, and hypervolemia. Most patients recover from AKI, although CKD may be a long-term complication. (Images and text provided by Mark A. Perazella, MD, Yale University School of Medicine, New Haven, Connecticut, and Glen S. Markowitz, MD, Columbia University College of Physicians and Surgeons, New York)