Editorials

723 Hemostatic Factors, APOL1, and ESRD Risk: Another Piece of the Puzzle?
Walter G. Wasser and Etty Kruzel-Davila
See related article on page 784.

726 Evolving Calciphylaxis—What Randomized, Controlled Trials Can Contribute to the Capture of Rare Diseases
Markus Ketteler and Patrick H. Biggar
See related article on page 800.

729 Posthemodialysis Weights and Mortality: Another Narrow Range Target?
Kristen L. Jablonski and Michel Chonchol
See related article on page 808.

Original Articles

Chronic Kidney Disease

732 Statins and Cardiovascular Primary Prevention in CKD: A Meta-Analysis
Rupert W. Major, Chee Kay Cheung, Laura J. Gray, and Nigel J. Brunskill

740 Association of Serum Ig Free Light Chains with Mortality and ESRD among Patients with Nondialysis-Dependent CKD
James Ritchie, Lakhvir K. Assi, Anne Burmeister, Richard Hoefield, Paul Cockwell, and Philip A. Kalra

Clinical Nephrology

750 Clinicopathologic Characteristics and Outcomes of Renal Thrombotic Microangiopathy in Anti-Neutrophil Cytoplasmic Autoantibody-Associated Glomerulonephritis
Su-Fang Chen, Huan Wang, Yi-Min Huang, Zhi-Ying Li, Su-Xia Wang, Feng Yu, Ming-Hui Zhao, and Min Chen

759 Effects of Sevelamer Carbonate on Advanced Glycation End Products and Antioxidant/Pro-Oxidant Status in Patients with Diabetic Kidney Disease
Elena M. Yubero-Serrano, Mark Woodward, Leonid Poretsky, Helen Vlassara, and Gary E. Striker on behalf of AGE-less Study Group

Epidemiology and Outcomes

767 Mineral Metabolism in European Children Living with a Renal Transplant: A European Society for Paediatric Nephrology/European Renal Association–European Dialysis and Transplant Association Registry Study
Marjolein Bonthuis, Marco Busutti, Karlijn J. van Stralen, Kitty J. Jager, Sergey Baiko, Sevcan Bakkaloğlu, Nina Battelino, Maria Gaydarova, Bruno Gianoglio, Paloma Parvex, Clara Gomes, James G. Heat, Ludmila Podracka, Dafina Kuzmanovska, Maria S. Molchanova, Tatiana E. Pankratenko, Fotios Papachristou, György Reusz, Maria José Sanahuja, Ruksana Shroff, Jaap W. Groothoff, Franz Schaefer, and Enrico Verrina

776 Plasma Urate and Risk of a Hospital Stay with AKI: The Atherosclerosis Risk in Communities Study
Keiko I. Greenberg, Mara A. McAdams-DeMarco, Anna Köttgen, Lawrence J. Appel, Josef Coresh, and Morgan E. Grams

784 Hemostatic Factors, APOL1 Risk Variants, and the Risk of ESRD in the Atherosclerosis Risk in Communities Study
Adrienne Tin, Morgan E. Grams, Nisa M. Maruthur, Brad C. Astor, David Couper, Thomas H. Mosley, Myriam Fornage, Rulan S. Parekh, Josef Coresh, and Wen Hong Linda Kao
See related editorial on page 723.
ESRD and Chronic Dialysis

791 The Effects of Cinacalcet in Older and Younger Patients on Hemodialysis: The Evaluation of Cinacalcet HCl Therapy to Lower Cardiovascular Events (EVOLVE) Trial

800 The Effect of Cinacalcet on Calcific Uremic Arteriolopathy Events in Patients Receiving Hemodialysis: The EVOLVE Trial
Jürgen Floege, Yumi Kubo, Anna Floege, Glenn M. Chertow, and Patrick S. Parfrey
See related editorial on page 726.

808 Associations of Posthemodialysis Weights above and below Target Weight with All-Cause and Cardiovascular Mortality
Jennifer E. Flythe, Abhijit V. Kshirsagar, Ronald J. Falk, and Steven M. Brunelli
See related editorial on page 729.

817 Outcomes of Infection-Related Hospitalization according to Dialysis Modality
Louis-Philippe Laurin, Hind Harrak, Naoual Elftouh, Denis Ouimet, Michel Vallée, and Jean-Philippe Lafrance

Genetics

825 Clinical and Molecular Characterization of Patients with Heterozygous Mutations in Wilms Tumor Suppressor Gene 1
Anja Lehnhardt, Claartje Karnatz, Thurid Ahlensiel-Grunow, Kerstin Benz, Marcus R. Benz, Klemens Budde, Anja K. Büscher, Thomas Fehr, Markus Feldkötter, Norbert Graf, Britta Höcker, Therese Jungraithmayr, Günter Klaus, Birgit Koehler, Martin Konrad, Birgitta Kranz, Carmen R. Montoya, Dominik Müller, Thomas J. Neuhaus, Jun Oh, Lars Pape, Martin Pohl, Brigitte Royer-Pokora, Uwe Querfeld, Reinhard Schneppenheim, Hagen Staud, Giuseppina Spartà, Kirsten Timmermann, Frauke Wilkening, Simone Wygoda, Carsten Bergmann, and Markus J. Kemper

Geriatric Nephrology

832 Frailty and Mortality in Dialysis: Evaluation of a Clinical Frailty Scale
Talal A. Alfaadhel, Steven D. Soroka, Bryce A. Kiberd, David Landry, Paige Moorhouse, and Karthik K. Tennankore

Nephrolithiasis

842 CKD and Its Risk Factors among Patients with Cystinuria

Renal Physiology

852 Osmotic Homeostasis
John Danziger and Mark L. Zeidel

Role of the Medical Director

863 Infection Prevention and the Medical Director: Uncharted Territory
Toros Kapoian, Klemens B. Meyer, and Douglas S. Johnson
In-Depth Review

875 Extracorporeal Treatment for Lithium Poisoning: Systematic Review and Recommendations from the EXTRIP Workgroup

Brian S. Decker, David S. Goldfarb, Paul I. Dargan, Marjorie Friesen, Sophie Gosselin, Robert S. Hoffman, Valéry Lavergne, Thomas D. Nolin, and Marc Ghannoum on behalf of the EXTRIP Workgroup

Public Policy Series

888 How the ESRD Quality Incentive Program Could Potentially Improve Quality of Life for Patients on Dialysis

Alvin H. Moss and Sara N. Davison

Special Features

894 Cross-Disciplinary Biomarkers Research: Lessons Learned by the CKD Biomarkers Consortium


903 American Society of Nephrology Quiz and Questionnaire 2014: Transplantation

Michelle A. Josephson, Mark A. Perazella, and Michael J. Choi

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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 ferrirheme (or hematin), 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)