AKI: A Path Forward

Joseph V. Bonventre, David Basile, Kathleen D. Liu, Dianne McKay, Bruce A. Molitoris, Karl A. Nath, Thomas L. Nickolas, Mark D. Okusa, Paul M. Palevsky, Rick Schnellmann, Krystyna Rys-Sikora, Paul L. Kimmel, and Robert A. Star, on behalf of the Kidney Research National Dialogue (KRND)

Summary

The Kidney Research National Dialogue, supported by the National Institute of Diabetes and Digestive and Kidney Diseases, asked the scientific community to formulate and prioritize research objectives that would improve our understanding of kidney function and disease. High-priority objectives for AKI were identified, including enhancing training and collaborative opportunities, improving phenotyping and development of clinical tools, expanding our understanding of the pathophysiology and interaction between injury and reparative processes, and identifying determinants of long-term outcomes. Research in animal models must be translated to improve diagnosis and treatment of patients. The objectives identified by the Kidney Research National Dialogue provide the research community with future opportunities for improving the prevention, diagnosis, and treatment of people with AKI.

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Due to the number of contributing authors, the affiliations are provided in the Supplemental Material.

Correspondence:
Dr. Paul L. Kimmel, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, 6707 Democracy Boulevard, Bethesda, MD 20892. Email: kimmelp@extra.niddk.nih.gov

AKI contributes to the public health burden by increasing morbidity, mortality, and health care costs, and is associated with increased risk for the development of CKD and ESRD (1). The incidence of AKI requiring dialysis has doubled over the last decade (2). Basic and clinical research has focused on predisposing factors, early diagnostic tools, pathophysiologic contributions of vascular, tubular, and interstitial compartments, normal adaptive and maladaptive repair pathways, and predictors of long-term outcome. Despite much progress, our knowledge remains limited and effective therapies are lacking (3).

The Kidney Research National Dialogue (KRND) recruited members from the renal community, including basic and clinical scientists, practitioners, and advocacy and professional groups, to provide the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) with advice regarding strategic opportunities, and emerging innovations in the field of AKI. The KRND AKI group then reviewed the responses to the KRND and outlined overarching and cross-cutting themes (Figure 1). The KRND AKI group identified several research objectives for AKI that can be divided into four categories, as outlined below. The complete list of areas of research emphasis, in the order of enthusiasm and consensus, is available on the NIDDK KRND webpage (http://www2.niddk.nih.gov/KUH/KUHHome/KRND.htm).

A key theme identified by the AKI working group was the importance of expanding the scientific base working on AKI, and promoting closer collaboration among basic scientists, physician scientists, engineers, biophysicists, radiologists, and nephrologists, as well as the National Institutes of Health (NIH), the Food and Drug Administration (FDA), and industry (Figure 1). It is also important to encourage collaboration between academia, the NIH, industry, and regulatory agencies to develop state-of-the-art and improve existing investigative technologies.

1. Predisposing Factors, Clinical Phenotypes, and Early Diagnostic, Prognostic, and Therapy-Guiding Tools
   - Refine and standardize the clinical phenotypes of AKI in different populations. This will facilitate interventional trials and comparisons across groups.
   - Qualify existing blood and urine biomarkers in clinical trials. Design and implement large-scale longitudinal clinical studies and trials that evaluate the relationship between biomarker levels and clinical and pathologic severity and outcomes of kidney injury. Establish the role of novel and traditional blood and urine AKI biomarkers in clinical trials to stratify risk, stage severity, predict outcomes, and inform treatment decisions.
   - Pursue discovery efforts to identify biomarkers that will help in the early diagnosis and prognosis of AKI, and guide clinical trial design and clinical decision making. Evaluate genomic, proteomic, and metabolomic profiles of blood, urine, and biopsy tissue, at different AKI stages and in different clinical settings. Develop further animal studies to test the sensitivity and specificity of biomarkers for injury of specific nephron segments, endothelium, and interstitium. Characterization of the origin of the biomarkers and the pathophysiologic and physiologic conditions that regulate their expression will inform their clinical use.

2. Pathophysiology of Injury and Development of Bedside Tools to Monitor and Characterize Extent of Injury and Repair
   - Use cellular, biochemical, molecular, pharmacologic, and genetic approaches to refine the understanding of injury and repair. For example, genetic cell fate mapping can define progenitor cells involved in injury and repair. Tools such as conditional gene-deficient mice, bacterial artificial chromosome-based gene

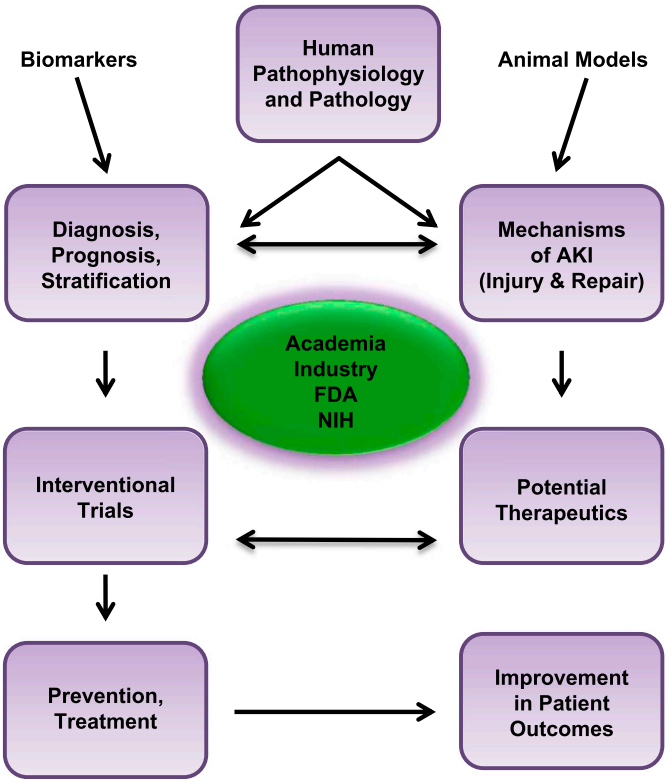

Figure 1. | Multidisciplinary collaboration can facilitate the integration of diverse topics into a unified, iterative research program focused on improving the prevention, prognosis, treatment, and outcomes of AKI. Core investigative areas, in human and animal studies, include understanding pathophysiology, injury and repair mechanisms, enhancing diagnosis and stratification in clinical settings and within clinical trials, and developing the therapeutic armamentarium. Interaction among academia, industry, regulatory agencies, and funders is critical, and can synergize knowledge acquisition and translation. FDA, Food and Drug Administration; NIH, National Institutes of Health.

reporter technology, and time-lapse imaging technologies should be applied.

- Better define the role of both innate and adaptive mediators of inflammation in AKI. Dissect the complex interactions of parenchymal and immune cells, and define the molecular events that lead to early and late cellular injury in well defined animal models of AKI. Compare and contrast the defined molecular, biochemical, and cellular events associated with AKI in animal models and human disease.
- Develop bedside technologies to evaluate renal perfusion, distribution of blood flow, oxygenation, inflammation, tubular function, and other pathophysiologic and therapeutic markers, including those important for fibrosis. Develop and validate new methods to determine real-time GFR for clinical studies.
- Capture the power of Doppler ultrasonography, contrast-enhanced ultrasonography, positron emission tomography scanning, near infrared spectroscopy, renal venous oxygenation, and sodium magnetic resonance imaging techniques to provide information about kidney physiology, AKI pathophysiology, and therapeutic responses.

3. Determinants of Normal versus Abnormal Repair that Lead to Fibrosis and CKD
   - Characterize clinical factors that modulate recovery of renal function after AKI episodes. Identify germane biomarkers, delineate the role of individual characteristics in determining responses, and determine genetic factors influencing recovery of renal function. Define the role of inflammation and anti-inflammatory responses in determining outcomes. Delineate why the aging kidney is more likely to develop CKD after an episode of AKI.
   - Understand how pathophysiologic processes in the acutely injured kidney can initiate and maintain such pathologic processes as glomerular sclerosis, vascular dropout, interstitial inflammation, as well as fibrosis and tubular atrophy—all histologic hallmarks of CKD. Define factors triggering cell fate decisions and determine whether they are amenable to manipulation. Determine what governs the balance between vascular dropout and angiogenesis and which cells in the circulation and kidney parenchyma modify repair.
   - Identify drugs that can stimulate repair and regeneration, and minimize fibrotic responses. Investigate new targets, including the cell cycle and mitochondria, that are related to repair mechanisms elucidated by basic research.
4. Pathways to Enhance Treatment of People with AKI
   - Refine animal models to adequately reflect the range, variety, and clinical characteristics of human AKI and predict which therapies will likely work in humans. Investigate the roles of aging and the effects and mediators of changes engendered by AKI in distant organs, and on microvascular, mitochondrial, and tubular function in

clinically relevant animal models as well as in human studies. In certain circumstances, nonmammalian models might be very informative and could be used for initial target validation or small molecule screening approaches. Develop preclinical models of various forms of AKI superimposed on CKD to evaluate both short-term and long-term effects of AKI.

- Explore cell-based immunotherapy, including the use of mesenchymal stromal cells. Establish the therapeutic potential of subtypes of multipotent stem and immune cells in treating AKI in animal models and in human disease. Determine the efficacy, pharmacokinetics, durability, adverse events, and mechanism of action of cellular therapies in animal models and in human disease.
- Explore the efficacy of current drugs and identify new therapeutics that target signaling pathways that mediate renal repair and regeneration in animal models and in human disease. It is of particular importance that potential therapeutics are tested after AKI has occurred.
- Create cell systems *in vitro* that adequately mimic epithelial and endothelial cell responses *in vivo*, which can be used to evaluate nephrotoxins and potential therapeutics. Exploit the use of high-throughput drug screening methods to identify therapeutic candidates.
- Establish the optimal timing of initiation and cessation of dialysis. Conduct definitive multicenter randomized controlled trials, with sufficient statistical power to detect clinically meaningful differences in survival and recovery of kidney function. Such studies should include all individuals eligible for early initiation of renal replacement therapy even if they die or recover kidney function before meeting criteria for delayed initiation. Studies should include economic analyses of therapeutic cost-effectiveness.
- Establish AKI collaborative networks with a number of linked clinical sites and public–private partnerships in collaboration with the FDA. This infrastructure can be used by the private sector to facilitate clinical trials in AKI. This will encourage investment in drug and device development.
- Determine the best ways to risk stratify people for clinical trials of prevention and therapy. As novel endpoints for clinical trials are developed, consultation with regulatory agencies about the acceptability of such endpoints for drug approval will be critical.
- Identify endpoints that are more closely associated with renal physiology or response to therapy than mortality. Continuous, rather than categorical, endpoints might provide more power. Novel endpoints, including surrogate biomarkers, may be useful in phase 2 clinical trials to help evaluate the effect of novel therapeutic agents before conducting larger phase 3 trials with "harder," more well accepted endpoints.
- Expand the scope of our therapeutic endpoints to include renal function 3 months and longer after the acute event. Some agents may be effective in mitigating fibrosis or modifying long-term outcomes, although they may not alter the acute course of AKI.

Research in AKI must include improving development of clinical phenotyping tools, utilizing animal models that mimic human disease, elucidating the interaction between injury and repair, developing novel clinical trial designs, and identifying determinants of long-term outcomes. Enhancing training and multidisciplinary collaboration, with interactions between academia, industry, regulatory agencies, and funders, will facilitate research translation that is focused on improving the prevention, prognosis, treatment, and outcomes of human AKI.

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Disclosures

J.V.B. has consultancy agreements with Genzyme Corp, Eli Lilly, PTC, AstraZeneca, Novartis, Janssen, USB Celltech, and Keryx; has ownership interests in PatientKeeper, Amag, Pacific Biosciences, Theravance, and Dicerna; received research funding from Novo Nordisk and honoraria from Genzyme and Pfizer; and has Kim-1 patents licensed by Partners Healthcare to Johnson and Johnson, Biogen Idec, Novartis, and Sekisui. In addition, J.V.B. has served as a scientific advisor to or a member of the following: National Space Biology Research Institute (board of directors), Amag (board of directors), Genzyme, CorMedix, and the *Journal of Clinical Investigation*. J.V.B. is editor of *Seminars in Nephrology*, associate editor of *Cell Tissue Research*, and an editorial board member of the *American Journal of Physiology: Renal Physiology*. K.D.L. has consulted for Astute Biomedical and Complexa and has had reagents for her work donated by Abbott and CMIC; she also owns stock in Amgen. D.M. has ownership interest in Home Dialysis Therapies of San Diego, and her laboratory is funded in part through a grant by Novartis Pharmaceuticals. B.A.M. is cofounder and medical director of FAST BioMedical, a company developing rapid GFR technology. T.L.N. has licensed patents on NGAL *via* Columbia University to Abbott Diagnostics and Alere. M.D.O. discloses the following relationships: AM Pharma, Nature Publishing Group, Lilly, Daiichi-Sankyo, American Physiological Society, International Society of Nephrology, PGX Health/Adenosine Therapeutics, LLC, and the University of Virginia Patent Office. P.M.P. consults for Sanofi, Cytopherex, and Complexa, and is the deputy editor of *CJASN*. R.G.S. is the associate editor of *American Journal of Physiology*: *Renal Physiology*, and a cofounder of MitoChem, Inc. and MitoHealth, Inc.

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Complete List of Authors:

Bonventre, Joseph: Brigham and Women's Hospital, Harvard Medical School, Renal Division and Biomedical Engineering Division, Boston, MA

Basile, David: Indiana University School of Medicine, Department of Cellular & Integrative Physiology, Indianapolis, IN

Liu, Kathleen: University of California San Francisco, Department of Medicine, San Francisco, CA

McKay, Dianne: University of California San Diego, Department of Medicine, San Diego, CA

Molitoris, Bruce: Indiana University School of Medicine, Department of

Medicine, Division of Nephrology, Indianapolis, IN

Nath, Karl: Mayo Clinic, Division of Nephrology and Hypertension, Rochester, MN

Nickolas, Thomas: Columbia University Medical Center, Department of Medicine, New York, NY

Okusa, Mark: University of Virginia, School of Medicine, Charlottesville, VA

Palevsky, Paul: Veterans Affairs Pittsburgh Healthcare System, Renal Section (111F-U),

Pittsburgh, PA

Schnellmann, Rick: Medical University of South Carolina, College of Pharmacy, Charleston, SC

Rys-Sikora, Krystyna: National Institute of Diabetes and Digestive and Kidney Diseases, Division of Kidney, Urologic and Hematologic Diseases, Bethesda, MD

Kimmel, Paul: National Institute of Diabetes and Digestive and Kidney Diseases, Division of Kidney, Urologic and Hematologic Diseases, Bethesda, MD

Star, Robert: National Institute of Diabetes and Digestive and Kidney Diseases, Division of Kidney, Urologic and Hematologic Diseases, Bethesda, MD