December 2015 • Vol. 10 • No. 12

Editorials

2101 Infections Requiring Hospitalization in Patients on Hemodialysis
David T. Gilbertson and James B. Wetmore
See related article on page 2170.

2104 Frailty and Cognitive Impairment in ESRD: Brain-Body Connections
Stephen L. Seliger
See related article on page 2181.

2107 Targeting Blood Vessel Stiffness to Protect Kidney Function
Neeraj Dhaun and David J. Webb
See related article on page 2190.

Original Articles

Acute Kidney Injury

2110 AKI in Children Hospitalized with Nephrotic Syndrome
Michelle N. Rheault, Lei Zhang, David T. Selewski, Mahmoud Kallash, Cheryl L. Tran, Meredith Seamon, Chryso Katsoufis, Isa Ashoor, Joel Hernandez, Katarina Supe-Markovina, Cynthia D’Alessandri-Silva, Nilka DeJesus-Gonzalez, Tetyana L. Vasylyeva, Cassandra Formeck, Christopher Woll, Rasheed Gbadegesin, Pavel Geier, Prasad Devarajan, Shannon L. Carpenter, Bryce A. Kerlin, and William E. Smoyer on behalf of the Midwest Pediatric Nephrology Consortium

Chronic Kidney Disease

2119 Plasma Vitamin D Level and Change in Albuminuria and eGFR According to Sodium Intake

2128 Examination of Potential Modifiers of the Association of APOL1 Alleles with CKD Progression
Teresa K. Chen, Michael J. Choi, W.H. Linda Kao, Brad C. Astor, Julia J. Scialla, Lawrence J. Appel, Liang Li, Michael S. Lipkowitz, Myles Wolf, Rulan S. Parekh, Cheryl A. Winkler, Michelle M. Estrella, and Deidra C. Crews

Diabetes and the Kidney

2136 Randomized Clinical Trial of Sodium Polystyrene Sulfonate for the Treatment of Mild Hyperkalemia in CKD
Laurence Lepage, Anne-Claude Dufour, Jessica Doiron, Katia Handfield, Katherine Desforges, Robert Bell, Michel Vallée, Michel Savoie, Sylvie Perreault, Louis-Philippe Laurin, Vincent Pichette, and Jean-Philippe Lafrance

2143 Association of Serum C3 Concentration and Histologic Signs of Thrombotic Microangiopathy with Outcomes among Patients with ANCA-Associated Renal Vasculitis
Lucio Manenti, Augusto Vaglio, Elisa Gnappi, Umberto Maggiore, Landino Allegri, Marco Allinovi, Maria L. Urban, Marco Delsante, Maricla Galetti, Maria Nicastro, Francesco P. Pilato, and Carlo Buzio

Urinary Potassium Excretion and Renal and Cardiovascular Complications in Patients with Type 2 Diabetes and Normal Renal Function
Shin-ichi Araki, Masakazu Haneda, Daisuke Koya, Keiko Kondo, Sachiko Tanaka, Hisatomi Arima, Shinji Kume, Jun Nakazawa, Masami Chin-Kanasaki, Satoshi Ugi, Hiromichi Kawai, Hisazumi Araki, Takashi Uzu, and Hiroshi Maegawa
Original Articles (Continued)

Diabetes and the Kidney (Continued)

2159 **BP and Renal Outcomes in Diabetic Kidney Disease: The Veterans Affairs Nephropathy in Diabetes Trial**
David J. Leehey, Jane H. Zhang, Nicholas V. Emanuele, Adam Whaley-Connell, Paul M. Palevsky, Robert F. Reilly, Peter Guarino, and Linda F. Fried for the VA NEPHRON-D Study Group

Epidemiology and Outcomes

2170 **Risk Factors for Infection-Related Hospitalization in In-Center Hemodialysis**
Lorien S. Dalrymple, Yi Mu, Danh V. Nguyen, Patrick S. Romano, Glenn M. Chertow, Barbara Grimes, George A. Kaysen, and Kirsten L. Johansen
See related editorial on page 2101.

2181 **Frailty and Cognitive Function in Incident Hemodialysis Patients**
Mara A. McAdams-DeMarco, Jingwen Tan, Megan L. Salter, Alden Gross, Lucy A. Meoni, Bernard G. Jaar, Wen-Hong Linda Kao, Rulan S. Parekh, Dorry L. Segev, and Stephen M. Sozio
See related editorial on page 2104.

2190 **Arterial Stiffness and Decline in Kidney Function**
Sanaz Sedaghat, Francesco U.S. Mattace-Raso, Ewout J. Hoorn, Andre G. Uitterlinden, Albert Hofman, M. Arfan Ikram, Oscar H. Franco, and Abbas Dehghan
See related editorial on page 2107.

2198 **Long-Term Risk of Cancer in Survivors of Pediatric ESRD**
Sophie Ploos van Amstel, Judith L. Vogelzang, Marcus V. Starink, Kitty J. Jager, and Jaap W. Groothoff
ESRD and Chronic Dialysis

2205 **Insulin Resistance in Nondiabetic Peritoneal Dialysis Patients: Associations with Body Composition, Peritoneal Transport, and Peritoneal Glucose Absorption**
Ana Paula Bernardo, Jose C. Oliveira, Olivia Santos, Maria J. Carvalho, Antonio Cabrita, and Anabela Rodrigues

Renal Transplantation

2213 **Risk Stratification for Rejection and Infection after Kidney Transplantation**
Pietro E. Cippà, Marc Schiesser, Henrik Ekberg, Teun van Gelder, Nicolas J. Mueller, Claude A. Cao, Thomas Fehr, and Corrado Bernasconi

2221 **Emotional and Financial Experiences of Kidney Donors over the Past 50 Years: The RELIVE Study**

Renal Physiology

2232 **Acid-Base Homeostasis**
L. Lee Hamm, Nazih Nakhoul, and Kathleen S. Hering-Smith

Renal Immunology

2243 **Cytokines: Names and Numbers You Should Care About**
Stephen R. Holdsworth and Poh-Yi Gan

Attending Rounds

2255 **A Patient with Recurrent Arteriovenous Graft Thrombosis**
Michael Allon
**Ethics Series**

2263   Balancing the Duty to Treat Patients with Ebola Virus Disease with the Risks to Dialysis Personnel

Nicholas G. Evans

**In-Depth Review**

2268   Mild Chronic Hyponatremia in the Ambulatory Setting: Significance and Management

Helbert Rondon-Berrios and Tomas Berl

**Special Feature**

2279   Human Heredity and Health (H3) in Africa Kidney Disease Research Network: A Focus on Methods in Sub-Saharan Africa

Charlotte Osafo, Yemi Raheem Raji, David Burke, Bamidele O. Tayo, Nicki Tiffin, Marva M. Moxey-Mims, Rebekah S. Rasooly, Paul L. Kimmel, Akinlolu Ojo, Dwomoa Adu, Rulan S. Parekh, and the H3Africa Kidney Disease Research Network Investigators as members of The H3Africa Consortium

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**On the Cover**

What’s the diagnosis? A 63-year-old woman with an aggressive B-cell lymphoma underwent therapy with high-dose methotrexate following bicarbonate-containing intravenous fluid prophylaxis. Acute kidney injury (AKI) developed over the next 48 hours with serum creatinine rising to 1.7 mg/dl. Urine microscopy revealed numerous brownish/gold methotrexate crystals both in clumps (cover image) and in casts. Acute kidney injury from methotrexate-associated crystalline nephropathy was considered likely. Intravenous fluids containing bicarbonate were continued with the goal of high urine flow rates (> 150 ml/hour) and a urine pH of > 7.0. Over the next 48-72 hours, kidney function improved with serum creatinine approaching baseline. Methotrexate is a dihydrofolate reductase inhibitor that is employed to treat various malignancies, in particular high-grade lymphomas. Methotrexate when employed in high doses has been described to cause kidney injury through multiple possible mechanisms. In general, intratubular crystal precipitation is the most commonly described form of acute nephrotoxicity. AKI may occur from some combination of tubular obstruction from the crystals or an inflammatory reaction to the crystals. The former cause may have been more likely in our patient due to the rapidity of AKI following methotrexate administration, but a component of interstitial inflammation is impossible to exclude without a kidney biopsy. Risk factors for intratubular precipitation of methotrexate and its metabolites include low urine pH, volume depletion with low urinary flow rates, and with high urinary methotrexate concentrations associated with high dose therapy. Another potential cause of AKI includes tubular apoptosis/necrosis from lipid peroxidation that is associated with decreased adenosine deaminase activity following methotrexate therapy. (Images and text provided by Mark A. Perazella, MD, Yale University School of Medicine, New Haven, Connecticut)