ASN American Society of Nephrology

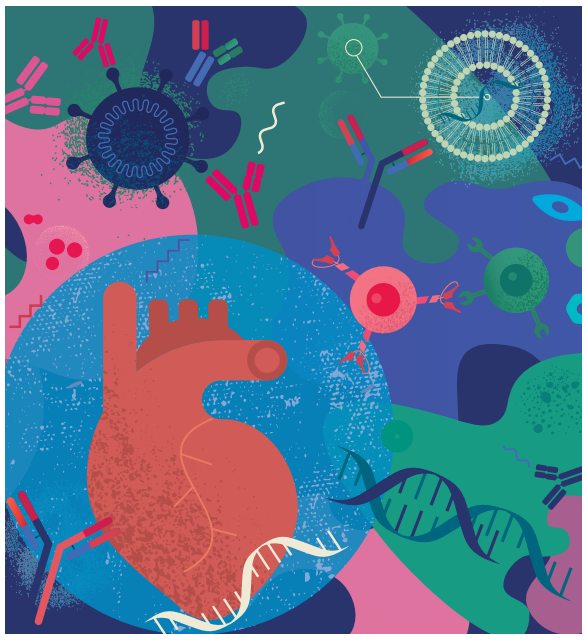
Kidney News

May 2026 | Vol. 18, Number 5

microRNAs May Drive Heart Disease, Predict Kidney Disease Progression

By Bridget M. Kuehn

https://doi.org/10.62716/kn.003332026



Exposure to microRNAs (miRNAs) released from damaged kidneys in vesicles contributes to heart cell damage and may provide a key tool for tracking kidney disease progression and complications, according to recent studies.

A study published in *Circulation* in January provides direct evidence, in human cells and mouse models, that exposure to miRNAs carried in extracellular vesicles from the kidneys of people with chronic kidney disease (CKD) can damage heart cells (1). The study provides a potential explanation for why kidney disease and heart disease are so closely linked and may provide new potential treatment targets for both diseases. This recent study (and a growing number of others) suggests that the miRNAs in the extracellular vesicles released by the kidney may provide a new tool for diagnosing kidney diseases, tracking progress, and identifying emerging complications like heart disease.

"There are no known biomarkers that can specifically identify when kidney failure leads to heart failure," explained senior author Susmita Sahoo, PhD, an associate professor of medicine in cardiology at the Icahn School of Medicine at Mount Sinai, New York, NY. "Our discovery is that these circulating particles that come from the kidney cause heart failure—we call them cardiotoxic extracellular vesicles. We are doing follow-up studies right now to understand and probably demonstrate that using these microRNAs, we can detect which patients would go on to develop heart failure," she said.

Manipulating gene expression

Christopher Chan, MD, director of the Division of Nephrology at University Health Network and professor of medicine at the University of Toronto in Ontario,

Continued on page 3

Kidney Community Responds to Growing Pollution, Heat, Disaster Threats

By Bridget M. Kuehn

https://doi.org/10.62716/kn.003492026

Each 1°C increase in annual average temperature is associated with an additional 1.37 cases of kidney failure per 100,000 people and about a quarter of a percentage point increase in cases of chronic kidney disease (CKD), according to a recent analysis of data from the Kidney Disease Surveillance System and the US Renal Data System (1).

Previous studies have linked heat exposure to increased cases of acute kidney injury and kidney stones, but this recent study suggests that chronic exposure to elevated temperatures may also lead to lasting kidney harm.

"The tip of the iceberg is when somebody comes in with a heat stroke and is admitted and has acute kidney injury and gets put on dialysis and then develops chronic kidney disease and over time, reaches end stage kidney disease," said the study's senior author Rajiv Saran, MBBS, MD, MRCP (UK), MS, professor of internal medicine and the Florence E. Bingham Research Professor of Nephrology in the Division of Nephrology at the University of Michigan Medical School in Ann Arbor. "There may be a lot of existing patients whose kidney disease gets worse when they're exposed to higher environmental temperatures for whatever reason. Adequate protection for people with chronic diseases, such as kidney disease from heat, is vital for their survival."

The study is one of a growing number of efforts around the globe to better understand the inter-related

Continued on page 4

Inside

ASN American Society of Nephrology

KidneyNews

ASN Kidney News is published by the American Society of Nephrology
1401 H Street, NW, Suite 900, Washington, DC 20005. Phone: 202-640-4660

www.asn-online.org

Postmaster: Please send address changes to *ASN Kidney News*, c/o Customer Service, American Society of Nephrology, 1401 H Street, NW, Suite 900, Washington, DC 20005.

Publications mail agreement No. 40624074.

ASN Kidney News (ISSN print 1943-8044 and online 1943-8052) is an official publication of the American Society of Nephrology, 1401 H Street, NW, Suite 900, Washington DC 20005, and is published monthly 11 times a year except November. Periodicals postage paid at Washington, DC and at additional mailing offices. Subscription rates: $12 per year. To order, please email bhenkel@asn-online.org. Subscription prices subject to change. Annual ASN membership dues include $20 for *ASN Kidney News* subscription.

★ WINNER OF 5 DESIGN AWARDS ★

CORPORATE SUPPORTERS 2025

ASN gratefully acknowledges the Society's Diamond and Platinum Corporate Supporters for their contributions in 2025.

DIAMOND LEVEL

Akebia Therapeutics
ardelyx
NOVARTIS
novo nordisk®
Otsuka
TRAVERE THERAPEUTICS
Vantive
vera therapeutics
VERTEX

PLATINUM LEVEL

AstraZeneca
FRESENIUS MEDICAL CARE
Genentech
A Member of the Roche Group

microRNAs May Drive Heart Disease, Predict Kidney Disease Progression

Continued from cover

Canada, explained that circulating miRNAs have been identified as both biomarkers and potential contributors to chronic diseases. He emphasized that miRNAs are distinct from mRNAs, which transmit instructions for building proteins and are the backbone of mRNA-based vaccines deployed during the pandemic. "microRNAs are small, noncoding pieces of RNA that regulate gene expression," Chan explained.

A recent article by Chan and his colleagues in *CJASN* noted that circulating miRNAs are modified by transplant and different dialysis modalities and intensities (2). Additionally, people at various stages of kidney disease have distinct miRNA profiles, which could provide valuable prognostic information or potentially new disease targets. So far, kidney disease research on miRNAs has lagged behind miRNA research in other fields, but it is an area with significant opportunity, he said. "It opens up a new avenue for investigators in kidney disease to think about how gene expression could be modifiable," he explained.

Chan noted that miRNA may be particularly useful for monitoring people on dialysis, since blood is already being routinely collected from them. Studying miRNAs from these individuals may also help explain the disease better.

"It is not only just the accumulation of toxins that causes the symptoms [in people with kidney failure], perhaps it's also the accumulation of other components, such as microRNAs that turn genes on and off, that ultimately results in this malignant accelerated aging phenotype that we see in our [population on dialysis]," he explained.

By more closely modeling normal physiology with more intensive dialysis regimens, he hopes to normalize gene expression via miRNAs, turning gene expression up or down. "We see this emerging field as another adjunct to how dialysis dose can modify the normal physiology of someone," he said.

He is also optimistic about the potential of miRNA targeting therapies. Already, companies are developing small molecules targeting miRNAs to manipulate gene expression. "Our current technology can make an analog of these microRNAs or even inhibitors of these microRNAs," Chan said.

Kidney–heart cross talk

Sahoo and one of her coauthors, Uta Erdbrügger, MD, a nephrologist, physician-scientist, and associate professor of medicine at University of Virginia Health in Charlottesville, took advantage of this avenue to study the role of miRNAs in cross talk between the kidneys and heart. "When your kidneys are healthy, your heart is healthy and vice versa," Erdbrügger said.

Yet traditional risk factors have failed to fully explain why disease in one of these organs often cascades into the other. A better understanding of this bidirectional interaction is critical to developing interventions to preserve kidney and heart health and to determine when to deploy the growing toolbox of available medications, Erdbrügger said. The multidisciplinary team decided to examine the role of extracellular vesicles in this heart–kidney cross talk. Extracellular vesicles are packets containing miRNAs, proteins, lipids, and other cargo that play an important role in communication between organs.

"Normally, in a healthy individual who does not have kidney or heart failure, these molecules are responsible for talking between the organs, between the cells," Sahoo said. But when a pathological situation arises, these vesicles may be the organ's way of alerting other organs to their distress.

To better assess this, they isolated vesicles from 35 individuals with CKD and added them to human cardiomyocytes grown from pluripotent stem cells in the laboratory. In the presence of the vesicles, the cardiomyocytes do not contract as well, they express fewer genes responsible for heart contractions, and some cells die. Extracellular vesicles from mice with kidney disease were similarly toxic to heart cells, and depleting these vesicles in these mice restored heart function and ameliorated heart failure despite the ongoing kidney disease. "If we develop drugs to counteract these toxic molecules, we might be able to alleviate the heart's pathological symptoms," Sahoo said.

The team also found a signature set of miRNAs in mice and humans with kidney disease compared with healthy mice and humans. "We are very excited to use these microRNAs as biomarkers because ideally our wish is that they detect early heart disease," Erdbrügger said.

They are currently working on a larger study to confirm their result. If these kidney disease-associated miRNAs are validated as biomarkers, they might enable clinicians to intervene more effectively with existing medications, Erdbrügger said. Sahoo also noted that such biomarkers may also help clinicians determine if therapies are working.

Erdbrügger noted that the team also wants to study the underlying mechanisms in more detail and determine whether other cargo in the vesicles contributes to heart cell dysfunction. Sahoo said that the researchers would also like to conduct additional studies of echocardiograms and magnetic resonance imaging from individuals to understand how miRNA toxicity affects the heart before they develop heart failure symptoms. In addition, the team wants to study whether heart toxic miRNAs are also produced in individuals with acute kidney injury. Other groups are studying how cellular cargo in patients with heart failure might contribute to the development of kidney disease, Erdbrügger noted. "We don't even know if it is the same pathological signal when it originates at the heart and goes to the kidney," Sahoo said. "There is so much to learn, and it's just the tip of the iceberg."

Early warning

Other groups are also developing ways to use miRNA profiles to predict kidney progression and cardiovascular and metabolic risks in individuals with kidney diseases. Shintaro Mandai, MD, PhD, FASN, an associate professor in the Department of Nephrology in the Graduate School of Medical and Dental Sciences at the Institute of Science Tokyo in Japan, and his colleagues developed a risk equation using vesicle-derived miRNAs to predict kidney outcomes, including dialysis initiation, cardiovascular events, and all-cause mortality among people with CKD (3). They found that depletion of three miRNAs was linked to worsening CKD based on Kidney Disease: Improving Global Outcomes' (KDIGO's) CKD heat map strata and progression of cardiovascular-kidney-metabolic (CKM) syndrome corresponding with the American Heart Association's CKM syndrome stages.

"Even more striking, within each clinical stage, our high- versus low-risk equation groups showed further prognostic discrimination," Mandai said. "This indicates that [extracellular vesicle] miRNA depletion reflects underlying CKD/CKM pathophysiology and may capture subclinical disease activity not visible to current laboratory markers."

He explained that the equation's strong predictive value likely stems from the fact that many of the miRNAs used in the equation originate in the endothelial cells. Inflammation and injury in the endothelial cells are known to drive CKM progression. "[Extracellular vesicle] miRNAs may serve as biologically anchored markers suitable for future CKM staging refinement or augmentation," he said.

Mandai said that he believes the equation, which his team tested with computer modeling, could be used in primary care to help identify people with preclinical or early-stage CKD or CKM who may benefit from preventive interventions or referral to a specialist. It may also provide an early warning of clinical deterioration in people already receiving care for stage G2 or G3 CKD or early stages of CKM, enabling clinicians to intervene.

"The miRNA-based model captures systemic pathways involving inflammation, metabolic dysregulation, and biological aging—core mechanisms of CKM syndrome," Mandai explained. "Because these molecular signals emerge earlier than overt organ dysfunction, the tool can identify patients with 'invisible' or subclinical risk, allowing clinicians to distinguish fast progressors from stable individuals and those with disproportionate cardiovascular vulnerability."

That could make the tool especially valuable for guiding the uses of glucagon-like peptide-1 (GLP-1) receptor agonists, sodium-glucose cotransporter-2 inhibitors, and nonsteroidal mineralocorticoid receptor antagonists, Mandai said. He noted that previous studies show that GLP-1 receptor agonists upregulate let-7d-5p, one of the three miRNAs in which depletion is linked with CKD and CKM progression. That may suggest that patients with high-risk scores in the equation may disproportionately benefit from GLP-1 receptor agonists. But he said that validation of his equation in contemporary patient cohorts is needed because the patient cohort used in the study predated widespread use of that class of drugs.

Previously, Mandai and his colleagues showed that miRNAs depleted in CKD help protect against vascular calcification, which may contribute to the breakdown of endothelial homeostasis and collapse of protective multiorgan signaling networks. He said that it would be difficult to directly target depleted miRNAs, but there may be potential to develop therapies that prevent miRNA depletion or prevent its triggering of downstream disease pathways.

Mandai and his colleagues plan to validate their equation in larger, more diverse patient cohorts and in people with earlier stages of CKD and CKM. They also want to develop an miRNA screening kit for clinical use. He said that such a tool could become a foundational piece of CKM therapy.

"[miRNA-Based risk assessment] could function as a 'fifth pillar,' supporting the timely initiation of the CKM four-pillar therapy set," he said. "By enabling earlier risk recognition and treatment, this approach could reduce major cardiovascular events, [kidney failure], and premature death, contributing meaningfully to public health and health care economics." ■

References

1. Li X, et al. Circulating extracellular vesicles in the pathogenesis of heart failure in patients with chronic kidney disease. *Circulation* 2026; 153:94–114. doi: 10.1161/CIRCULATIONAHA.125.075579
2. Alberga CA, et al. The role of microRNA regulation on clinical outcomes in kidney disease. *Clin J Am Soc Nephrol* (published online January 12, 2026). doi: 10.2215/CJN.0000001002
3. Inaba S, et al. Circulating extracellular vesicle microRNAs as predictive biomarkers for kidney and cardiovascular events. *J Am Heart Assoc* 2026; 15:e045148. doi: 10.1161/JAHA.125.045148

Kidney Community Responds to Growing Pollution, Heat, Disaster Threats

Continued from cover

impacts of climate change, pollution, and environmental disasters on people with kidney diseases and to develop strategies to mitigate these impacts. Previous studies by Saran's group and others have linked levels of particulate matter less than 2.5 μm in size ($PM_{2.5}$) to elevated rates of kidney diseases. Climate-driven disasters, like hurricanes and wildfires, have also taken a growing toll on people with kidney diseases who are often vulnerable to life-threatening consequences due to disruptions in care.

David S. Goldfarb, MD, FASN, professor of medicine and physiology at the New York University (NYU) Grossman School of Medicine in New York City and chair of ASN's Sustainability Subcommittee, explained that the effects of heat, pollution, and climate-linked disasters on the kidney are inter-related and complex. "Burning fossil fuels both increases the amount of $PM_{2.5}$ in the atmosphere and increases greenhouse gases that contribute to climate change," he said.

Climate risks

As the principal investigator of the US Centers for Disease Control and Prevention's national Kidney Disease Surveillance System, Saran has been helping track various aspects of CKD in the United States since 2006. He collaborated on the heat exposure study with investigators at Peking University in Beijing, China. "Climate change obviously has brought heat and higher ambient temperatures to the fore," said Saran, who is also professor of epidemiology at the University of Michigan's School of Public Health.

The team has previously shown that counties with higher exposure to $PM_{2.5}$ also have higher rates of CKD (2), a finding that was recently confirmed in a large study conducted in China (3). The study used health records on more than 870,000 patients in China along with pollution data and showed that higher levels of exposure to particulate pollution were associated with a decline in the estimated glomerular filtration rate. "Air pollution is also associated with kidney disease, as it is with cardiovascular and pulmonary diseases," Saran said.

Exactly how particulate pollution may contribute to kidney diseases is unclear. However, Goldfarb suggested that exposure may cause inflammation, which is bad for kidney health, or that particulates taken up by the lungs may appear in the kidneys, directly causing damage.

Saran and his coauthors' latest study found that the number of heat waves in an area was linked to kidney diseases and that high-poverty and nonmetropolitan areas were at higher risk (1). Southern and Northwestern regions of the country were also most affected by higher rates of heat-linked kidney diseases. Although the epidemiologic study cannot prove a causal relationship between rising temperatures and kidney diseases, Saran said, it lays the groundwork for additional research. The team is now trying to better understand the relationship by examining health care claims data and climate data, according to one of the study's coauthors, Yun Han, PhD, MS, who helped lead the project as an assistant research scientist at the University of Michigan and is now a senior research scientist at Precision AQ. Han noted that they want to encourage other researchers to study individual patient risks and evaluate potential interventions, such as clinical guidelines, patient education, or community-level recommendations, to mitigate heat-related kidney risks.

Saran said interventions targeting agricultural workers and migrant populations, who have previously been found to be at risk of CKD of unknown origin—a condition linked to exposure to extreme heat and agricultural chemicals—will be especially important. He suggested that asking patients about where they live and their occupations is "crucial in identifying potential susceptibility to heat-related illnesses." Discussing their outdoor activities and home heating and cooling may also be helpful, he suggested.

Goldfarb agreed that it is important for nephrologists to identify patients at risk of heat-related kidney harm. He noted that physicians can talk with patients about staying hydrated, moving to cooler areas, or using cooling centers during heat waves. But he acknowledged that there may be challenges to that. "We're talking about older people [with frailty] and [who] lack mobility [or] may not have family contacts and friends or relatives [who] can get them to places that are significantly cooler," he explained. "Many of these people don't recognize the signs of heat stress until it's too late."

Goldfarb explained that these patients at risk may have reduced thirst and diminished autonomic nervous system reflexes during extreme heat events and that their ability to regulate their body temperature may also be impaired. He said that he and his colleagues at the Kidney Stone Prevention Program at NYU Langone and at the New York Veterans Affairs Medical Center work to proactively identify those at risk and provide handouts about kidney stone prevention that address climate threats alongside risk factors, such as diet, to help patients prepare in advance for heat exposure.

Resilient and sustainable

In addition to the direct effects of pollution and heat on people living with kidney diseases, climate change also contributes to more extreme weather events that can put this population at risk of life-threatening care disruptions. "As a result of global warming, there are more climate events, hurricanes, floods, storms, and even snowstorms, which lead to interruption of dialysis services," Goldfarb said. For example, Hurricanes Katrina and Sandy led to major disruptions in access to care in the United States.

Some extreme weather events can also worsen pollution. For example, Shaifali Sandal, MD, an associate professor in the Division of Nephrology and a transplant nephrologist at McGill University Health Centre in Montreal, Quebec, Canada, noted that particulate matter from Canadian wildfires in 2023 has been linked to increased hospitalization among people undergoing dialysis. Sandal said it is incumbent on the kidney care community to prepare for extreme weather events as they become more frequent. "The crisis cannot be avoided," she said. She noted that addressing climate change will require concerted global government-level initiatives. "In the absence of that, all we can do is be more prepared."

Goldfarb expressed concern about recent shifts in US climate policy. "It's worrisome that right now, the Environmental Protection Agency and the federal government have withdrawn support for many ways of dealing with climate change," he said, for example, removing warnings about the role of carbon dioxide as a greenhouse gas or statements suggesting that climate change is a hoax. "That's very dangerous; there are lives that are going to be lost as a result of that."

Sandal noted that in Canada, she and her colleagues are working on vulnerability and adaptation assessments recommended by the United Nations and the World Health Organization. For nephrologists and dialysis clinics, she noted that increasing preparedness takes a multilayered approach. "There is system-level preparedness, [clinician]-level preparedness, and there is patient-level preparedness," Sandal said. She noted that after Hurricane Katrina, significant steps were taken in the United States to improve system- and patient-level preparedness that paid off during Hurricane Sandy. The Kidney Community Emergency Response program was created shortly after Hurricane Katrina, with funding from the Centers for Medicare & Medicaid Services, to support disaster preparedness and reduce disruptions in care.

Sandal said it is important to consider the patient perspective in disaster planning to be successful. She noted that during prior events, some patients waited or refused to evacuate their homes because they did not want to leave their pets behind or leave without their caregiver and added that there is currently limited understanding of patient needs and perspectives.

The kidney community is also looking inward to better mitigate its environmental impact by adopting more sustainable practices. The International Society of Nephrology's GREEN-K initiative is helping to unite nephrologists around the world in taking steps to reduce greenhouse emissions and the use of single-use plastics and to more sustainably use water in dialysis (4). Goldfarb, who represents ASN as part of the GREEN-K initiative, said the goal is: "How can nephrology generate less waste, use less water, and in general be greener?"

Focusing on providing the best possible kidney care may also help improve sustainability in nephrology by reducing the need for resource-intensive dialysis, Goldfarb said. Sandal noted that the rise in diabetes, obesity, and hypertension also contributes to rising rates of CKD and kidney failure and that the effects of climate change may exacerbate those conditions, for example, through food insecurity.

"It is an amalgamation of socioeconomic and climate change factors that is driving the increase in CKD," Sandal said. Conversely, newer medications, such as sodium-glucose cotransporter-2 inhibitors or glucagon-like peptide-1 agonists, which may help preserve kidney function or even reverse kidney diseases, along with increase rates of transplantation, may reduce the need for dialysis long term.

Sandal and her colleagues at McGill have created a research fellowship in resilient and sustainable nephrology to help mentor the next generation of nephrologists as they study these challenges and help develop solutions. She said fellows will be able to choose their research focus. Eventually, she and her colleagues also hope to develop a dedicated resilient and sustainable nephrology curriculum that can inform clinical training.

Sandal emphasized that the impact of climate change on kidney health, sustainability in kidney care, and disaster resilience are three interwoven streams that must be addressed through cohesive, coordinated policy efforts. "They are all tied together," she said. ■

References

1. Wang F, et al. The association of high ambient temperatures and kidney disease: A kidney disease surveillance system ecological study. *Clin J Am Soc Nephrol* (published online January 9, 2026). doi: 10.2215/CJN.0000000935
2. Bragg-Gresham J, et al.; Centers for Disease Control and Prevention CKD Surveillance System. County-level air quality and the prevalence of diagnosed chronic kidney disease in the US Medicare population. *PLoS One* 2018; 13:e0200612. doi: 10.1371/journal.pone.0200612
3. Wu J-L, et al. Association between exposure to air pollution and kidney function decline. *Nephrol Dial Transplant* 2025; 41:112–124. doi: 10.1093/ndt/gfaf143
4. Stigant CE, et al. Our shared responsibility: The urgent necessity of global environmentally sustainable kidney care. *Kidney Int* 2023; 104:12–15. doi: 10.1016/j.kint.2022.12.015

The Silent Epidemic: Unraveling CKDu

By Lori-Ann Fisher and Bernard Jaar

https://doi.org/10.62716/kn.003372026

In the last 2 decades, a significant burden of kidney failure requiring dialysis in endemic regions of Central America and South Asia has been attributed to chronic kidney disease of undetermined etiology (CKDu) (1). Despite gains in the knowledge of CKDu risk factors, its etiology and true prevalence remain elusive. In a recent report by the International Society of Nephrology i3C Working Group and others, the challenges in and solutions to ascertain the unknown in CKDu are discussed (2).

A rose by any other name—CKDu nomenclature

Mesoamerican nephropathy, chronic interstitial nephritis in agricultural communities, and CKDu have been used to describe chronic impaired kidney function, an estimated glomerular filtration rate (eGFR) of less than 60 mL/min/1.73 m^2, absence of significant albuminuria, and lack of traditional risk factors (e.g., diabetes, glomerular disease) in the absence of alternate diagnoses, particularly in low- and middle-income settings (2–4). The first reports have described premature kidney failure in rural agricultural communities in Mexico, Sri Lanka, and Nicaragua. The problems with the aforementioned case definition are several-fold (1). An exclusionary diagnosis requires diagnostics (e.g., kidney biopsy, genetic testing to exclude other causes of tubulointerstitial disease), which are often limited in low- and middle-resource settings. In endemic regions, where alternate diagnoses are less likely, this is less problematic, but identifying cases in nonendemic regions is more challenging. A proposed difference in nomenclature of CKD without diagnosis could refer to such cases. Furthermore, global variability in standardization of creatinine testing (the Jaffe method versus enzymatic methods); lack of albuminuria testing; use of an eGFR cutoff of 60 mL/min/1.73 m^2 in a young population, in which an expected GFR is more than 90 mL/min/1.73 m^2; and limitations of creatinine as a kidney function biomarker add to the diagnostic uncertainty (5, 6). Potential solutions include: 1) standardization in terminology and case definitions and 2) identification of novel biomarkers to identify early tubular dysfunction.

Many risk factors, no etiology

A multifaceted disease, CKDu risk factors include male sex, rural residence, heat stress, high altitude, and agricultural exposure (1–3). In addition to these, environmental toxins (e.g., heavy metals, agricultural toxins), infections, and chronic dehydration leading to repeated subclinical acute kidney injury events may initiate and propagate progression to kidney failure in CKDu (3). Importantly, these factors may also lead to progression to kidney failure in CKD of other etiologies, leading to confusion in their definitive role (initiating vs exacerbating factors) in CKDu pathogenesis. Thus, rather than ascribing risk as multifactorial, a deeper understanding of initiation and progression exposures in CKDu across populations is needed.

Why should we care about CKDu?

At the heart of this problem are the people who live with CKDu, their families, and communities. CKDu disproportionately affects young people from low- and middle-income settings with limited access to health care. Indeed, the highest mortality and disability adjusted life-years in CKD exist in Central America and Southeast Asia, which are known CKDu hot spots (7). Urgency in clarifying the unknown in CKDu is needed to guide cost-effective, culturally appropriate management strategies for early detection and treatment, thereby possibly improving outcomes. ■

Lori-Ann Fisher, MBBS, is with the Epidemiology Research Unit and the Department of Medicine, Caribbean Institute for Health Research, The University of the West Indies, Mona, Kingston, Jamaica. Bernard Jaar, MD, MPH, FASN, is an associate professor and clinical director of the Division of Nephrology, Department of Medicine, Johns Hopkins School of Medicine, with joint appointment in the Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD.

The authors report no conflicts of interest.

References

1. Anand S, et al.; ISN's i3C. Epidemiology, molecular, and genetic methodologies to evaluate causes of CKDu around the world: Report of the Working Group from the ISN International Consortium of Collaborators on CKDu. *Kidney Int* 2019; 96:1254–1260. doi: 10.1016/j.kint.2019.09.019
2. Caplin B, et al.; ISN i3C Working Group. Taking the "unknown" out of CKDu—optimizing approaches to uncover the cause(s) of epidemic-level kidney disease in low- and middle-income settings: A report from the ISN's International Consortium of CKDu Collaborators (ISN i3C). *Kidney Int* 2026; 109:652–660. doi: 10.1016/j.kint.2025.12.027
3. Gonzalez-Quiroz M, et al. Decline in kidney function among apparently healthy young adults at risk of Mesoamerican nephropathy. *J Am Soc Nephrol* 2018; 29:2200–2212. doi: 10.1681/ASN.2018020151
4. Wesseling C, et al. Mesoamerican nephropathy: Geographical distribution and time trends of chronic kidney disease mortality between 1970 and 2012 in Costa Rica. *Occup Environ Med* 2015; 72:714–721. doi: 10.1136/oemed-2014-102799
5. Jha V, Modi GK. eGFR testing around the world: Justice, access, and accuracy. *Clin J Am Soc Nephrol* 2021; 16:963–965. doi: 10.2215/CJN.16001020
6. Delanaye P, et al. Performance of creatinine-based equations to estimate glomerular filtration rate in White and Black populations in Europe, Brazil and Africa. *Nephrol Dial Transplant* 2023; 38:106–118. doi: 10.1093/ndt/gfac241
7. Mark PB, et al.; GBD 2023 Chronic Kidney Disease Collaborators. Global, regional, and national burden of chronic kidney disease in adults, 1990–2023, and its attributable risk factors: A systematic analysis for the Global Burden of Disease Study 2023. *Lancet* 2025; 406:2461–2482. doi: 10.1016/S0140-6736(25)01853-7

ASN President's and Executive Vice President's Update

Being Unranked by the Unchecked

By Samir M. Parikh and Tod Ibrahim

https://doi.org/10.62716/kn.003612026

In "The Order of Things," Malcolm Gladwell observes, "Who comes out on top, in any ranking system, is really about who is doing the ranking" (1). But what if the "who" doing the ranking decides to stop considering a critical aspect of the US health care system? That is exactly what happened when U.S. News & World Report (USNWR) removed adult nephrology as a ranked specialty starting with its 2021–2022 "Best Hospitals Rankings and Ratings."

By disenfranchising more than 37 million Americans living with kidney diseases and the nearly 12,500 nephrologists caring for them, USNWR degraded the credibility of its ranking system. Since then, the "Best Hospitals Rankings and Ratings" have come under increased scrutiny due to ethical concerns, data limitations, and inherent biases—as well as an overall lack of accountability (2).

USNWR claimed in 2021 that the decision to delete nephrology was due to a methodologic change. By replacing the comprehensive "nephrology" specialty ranking with a more targeted rating for "kidney failure," the digital media company argued that most patients seek care related to the specific outcome of treating acute kidney failure rather than a generalized specialty ranking (see the Box). USNWR failed to recognize that 1) acute kidney failure is a narrow subset of conditions that afflict people living with kidney diseases and 2) most people, when they seek care, do not know they have kidney failure.

Despite making this assertion 5 years ago, USNWR continues to rank 15 other medical specialties, and nephrology remains the *only* specialty completely removed and replaced with a "Procedures and Conditions" rating (Table). As of the 2025–2026 rankings, other medical specialties—such as "diabetes and endocrinology"—are included *both* among the ranked specialties and in the corresponding "Procedures and Conditions" ratings (3).

Without the specialty ranking for nephrology, patients struggle to identify centers for kidney care beyond just acute failure management, especially people living in rural and underserved communities. "This significant, first-time instance of dropping a major specialty established a barrier for 37 million Americans living with kidney diseases," ASN argued at the time (4). "Often part of historically disadvantaged populations with low levels of awareness of their conditions, patients with kidney diseases now cannot access information to guide nephrology care decisions."

Ranking only acute kidney failure *ignores* the comprehensive work of nephrologists and the extensive challenges that their patients face. Among many responsibilities, nephrologists are committed to preventing the progression of kidney diseases, diagnosing and treating rare congenital syndromes, handling complex electrolyte disorders, managing multiorgan complications of kidney diseases, and enabling kidney transplantation. Reducing the entire field of nephrology to a singular condition means that USNWR is not meeting the needs of anyone—patients, physicians, other health professionals, trainees, payors, and even policymakers—whose needs could be served by these rankings.

Being unranked by USNWR also diminishes the prestige of nephrology in the eyes of stakeholders, especially medical students, residents, and hospital leaders. Because nephrology is not on the list of ranked specialties, hospitals are less likely to support nephrology divisions, invest in nephrology fellowship training programs, or hire advanced practice providers to help provide care.

In its "Best Children's Hospitals," USNWR continues to rank pediatric nephrology as a specialty, because the data for children's hospitals are collected through a separate, specialized survey (the Research Triangle Institute [RTI] International survey). Treating pediatric and adult nephrology differently, however, is inconsistent, confusing, and indefensible, creating challenges for young Americans transitioning from pediatric to adult nephrologists.

In addition to making adult nephrology a unique case as the only deleted specialty, USNWR's decision disadvantages nephrology at a time when cardiovascular-kidney-metabolic syndrome merits the first superspecialty in medicine (5). USNWR should instead consider moving toward a holistic approach of evaluating health systems that treat the constellation of kidney diseases rather than ranking artificially atomized elements of medicine.

By focusing on acute kidney failure solely as a condition, USNWR also believed it could use more standardized, outcome-based data (like survival rates and "discharge-to-home" metrics) that apply to a broader range of hospitals, including community centers, rather than just large academic institutions. Like many other specialties, nephrology rankings were historically influenced by "expert opinion" collected from physician surveys distributed by Doximity. USNWR said it was moving away from reputational surveys in favor of "risk-adjusted" data.

Five years later, however, USNWR still ranks specialties like ophthalmology, psychiatry, and rheumatology differently because they lack standardized, nationwide Medicare data for outcomes. These specialties have not been erased but continue to be ranked entirely on expert opinion (physician surveys) rather than the 75% outcome-based weighting used for other fields. If USNWR believes "hard data" are not a prerequisite for inclusion as a field, why hold nephrology to a different standard?

By continuing to rank other specialties, USNWR has in fact *eliminated* specific data points that once defined a specialty's rank. For example, in the latest 2025–2026 rankings, the digital media company ceased using structural metrics, such as "number of advanced technologies" or "intensive care unit specialist availability," and removed nurse-to-patient ratios in favor of patient-reported "nursing communication" scores (3). Given these approaches to other specialties with data limitations, USNWR must have other reasons to disenfranchise people living with kidney diseases.

Kidney diseases disproportionately affect Americans with lower socioeconomic status as well as American Indian or Alaska Native, Black, Hispanic, and Native

An entire field in one code?

How does USNWR define its kidney failure measure? The denominator is all people with Medicare Fee-for-Service or Medicare Advantage admitted with the *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision* (*ICD-10*) code for "acute kidney failure." The outcomes include 30-day mortality for these individuals, as well as discharge to a site other than home. Additionally, larger hospitals that treat more people with acute kidney failure receive a ratings boost, with USNWR mistakenly applying a standard from surgery—in which more technical expertise is proven better—to people with a diagnosis code for acute kidney failure.

This metric does little to inform the quality of nephrology care, as few of these people with acute kidney failure see nephrologists, and the performance on this metric is likely far more a function of aggressive coding of comorbid conditions than of true differences in clinical care. Critically, with no existing *ICD-10* codes that differentiate among the various stages of acute kidney injury, an admission diagnosis with "acute kidney failure" could be as straightforward as a 0.3-mg/dL rise in serum creatinine due to medications or mild gastroenteritis that resolves with fluid administration or could be as complex as rapidly progressive glomerulonephritis.

Notably, individuals admitted with a primary diagnosis of acute kidney failure who die within 30 days may exemplify patient-centered care, particularly given the restriction of the measure to individuals with Medicare coverage. Dialysis is a highly effective therapy for acute kidney failure, but, for many people, dialysis may not be within their life goals. By incentivizing the initiation of dialysis, USNWR may be causing lower quality care.

The current USNWR rating for acute kidney failure represents less than 2% of the millions of Americans living with kidney diseases. It is a lagging indicator, assessing those who did not die in the hospital. By removing the nephrology specialty ranking, USNWR ignores the 33% of the US population who are at risk for kidney diseases. This staggering number (more than 112 million Americans) is the equivalent of saying that none of the people living in California, Florida, New York, and Texas matter.

Hawaiian or Other Pacific Islander individuals and Americans living in rural areas, all of whom often face significant barriers to specialized care. These vulnerable populations rely on all available sources of information to find the best possible centers for complex kidney care and transplantation. Removing the specialty ranking has created an information gap, making it harder for Americans who are resource-limited to navigate the complexities of the health care system.

In 2023, the San Francisco city attorney investigated "questionable methodology and undisclosed financial links" between USNWR and "highly ranked hospitals," alleging that the rankings are biased toward wealthier patients (6). USNWR gives significant weight to conditions like cystic fibrosis (primarily affecting White Americans) but historically underweights or ignores conditions like kidney diseases and sickle cell disease (disproportionately and primarily affecting Black Americans, respectively). Hospitals in low-income or rural areas often rank lower because they serve populations with more challenging social determinants of health (such as a lack of transportation), for which the current risk-adjustment models do not fully account.

Another reason that USNWR cited for moving to condition-based ratings was the difficulty in attributing a patient's death to a specific specialty. If a patient is admitted with kidney failure but dies of a heart attack, this death is difficult to "assign" to the correct unit. Also, hospitals that provide care for patients who are most ill are often penalized with lower scores, even if they provide excellent care. This aspect of the rankings encourages "cherry-picking" healthier patients to protect ranking scores, exactly the opposite of the responsibilities expected—and incentivized through favored tax status—by the most highly ranked hospitals.

In 2021 and 2022, ASN proposed developing refined mortality methodology that uses billing codes specific to kidney care, detailed in the 2023 *Kidney Medicine* article (4). Importantly, this methodology requires the entire kidney community, besides ASN, to embrace the development of new billing codes for kidney care. Historically, some members of the community have focused on supporting the status quo related to kidney failure—and therefore dialysis—causing them to oppose more billing codes that would recognize and reward the full spectrum of care that nephrologists deliver.

Nephrology is on the crest of a wave of innovation, including new precision medications (particularly for people with rare kidney diseases), therapies to treat cardiovascular-kidney-metabolic syndrome, and progress toward xenotransplantation. A return to ranking nephrology as a specialty rewards structural innovation in hospitals, such as participating in clinical trials, focusing on going "upstream" to identify and treat people at risk for kidney diseases and kidney failure, and managing the transplant waitlist successfully.

At the same time, why have hospital leaders, the public, and even physicians and surgeons accepted USNWR's role in determining "Best Hospitals"? As the situation with nephrology underscores, these rankings can act as a mirage of quality, masking systemic biases and flawed data. This system creates perverse incentives, in which some hospitals prioritize high-profile, ranked specialties rather than essential but unranked areas like nephrology, infectious diseases, and primary care.

Claiming editorial independence, USNWR warrants regulatory scrutiny for financial relationships with hospitals. Since ceasing operations as an independent newsmagazine in 2015, USNWR's sole business appears to be "the ranking game," and that business is strictly "pay to play" (1). Hospitals pay to use the USNWR "Best Hospitals" logo in their marketing and for access to granular "under-the-hood" data to see how to improve their scores (7). At a minimum, USNWR should disclose exactly how much revenue it receives from hospitals that are paying to be *objectively* assessed.

USNWR asserts that the "annual Best Hospitals rankings has been helping patients find, in consultation with their doctors, the best hospital for their health needs" for more than 35 years (3). Besides USNWR's bottom line, who benefits from these rankings? Are people living with chronic diseases, acute illnesses, and other maladies being helped? How does USNWR's assertion stand when its rankings ignore kidney diseases, which afflict more Americans than most of the 15 ranked specialties, have increased in prevalence by approximately 20% since 2005, and are the ninth-leading cause of death in the United States?

Named for Robert McNamara—who served as Secretary of Defense when the United States entered the Vietnam War—"the McNamara fallacy" is the error of making decisions based solely on quantitative metrics while ignoring qualitative factors that cannot be easily measured. This approach often leads to a distorted reality, in which what cannot be counted is treated as if it does not exist, frequently resulting in disastrous real-world outcomes.

The McNamara fallacy is a 20th century interpretation of the 13th century story of Nasreddin Hodja. After losing his ring in a dark room of his house, he searches for it in the yard because the light is better outside. USNWR's approach to ranking specialties—and by extension, "Best Hospitals"—is a 21st century interpretation of this parable. ■

Samir M. Parikh, MD, FASN, is a professor of internal medicine and pharmacology and the Chief of Nephrology at The University of Texas Southwestern Medical School, Dallas, and ASN president. Tod Ibrahim, MLA, is chief executive officer and executive vice president, American Society of Nephrology, Washington, DC.

To comment on Dr. Parikh and Mr. Ibrahim's editorial, please contact email@asn-online or tibrahim@asn-online.org.

Table. Specialties, procedures, and conditions that USNWR currently ranks

Specialty	Procedures and conditions
Cancer[a]	Colon cancer surgery
	Gynecologic cancer surgery
	Leukemia, lymphoma, and myeloma
	Lung cancer surgery
	Prostate cancer surgery
Cardiology and heart and vascular surgery[a]	Abdominal aortic aneurysm repair
	Aortic valve surgery
	Heart arrhythmia
	Heart attack
	Heart bypass surgery
	Heart failure
	Pacemaker implantation
	Stroke
	Transcatheter aortic valve replacement
Diabetes and endocrinology[a]	Diabetes
Ear, nose, and throat	
Gastroenterology and gastrointestinal surgery[a]	
Geriatrics	
Neurology and neurosurgery[a]	
Obstetrics and gynecology	
Ophthalmology	
Orthopedics[a]	Back surgery (spinal fusion)
	Hip fracture
	Hip replacement
	Knee replacement
Psychiatry	
Pulmonology and lung surgery[a]	Chronic obstructive pulmonary disease
	Pneumonia
Rehabilitation	
Rheumatology	
Urology[a]	**Other**
	Kidney failure

[a]Included in USNWR's "Best Children's Hospitals" along with neonatology, nephrology, and pediatric/adolescent behavioral health (3).

References

1. Gladwell M. The order of things. *The New Yorker.* February 6, 2011. https://www.newyorker.com/magazine/2011/02/14/the-order-of-things
2. Frazier KM, et al. Fatally flawed—making sense of US News & World Report mortality scores. *JAMA Otolaryngol Head Neck Surg* 2021; 147:317–319. doi: 10.1001/jamaoto.2020.5323
3. Best hospitals 2025–2026. US News & World Report. 2025. https://health.usnews.com/best-hospitals
4. Warfield C, et al. Nephrology and the US News and World Report hospital-based specialty rankings. *Kidney Med* 2023; 5:100620. doi: 10.1016/j.xkme.2023.100620
5. Ibrahim T. CKM syndrome, a new superspecialty, and the Love Your Kidneys! campaign. *Kidney News*, February 2026; 18(2):6–7. https://doi.org/10.62716/kn.002922026
6. U.S. News & World Report faces legal scrutiny over dubious hospital rankings. City and County of San Francisco. June 20, 2023. https://www.sf.gov/news-us-news-world-report-faces-legal-scrutiny-over-dubious-hospital-rankings
7. Henderson J. Hospitals pay US News to promote their rankings—amid rankings pushback, the question of payment for use of the company's logo has resurfaced. *MedPage Today*. January 18, 2024. https://www.medpagetoday.com/special-reports/features/108313

Advancing Kidney Health Through Congressional Engagement, Supply-Chain Resilience, and Transplant System Reform

By Ryan Murray

https://doi.org/10.62716/kn.003502026

Advancing policies to improve kidney care through congressional engagement, supply-chain reform, and regulatory modernization of the transplant system: ASN focused on these and other advocacy efforts earlier this year. These goals reflect ASN's commitment to ensuring that the more than 37 million Americans living with kidney diseases have access to innovative therapies, reliable care delivery, and a high-functioning transplant system.

House Ways and Means Health Subcommittee hearing on improving kidney health

ASN's participation in March in a hearing before the House Ways and Means Subcommittee on Health, which focused on improving kidney health through prevention and innovation, was a central highlight of the society's advocacy efforts. During the hearing, ASN Health Policy Scholar Suzanne Watnick, MD, FASN, delivered compelling testimony, underscoring the urgent need to modernize the nation's approach to kidney care (1).

Watnick emphasized that the current system remains heavily weighted toward costly, late-stage treatment rather than early detection and prevention. She urged Congress to prioritize a more proactive, patient-centered framework that aligns dialysis care with transplantation and supports earlier intervention across the disease continuum. Watnick's testimony highlighted that despite significant advances in other disease areas, kidney diseases have not seen comparable levels of innovation or investment.

Importantly, Watnick reinforced the need for substantially increased federal research funding, referencing ASN's "Transforming Kidney Health Research" report (2). She noted that accelerating discovery and expanding access to innovative therapies have the potential not only to improve patient outcomes but also to reduce long-term health care costs. By shifting the focus toward prevention, early diagnosis, and novel treatments, policymakers can help bend the cost curve while delivering better care to patients.

Advancing ASN priorities and kidney care across the executive branch

Complementing its congressional engagement, ASN also took action to address a critical but often underappreciated issue: the resilience of the kidney care supply chain. In a letter by ASN President Samir M. Parikh, MD, FASN, comments on the Centers for Medicare & Medicaid Services (CMS) Advanced Notice of Proposed Rulemaking and ensuring the safety of personal protective equipment and essential medicine in Medicare-participating hospitals outlined ongoing vulnerabilities affecting the availability of essential supplies used in dialysis and transplantation (3).

Significant weaknesses in global supply chains have been exposed by events such as the COVID-19 pandemic, natural disasters, and other unanticipated disruptions, many of which persist today. ASN's letter highlights that kidney care is particularly susceptible to these disruptions due to its reliance on a steady supply of specialized products, including dialysis fluids, medications, and equipment. Even temporary shortages can have immediate and serious consequences for patients who depend on regular, life-sustaining treatment.

To address these risks, ASN called for a series of policy interventions aimed at strengthening domestic manufacturing capacity and improving supply-chain transparency. Increasing US-based production of critical kidney care supplies would reduce dependence on foreign sources and enhance preparedness for future public health emergencies. ASN also urged policymakers to consider mechanisms for tracking supply availability and anticipating shortages before they reach crisis levels.

In addition, ASN advocated for the development of strategic reserves of essential supplies to ensure continuity of care during emergencies. Such reserves could function similarly to existing federal stockpiles but be tailored to the unique needs of kidney care. By framing supply-chain resilience as a patient safety issue, ASN is working to elevate its importance within broader health care policy discussions.

Targeting reforms to strengthen OPO oversight, increase organ utilization, and improve the transplant system

The third major policy action earlier this year was ASN's detailed response to a proposed rule from CMS regarding organ procurement organizations (OPOs) (4). This proposed rule represents the next phase of efforts to improve accountability and performance in the organ procurement system following the 2020 final rule that introduced more objective metrics.

ASN commended the OPO community for increased organ procurement and transplantation since implementation of the 2020 rule, noting that the society, "celebrates the OPO community's growth in organ procurement over the last several years, efforts that have saved thousands of lives." The society commended CMS for issuing a proposed rule that aimed to bring greater clarity to OPO evaluation, recertification, and decertification processes.

ASN supported CMS' proposal to establish pathways for certifying new OPOs and to assign performance tiers at the donor service–area level rather than across entire organizations. The society endorsed several technical updates, including clarifying how pancreata used for islet cell research are counted in performance metrics and revising the definition of "adverse events" to encourage broader reporting and quality improvement. However, ASN urged CMS to clearly distinguish "adverse events" from "unsound medical practices," given that, as proposed, the latter could lead to immediate termination.

Although supporting CMS' efforts to define and increase use of "medically complex organs" for OPO quality assessment and performance improvement efforts, ASN emphasized that underuse of some organs that may benefit certain patients reflects broader systemic challenges, including misaligned incentives between OPOs and transplant centers, regulatory pressures on transplant outcomes, and limited incorporation of patient preferences. ASN cautioned that definitional changes alone are unlikely to meaningfully increase utilization without more comprehensive reforms. Overall, ASN encouraged CMS to pursue a more holistic, patient-centered approach to strengthen the transplant system and expand access.

Whether addressing a lack of prevention and innovation in kidney care, supply-chain vulnerabilities, or opportunities to strengthen the transplant system, ASN is working to ensure that federal policies are informed by clinical expertise and grounded in the realities faced by patients and kidney care professionals. ASN's advocacy also reflects a broader recognition that kidney health policy does not exist in isolation. It is influenced by, and in turn influences, policies related to public health, infrastructure, and health care delivery. By engaging across these domains, ASN is positioning itself as a leading voice in shaping a more integrated and forward-looking approach to kidney health. In the coming months, ASN will continue to engage with federal agencies, Congress, and other stakeholders to advance these priorities. ■

To keep track of ASN's policy efforts throughout the year, follow coverage in *Kidney News* and the ASN podcast feed, and visit ASN's Kidney Health Advocacy policy webpage (www.asn-online.org/policy/kidney-health.aspx). For real-time updates from ASN Policy, follow @ASNAdvocacy on X.

Ryan Murray is the senior manager of Policy and Government Affairs at ASN.

References

1. US House Committee on Ways & Means. Chairman Jason Smith. Health Subcommittee Hearing on Improving Kidney Health Through Better Prevention and Innovative Treatment. March 18, 2026. https://waysandmeans.house.gov/event/health-subcommittee-hearing-on-improving-kidney-health-through-better-prevention-and-innovative-treatment/
2. American Society of Nephrology. *Transforming Kidney Health Research: A Research Agenda for the Future*. October 2025. https://www.asn-online.org/policy/webdocs/Transforming_Kidney_Health_Research_Report_Final.pdf
3. Parikh SM.; American Society of Nephrology. Letter to The Honorable Robert F. Kennedy, Jr., JD, and Mehmet Oz, MD, MBA, on MS-1516-ANPRM-Medicare program; ensuring safety through domestic security with made in America personal protective equipment (PPE) and essential medicine procurement in Medicare participating hospitals. March 30, 2026. https://www.asn-online.org/policy/webdocs/26.03.30DomesticSupplyChainLetterfinal.pdf
4. Parikh SM.; American Society of Nephrology. Letter to The Honorable Mehmet Oz, MD, on CMS 3409-P [RIN 0938-AV65]. March 31, 2026. https://www.asn-online.org/policy/webdocs/26.3.30FinalASNOPOruleresponse.pdf

Neutral Rules, Unequal Outcomes: Rethinking Equity in Kidney Allocation

By Douglas Whitmire and Li Yang Low

https://doi.org/10.62716/kn.003232026

Kidney transplant allocation systems distribute organs through clinically grounded criteria, and yet disparities in access, waitlisting, and outcomes persist across the transplant pathway (1). These patterns are not accidental. They reflect how allocation rules interact with the structural conditions shaping patients' health and access to care.

In the United States, allocation is also more than clinical practice: It is a federally authorized policy system. Congress created the Organ Procurement and Transplantation Network (OPTN) through the National Organ Transplant Act, and the Department of Health and Human Services implements national requirements through regulation, including the OPTN "Final Rule" in Title 42 of the Code of Federal Regulations, Part 121 (2). Within this framework, allocation criteria function as binding governance: They set national priorities under scarcity, shape how centers act, and distribute life-extending opportunities at scale.

Modern kidney allocation prioritizes medical utility. Metrics such as the Kidney Donor Profile Index and Estimated Post-Transplant Survival score operationalize goals of graft longevity and patient survival (3). The rationale is intuitive and global: Organs are scarce, transplantation offers a survival advantage compared with dialysis (4–6), and stewardship encourages efficient use of donated kidneys.

Utility frameworks also embed value judgments. Predictive models define "benefit," determine how outcomes are compared, and set acceptable levels of risk. Longevity matching emphasizes duration of survival, whereas comorbidity-sensitive measures steer offers toward candidates with higher predicted post-transplant survival. These policy choices influence who moves forward faster, who waits longer, and who receives which organs.

A large evidence base shows that transplant access and outcomes are patterned by race and ethnicity, socioeconomic status, geography, and other structural determinants of health (1). Patients with fewer resources face obstacles in referral, evaluation, waitlisting, and the ability to complete time-sensitive requirements (7–9). Clinical variables used in allocation (such as comorbidities and markers of cumulative disease burden) are themselves influenced by unequal exposure to environmental risk, inconsistent health care access, and chronic stressors (10). When allocation criteria rely on clinical variables that correlate with these determinants, distributional effects emerge.

Age-related prioritization illustrates this dynamic. Age correlates with cumulative disease burden and lifetime exposure to uneven health care access. Clinical risk factors used in survival prediction are also unevenly distributed across populations shaped by environmental exposure, health care continuity, and chronic stressors (8–10). Geography adds another layer: Regional organ supply, transplant center density, and travel burdens shape opportunity to receive a kidney (11–13). Although allocation rules operate downstream from these realities, they interact with them in ways that can amplify existing inequities.

These realities raise an accountability question that is partly ethical and partly legal: How should a national allocation system justify distributive trade-offs when measurable disparities persist? Across health care, attention is increasingly directed toward subgroup performance, fairness of standardized decision systems, and downstream consequences of neutral criteria (14). In parallel, federal civil rights frameworks prohibit discrimination in federally funded health programs (including Title VI [15] and the Affordable Care Act's Section 1557 [16]). Transplant allocation is rarely discussed in this register, but the normative logic translates: When a system creates predictable disparities, legitimacy turns on transparent objectives, evidence-based justification, and ongoing monitoring.

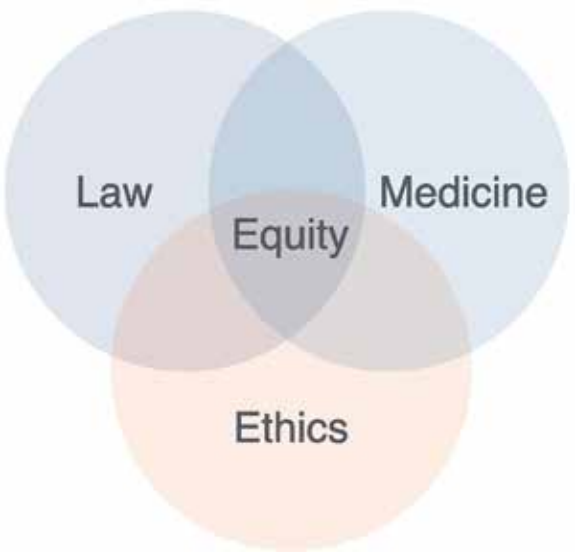
Equity work also requires attention upstream from the match run. Referral practices, evaluation completion, committee decision-making, and center-level processes function as primary access gates (8–10). Interventions focused solely on allocation metrics risk overlooking where barriers are most concentrated. Reducing administrative friction, standardizing evaluation steps where appropriate, and expanding patient navigation support may meaningfully alter who ultimately reaches the waiting list (17).

Policy design can respond through transparency and measurement. Allocation reforms can clearly state the objectives being optimized, evaluate anticipated subgroup impacts, and commit to routine disparity monitoring. Public reporting of subgroup outcomes would enhance transparency and strengthen trust in the system's stewardship.

Kidney allocation is an exercise in stewardship under scarcity. Its legitimacy depends on technical performance and on clear accounting of distributive consequences. Utility remains essential. Equity requires visibility, measurement, and reasoned justification. Scarcity demands prioritization. Justice demands visibility. ■

Douglas Whitmire, MPH, a Wurzburger Health Law Scholar, and Li Yang (Eric) Low, MS, are JD candidates at Case Western Reserve University School of Law, Cleveland, OH.

The authors report no conflicts of interest.



References

1. Nguyen KH, et al. Despite national declines in kidney failure incidence, disparities widened between low- and high-poverty US counties. *Health Aff (Millwood)* 2021; 40:1900–1908. doi: 10.1377/hlthaff.2021.00458
2. National Organ Transplant Act. 42 U.S.C. § 274. https://uscode.house.gov/view.xhtml?req=granuleid:USC-2007-title42-section274&num=0&edition=2007
3. Israni AK, et al. New national allocation policy for deceased donor kidneys in the United States and possible effect on patient outcomes. *J Am Soc Nephrol* 2014; 25:1842–1848. doi: 10.1681/ASN.2013070784
4. Wolfe RA, et al. Comparison of mortality in all patients on dialysis, patients on dialysis awaiting transplantation, and recipients of a first cadaveric transplant. *N Engl J Med* 1999; 341:1725–1730. doi: 10.1056/NEJM199912023412303
5. Tonelli M, et al. Systematic review: Kidney transplantation compared with dialysis in clinically relevant outcomes. *Am J Transplant* 2011; 11:2093–2109. doi: 10.1111/j.1600-6143.2011.03686.x
6. Zhang Y, et al. Quantifying the treatment effect of kidney transplantation relative to dialysis on survival time: New results based on propensity score weighting and longitudinal observational data from Sweden. *Int J Environ Res Public Health* 2020; 17:7318. doi: 10.3390/ijerph17197318
7. Purnell TS, et al. Racial differences in determinants of live donor kidney transplantation in the United States. *Am J Transplant* 2013; 13:1557–1565. doi: 10.1111/ajt.12258
8. Suah A, Saunders MR. Racial disparities in living donor kidney transplantation—how can we bridge the gap? *JAMA Netw Open* 2023; 6:e2347808. doi: 10.1001/jamanetworkopen.2023.47808
9. Clark-Cutaia MN, et al. Identifying when racial and ethnic disparities arise along the continuum of transplant care: A national registry study. *Lancet Reg Health Am* 2024; 38:100895. doi: 10.1016/j.lana.2024.100895
10. Ozieh MN, et al. The cumulative impact of social determinants of health factors on mortality in adults with diabetes and chronic kidney disease. *BMC Nephrol* 2021; 22:76. doi: 10.1186/s12882-021-02277-2
11. Ashby VB, et al. Geographic variability in access to primary kidney transplantation in the United States, 1996–2005. *Am J Transplant* 2007; 7:1412–1423. doi: 10.1111/j.1600-6143.2007.01785.x
12. Axelrod DA, et al. Accountability for end-stage organ care: Implications of geographic variation in access to kidney transplantation. *Surgery* 2014; 155:734–742. doi: 10.1016/j.surg.2013.12.010
13. Katz-Greenberg G, McElroy LM. Geography and access to kidney transplant—are we measuring what matters? *JAMA Netw Open* 2025; 8:e2549629. doi: 10.1001/jamanetworkopen.2025.49629
14. Obermeyer Z, et al. Dissecting racial bias in an algorithm used to manage the health of populations. *Science* 2019; 366:447–453. doi: 10.1126/science.aax2342
15. Title VI, 42 U.S.C. § 2000d et seq. https://www.govinfo.gov/content/pkg/USCODE-2008-title42/html/USCODE-2008-title42-chap21-subchapV.htm
16. National Archives. Part 92—Nondiscrimination in Health Programs or Activities. Code of Federal Regulations. ACA § 1557, 42 U.S.C. § 18116. https://www.ecfr.gov/current/title-45/subtitle-A/subchapter-A/part-92
17. Taber DJ, et al. Multilevel intervention to improve racial equity in access to kidney transplant. *J Am Coll Surg* 2023; 236:721–727. doi: 10.1097/XCS.0000000000000542

AI in Nephrology Hands-On Primer: Practical Applications and Clinical Integration

By Noppawit Aiumtrakul, Arjunmohan Mohan, Harshil A. Fichadiya, and Wisit Cheungpasitporn

https://doi.org/10.62716/kn.003482026

The rapid evolution of artificial intelligence (AI) in medicine is reshaping how clinicians access information, synthesize evidence, and interact with clinical data (1–3). The AI in Nephrology: A Hands-On Primer Workshop (March 16–17, 2026, in New York, NY), an impactful initiative led by ASN, the Renal Research Institute, the Windreich Department of Artificial Intelligence and Human Health at the Icahn School of Medicine at Mount Sinai, and the ASN AI Steering Committee, demonstrated that this transformation is not a distant future but a present-day reality. Key sessions included a hands-on data and generative AI workshop, as well as a creative AI applications session, both of which highlighted practical, real-world–use cases of AI across clinical and educational workflows.

From a trainee perspective, the workshop also highlighted how quickly AI tools are becoming part of everyday clinical thinking, shifting from optional exploration to practical skill building.

The rapid evolution of AI in medicine

The current wave of generative AI parallels the early internet era, defined by rapid adoption, expanding capabilities, and important uncertainty. Large language models (LLMs) can now summarize complex literature, generate clinical documentation, and assist in decision-making workflows within seconds. However, these systems rely on probabilistic pattern recognition rather than true understanding, which introduces risks such as hallucinations, contextual errors, and variability in outputs.

A key insight from the workshop was the inconsistency across AI platforms. Identical prompts entered into tools such as ChatGPT, Gemini, and Claude often produced meaningfully different responses. This variability highlights a critical challenge for clinical integration, in which reproducibility and reliability are essential.

For many participants, this variability was not just theoretical but directly observed during hands-on sessions, reinforcing the need for cautious interpretation and cross-validation in clinical contexts.

Overview of available AI tools

The workshop highlighted a rapidly expanding ecosystem of AI tools that support different aspects of clinical and academic workflows. Rather than focusing on individual platforms, these tools can be broadly categorized into functional domains:

- Knowledge synthesis and literature review. Tools such as NotebookLM enable structured summarization and extraction of key findings from research articles.
- Clinical documentation and workflow support. Platforms such as DoxGPT and Microsoft Copilot assist with note generation, summarization, and integration into existing workflows.
- Visual content and communication. Tools including Canva and Napkin AI facilitate the creation of figures, diagrams, and educational materials.
- Evidence-grounded clinical support. Platforms such as OpenEvidence provide curated, reference-linked clinical information.

These tools demonstrate how AI is transitioning from isolated applications to workflow-integrated support systems that can enhance efficiency while requiring ongoing human oversight.

For trainees, exposure to this ecosystem provided a practical framework for understanding how different tools can be combined within a single workflow, rather than used in isolation.

Practical cases from the workshop

Hands-on sessions provided real-world examples illustrating both the strengths and limitations of AI in nephrology. Selected examples included:

Case 1: Literature summarization and synthesis. AI tools performed well in summarizing complex research articles, extracting key findings, and generating structured outputs suitable for presentations. This significantly reduced the time required for literature review, although outputs required verification for accuracy and completeness.

Case 2: Image recognition—kidney dietary assessment and peritoneal dialysis catheter exit sites. AI demonstrated potential in interpreting visual data, including dietary images and peritoneal dialysis catheter exit sites, with occasional high agreement with expert assessment. However, important limitations were evident, including susceptibility to error, dependence on image quality, and lack of clinical context. More broadly, image-based applications highlighted recurring challenges across domains, including bias, variability in input quality, and the need for integration with clinical context and systematic evaluation. These findings reinforce that AI cannot replace expert clinical judgment in these settings at this stage.

The integration of AI into nephrology is no longer theoretical. The key challenge now is how to use these tools effectively, safely, and thoughtfully in clinical practice.

Case 3: Clinical reasoning variability across models. When applied to clinical scenarios, different LLMs produced variable reasoning pathways and recommendations. This variability underscores the importance of cross-checking outputs and maintaining clinical oversight, particularly in decision-making contexts.

In addition to these examples, the workshop highlighted emerging efforts to translate AI into clinician-facing tools through abstract presentations. One notable example was NephroResource, a web-based platform developed by Matthew Abramson, MD, and recognized as one of the top abstracts during the workshop (4). This platform integrates curated nephrology knowledge into a single, accessible interface for education and clinical support, representing an important step toward bridging general AI capabilities with practical clinical application.

Building the AI nephrology community

Beyond individual tools, the workshop emphasized the importance of community-driven learning. ASN is actively supporting this effort through workshops, webinars, and the AI-Powered Kidney Care Network (its dedicated AI Communities forum), which provides a platform for collaboration, knowledge sharing, and ongoing education (5).

For fellows and early-career clinicians, this community serves not only as a space for learning but also as an opportunity to actively contribute to the responsible development and real-world implementation of AI in nephrology.

As AI continues to evolve rapidly, sustained engagement with such communities will be critical for clinicians to stay current, exchange practical insights, and navigate emerging challenges in a collaborative manner. The integration of AI into nephrology is no longer theoretical. The key challenge now is how to use these tools effectively, safely, and thoughtfully in clinical practice. For nephrologists, this means moving beyond awareness toward active engagement: understanding both the capabilities and limitations of AI and participating in shaping its role in patient care. ■

Noppawit Aiumtrakul, MD; Arjunmohan Mohan, MBBS; and Harshil A. Fichadiya, MBBS, are nephrology fellows in the Division of Nephrology and Hypertension at the Mayo Clinic in Rochester, MN. Wisit Cheungpasitporn, MD, FASN, is a professor of medicine in the Division of Nephrology and Hypertension at the Mayo Clinic and Artificial Intelligence Content Lead and Course Director for the Mayo Clinic Alix School of Medicine.

The authors report no conflicts of interest.

References

1. McCarthy J, et al. A proposal for the Dartmouth summer research project on artificial intelligence, August 31, 1955. *AI Magazine* 2006; 27:12. https://doi.org/10.1609/aimag.v27i4.1904
2. Hasanzadeh F, et al. Bias recognition and mitigation strategies in artificial intelligence healthcare applications. *NPJ Digit Med* 2025; 8:154. doi: 10.1038/s41746-025-01503-7
3. Tangri N, et al.; American Society of Nephrology (ASN) Artificial Intelligence (AI) Workgroup. Responsible use of artificial intelligence to improve kidney care: A statement from the American Society of Nephrology. *J Am Soc Nephrol* 2026; 37:881–890. doi: 10.1681/ASN.0000000929
4. NephroResource. Clinical tools for nephrology practice. Accessed March 19, 2026. https://nephroresource.com/
5. ASN Communities: AI-Powered Kidney Care Network. Accessed March 19, 2026. https://community.asn-online.org/home

From "Blood Washing" to Intelligent Organ Support, the Dawn of Adaptive Extracorporeal Therapy

By Prakash Gudsoorkar

https://doi.org/10.62716/kn.003312026

The hollow-fiber hemodiayzer has labored for over 50 years to prevent immediate mortality for millions using its technology of kidney replacement therapy (KRT). However, its fundamental design philosophy of filtering blood primarily by size has long been a constraint. Its predominantly determinate delivery of therapy is most apparent among individuals who are critically ill, who require a more adaptive design. As we move into May 2026, this special section of *Kidney News* highlights a profound paradigm shift. Extracorporeal blood purification (EBP) is moving from passive filtration toward intelligent therapeutic subsystems that are more adaptable and integrative (Figure).

The technologic trifecta: Smart materials, sensors, and AI

The future of EBP is being propelled by the merging of three pillars: smart biomaterials, embedded sensing, and artificial intelligence (AI). Compared with current polymer membranes (simple sieves), which try to retain protein-bound uremic toxins but can prevent diffusion, we are now seeing the emergence of "smart" filtration that uses mixed matrix membranes that embed adsorptive particles directly into the polymer matrix. Even more precise are molecularly imprinted polymers, which act as "synthetic antibodies" by creating binding sites that "fit" specific target molecules.

However, materials science is only half of the story. Digital integration is transforming the delivery of bedside therapy (1). For example, the cartridge, as a sensor, can use optical monitoring of spent dialysate and calculate solute removal in real time, and with perpetual sensing, earlier detection is attainable. Models can now predict risks before symptoms appear, allowing for preliminary adjustments to ultrafiltration rates. The road map ahead for AI systems includes more precise risk stratification that shifts the nephrologist's role from manual dosing to high-level oversight of an adaptive system (2).

Polymyxin B hemoperfusion: Endotoxin adsorption in septic shock

Another important thread in this issue is endotoxin-directed adsorption using polymyxin B hemoperfusion. The therapeutic premise is based on the binding of the circulating endotoxin and attenuating the vasoplegia and inflammatory amplification that drive shock physiology (3). The clinical story reinforces a central lesson in modern EBP: Outcomes depend as much on who we treat and when we treat them as on the cartridge itself, and trial results to date have been mixed. Operationally, polymyxin B hemoperfusion must be integrated thoughtfully with continuous KRT (CKRT) when kidney support is concurrently needed, whether delivered sequentially or in parallel, while accounting for anticoagulation strategy, circuit complexity, and the potential for unintended adsorption of medications. Finally, endotoxin adsorption may ultimately find a role beyond classic gram-negative sepsis, in syndromes in which endotoxin translocation and immune dysregulation contribute to shock biology, even when cultures are negative, provided future studies can define actionable triggers and patient-centered endpoints.

Beyond clearance: Targeted immune modulation

One of the most exciting frontiers explored in this issue is the move from "washing" the blood to actively modulating the immune system. Acute kidney injury in the intensive care unit is frequently a result of dysregulated inflammation rather than just a lack of clearance. The selective cytopheretic device (SCD) represents a novel approach to this problem (4, 5). Rather than simply removing cytokines, the SCD targets the cellular drivers of inflammation, activated neutrophils, and monocytes.

By creating a low-calcium environment within the circuit (typically via citrate anticoagulation), the SCD promotes a shift in leukocyte behavior, marking activated proinflammatory cells for apoptosis and encouraging the differentiation of reparative M2 macrophages. Although early trials like SCD-003 faced logistical hurdles, the ongoing NEUTRALIZE-AKI trial (NCT05758077) is poised to provide definitive evidence on whether this cell-directed immunomodulation can reduce mortality and dialysis dependence in adults who are critically ill (6).

Similarly, hemoadsorption is expanding the nephrologist's role into hematologic emergencies. In cases of cytokine release syndrome following chimeric antigen receptor T cell

Continued on page 12

From "Blood Washing" to Intelligent Organ Support

Continued from page 11

therapy or hemophagocytic lymphohistiocytosis, traditional diffusive clearance is insufficient (7). Hemoadsorption cartridges, such as those using polystyrene-divinylbenzene beads, allow for the removal of large inflammatory mediators that would otherwise drive multiorgan failure. As proof-of-concept data mature, the multidisciplinary collaboration between nephrologists and hematologists will be essential to define the optimal timing and triggers for these interventions.

Engineering for the smallest patients

For too long, pediatric and neonatal CKRT was merely "small adult CKRT." This adaptation often resulted in prohibitive hemodynamic risks, as adult-sized circuits could exceed 15% of a neonate's total blood volume. This issue highlights the "game-changing" evolution of dedicated neonatal platforms like the Cardio-Renal Pediatric Dialysis Emergency Machine (CARPEDIEM) and the Newcastle Infant Dialysis and Ultrafiltration System (NIDUS) (8). These machines, designed for infants weighing as little as 2.5 kg, use miniaturized circuits (as small as 26–30 mL) and precision pumps to enable ultrafiltration accuracy of 1 g/hour.

This shift from adaptation to miniaturization is already saving lives. Comparative analyses suggest that dedicated neonatal platforms can improve survival to CKRT discontinuation from 44% (with adapted adult machines) to as high as 97% in infants under 5 kg. The success of these technologies demonstrates that when we tailor engineering to the patient's unique physiology, "extraordinary" interventions can become a feasible tool in routine neonatal care.

The rise of hybrid ECOS

Finally, we must recognize that the kidney does not fail in a vacuum. Multiorgan failure involves complex interorgan cross talk that a "siloed" approach to care cannot address. The emerging concept of extracorporeal organ support (ECOS), or multiple organ support therapy, envisions a single unit capable of delivering gas exchange, kidney support, liver detoxification, and acid-base balance (9).

Innovations in filter technology are making this integration possible. Systems like Advanced Organ Support (ADVOS) represent a leap forward by using a fluid-based approach that simultaneously removes CO_2 and hydrogen ions, correcting both respiratory and metabolic acidosis and regenerating albumin's toxin-binding capacity through pH and temperature modulation. These hybrid systems remind us that "filters define capability more than machines." By focusing on the biological target, whether water-soluble solutes, protein-bound toxins, or gas exchange, we can better protect failing organs and provide the "rest" necessary for recovery.

Challenges and the road ahead

Despite this technological enthusiasm, we must remain grounded in the "safety paradox" of innovation. As we push toward portability and wearable systems, we must ensure that biochemical safety is never compromised. Furthermore, as we integrate more adsorptive therapies, we must be vigilant about the "undesirable removal" of life-saving medications, such as antimicrobials and anticonvulsants, which require "rigorous therapeutic drug monitoring."

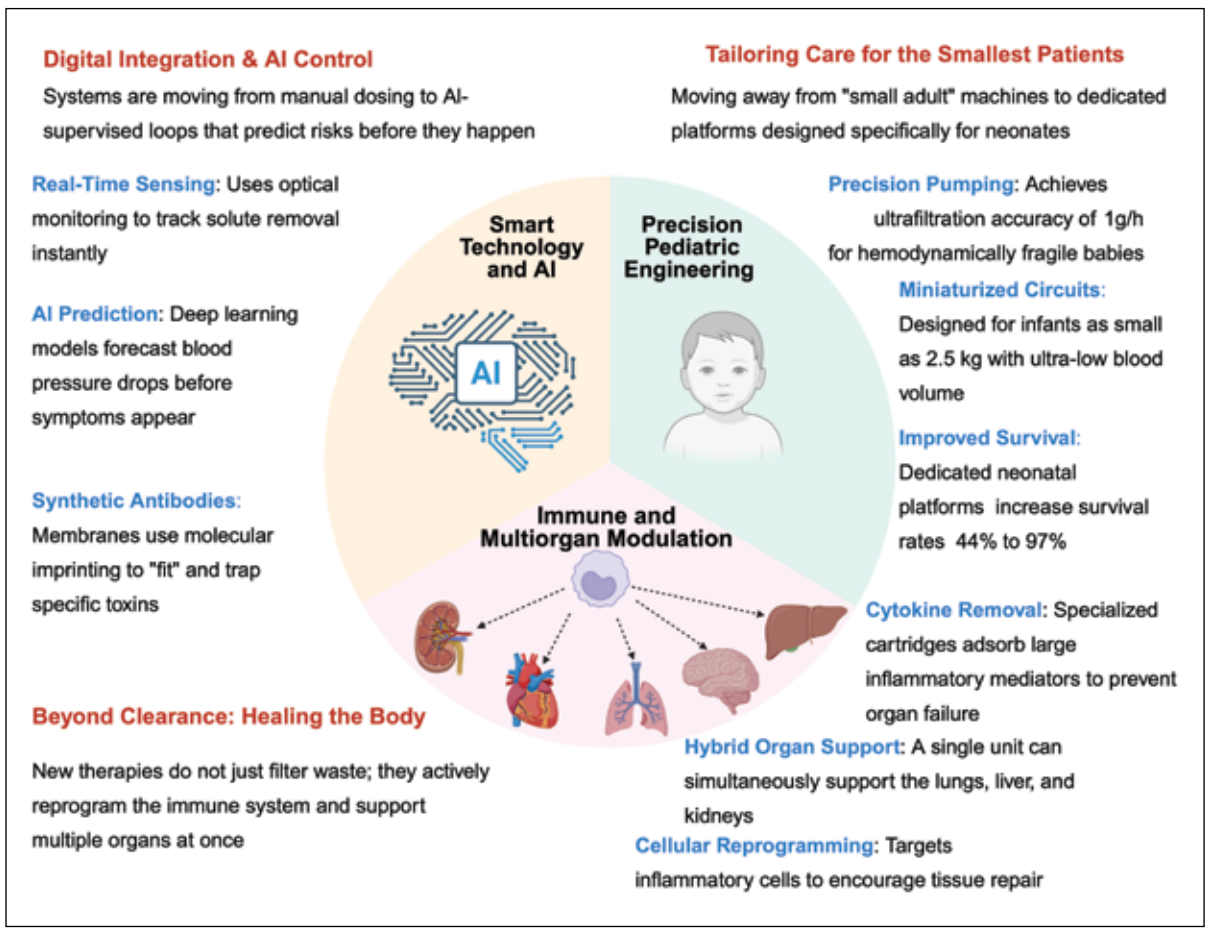
The future trajectory for intelligent extracorporeal therapy is not just engineering feasibility but also clinical translation. We must authenticate these new measures by safeguarding AI progression and proving through randomized controlled trials that these technologies can improve the care of our patients. We invite you to explore these articles and join us in redefining the future of critical care nephrology. ■

Prakash Gudsoorkar, MD, FASN, is an associate professor of medicine in the Division of Nephrology at the University of Cincinnati, OH. He is a deputy editor for Kidney News.

The author and section editor reports no conflicts of interest.

Acknowledgments: *Kidney News* thanks Editor-in-Chief Kenar D. Jhaveri, MD, FASN, and Deputy Editor Sam Kant, MD, FASN, FNKF, FACP, for their assistance with this issue's special section.

Figure. The evolution of adaptive extracorporeal therapy



References

1. Hammouda N, Neyra JA. Can artificial intelligence assist in delivering continuous renal replacement therapy? *Adv Chronic Kidney Dis* 2022; 29:439–449. doi: 10.1053/j.ackd.2022.08.001
2. Cheungpasitporn W, et al. Transforming nephrology through artificial intelligence: A state-of-the-art roadmap for clinical integration. *Clin Kidney J* 2026; 19:sfag004. doi: 10.1093/ckj/sfag004
3. Forin E, et al. Endotoxin removal therapy with polymyxin B immobilized fiber column: A single center experience from EUPHAS2 registry. *Sci Rep* 2023; 13:17600. doi: 10.1038/s41598-023-44850-9
4. Bateman RM. 36th International Symposium on Intensive Care and Emergency Medicine: Brussels, Belgium. 15–18 March 2016. *Crit Care* 2016; 20(Suppl 2):94. doi: 10.1186/s13054-016-1208-6 [Erratum: *Crit Care* 2016; 20:347. doi: 10.1186/s13054-016-1358-6].
5. Goldstein SL, et al. Selective cytopheretic device use in continuous kidney replacement therapy in children: A cohort study with a historical comparator. *Kidney Med* 2024; 6:100792. doi: 10.1016/j.xkme.2024.100792
6. Yessayan L, et al. Rationale and design of NEUTRALIZE-AKI: A multicenter, randomized, controlled, pivotal study to assess the safety and efficacy of a selective cytopheretic device in patients with acute kidney injury requiring continuous kidney replacement therapy. *Nephron* 2024; 148:43–53. doi: 10.1159/000531880
7. Köhler T, et al. Therapeutic modulation of the host defense by hemoadsorption with CytoSorb®—basics, indications and perspectives—a scoping review. *Int J Mol Sci* 2021; 22:12786. doi: 10.3390/ijms222312786
8. Vidal E, et al. Continuous veno-venous hemodialysis using the Cardio-Renal Pediatric Dialysis Emergency Machine™: First clinical experiences. *Blood Purif* 2019; 47:149–155. doi: 10.1159/000494437
9. Papamichalis P, et al. Extracorporeal organ support for critically ill patients: Overcoming the past, achieving the maximum at present, and redefining the future. *World J Crit Care Med* 2024; 13:92458. doi: 10.5492/wjccm.v13.i2.92458

Next-Generation Extracorporeal Blood Purification in Critical Care: AI-Integrated Control, Smart Biomaterials, and Adaptive Point-of-Care Systems

By Francesco Pesce, Charat Thongprayoon, and Wisit Cheungpasitporn

https://doi.org/10.62716/kn.002852026

For over half a century, the hollow-fiber hemodialyzer has stood as the workhorse of kidney replacement therapy. It prevents immediate mortality, but it remains limited in key ways: It filters mainly by size rather than biology, and it delivers a largely fixed prescription despite hour-to-hour physiologic variation. These limitations are most evident in people who are critically ill requiring continuous kidney replacement therapy, in which sepsis-associated acute kidney injury, rapid solute shifts, and hemodynamic instability expose the shortcomings of static membranes and retrospective dosing metrics. Extracorporeal blood purification (EBP) is now transitioning from static filtration toward systems that are selective, measurable, and adaptive by design. In this paradigm, future extracorporeal "filters" will function less as passive components and more as integrated therapeutic subsystems that combine clearance, sensing, and control within a single platform.

This transition is being driven by the convergence of three technologies: smart biomaterials that actively scavenge toxins, embedded sensing that quantifies therapy in real time, and artificial intelligence (AI) that personalizes therapy through closed-loop control (Figure).

Smart biomaterials: The end of passive filtration

Current polymer membranes function as sieves, but they struggle with protein-bound uremic toxins (PBUTs), such as indoxyl sulfate and *p*-cresol, which remain tightly bound to albumin and evade conventional diffusion (1). One solution is "smart" filtration using mixed matrix membranes that embed adsorptive particles (activated carbon, zeolites, or functionalized sorbents) directly into the polymer matrix. This hybrid design pairs filtration with adsorption, improving PBUT capture while preserving permeability and, in some designs, creating an additional barrier to dialysate-side contaminants (2).

Beyond membranes, customizable sorbent resins are re-emerging as modular tools. Instead of expecting one membrane to solve every clearance problem, future circuits may use swappable sorbent beds tuned to the clinical goal: PBUT capture (often via adsorption or displacement approaches), removal of inflammatory mediators, or targeted toxin or drug removal in specific intoxications (3). That modularity is especially attractive for decentralized care, in which indications vary, and lab support may be limited.

Molecularly imprinted polymers push specificity even further. By creating binding sites that "fit" a target molecule, molecularly imprinted polymers act like synthetic antibodies for the dialysis circuit. In tests using an imprinted zeolite incorporated into a mixed matrix membrane, *p*-cresol removal was reported to be over 180-fold higher than in a nonimprinted polymer control, illustrating the potential for precision detoxification (4).

Sensors and AI: From static prescription to closed-loop modulation

Whereas materials science improves the chemistry of clearance, digital integration is changing how therapy is delivered. Intradialytic hypotension remains common and is often driven by ultrafiltration that outpaces plasma refill. Closed-loop biofeedback systems aim to reduce this mismatch. By monitoring signals such as relative blood volume, these controllers can modulate the ultrafiltration rate in near-real time. A recent narrative review summarizes these approaches, while emphasizing that broader validation is still needed (5).

At the same time, the cartridge itself is becoming a sensor. Spent dialysate optical monitoring can estimate solute removal continuously using ultraviolet absorbance and fluorescence. Paats and colleagues developed models to estimate β2-microglobulin concentration in spent dialysate from these optical signatures (6). Earlier work in blood purification highlighted a key nuance: β2-Microglobulin itself is not a strong ultraviolet chromophore, so optical estimates may depend on correlated surrogate signals and can behave differently in hemodiafiltration versus hemodialysis (7).

Once sensing is continuous, prediction and control become feasible. Using multicenter clinical data, a deep learning model was developed to predict intradialytic hypotension risk using pre-dialysis features and compared against traditional models including eXtreme Gradient Boosting (XGBoost) (8). The near-term value is an early warning that prompts pre-emptive actions (ultrafiltration profiling, cooler dialysate, or staffing attention) before symptoms and rescue interventions are required. The long-term vision is an AI-supervised control loop that adjusts therapy within clinician-defined safety limits. Crucially, AI-enabled closed-loop systems in extracorporeal therapy should be conceived as clinician-constrained decision support, not autonomous treatment, operating within predefined safety envelopes and escalation rules that preserve human oversight and accountability.

Point-of-care and wearable systems: Engineering versus safety

Selective materials, real-time analytics, and closed-loop control are also what make decentralization plausible. Portable EBP could extend acute support to smaller hospitals, emergency settings, or step-down and home-adjacent environments. Coupled with telemonitoring and standardized cartridge workflows, these platforms could also support supervised home-based acute treatments for carefully selected patients.

Wearable systems remain the moonshot, and dialysate regeneration is still the hard part. Sorbent-based systems are effective but heavy and finite. Electro-oxidation has been explored as a lighter alternative for urea removal, but safety data urge caution. In a key study, electro-oxidation applied to glucose-containing fluids generated large increases in toxic glucose degradation products, including a more than 300-fold rise in methylglyoxal under high-glucose conditions (9). This safety paradox highlights that portability cannot come at the cost of biochemical safety.

EBP is evolving from "blood washing" to organ support. Smart biomaterials can make clearance more selective, biosensor-embedded cartridges can make clearance measurable in real time, and AI can make therapy adaptive (10). The next frontier is clinical translation: validating new clearance metrics beyond urea, defining safety boundaries for autonomy, and demonstrating that these innovations improve outcomes that matter to patients. Ultimately, the success of intelligent extracorporeal therapy will not be measured by clearance curves alone but by whether treatments become more stable, less interruptive, and more tolerable for patients. ■

Francesco Pesce, MD, PhD, FERA, is associate professor of nephrology at Università Cattolica del Sacro Cuore, Rome, Italy. Charat Thongprayoon, MD, MS, FASN, is an associate professor of medicine in the Division of Nephrology and Hypertension at the Mayo Clinic, Rochester, MN. Wisit Cheungpasitporn, MD, FASN, is a professor of medicine in the Division of Nephrology and Hypertension at the Mayo Clinic and serves as Artificial Intelligence Content Lead and Course Director for the Mayo Clinic Alix School of Medicine.

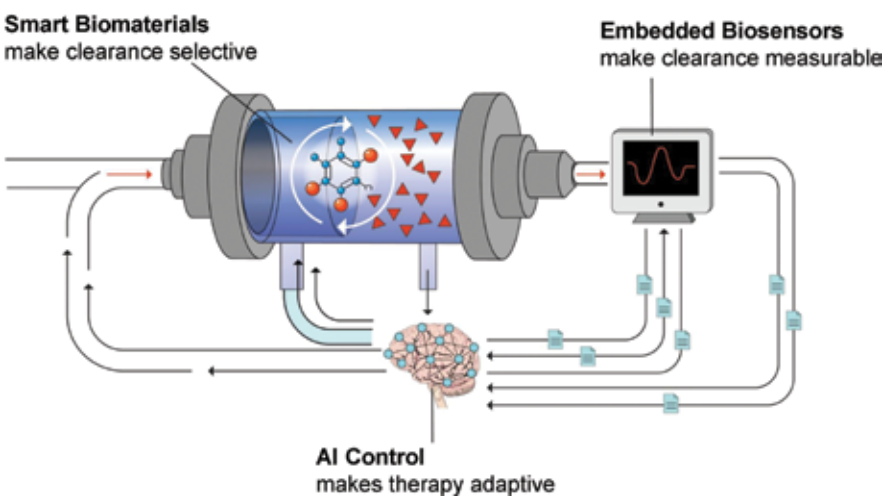
The authors report no conflicts of interest.

References

1. van Gelder MK, et al. From portable dialysis to a bioengineered kidney. *Expert Rev Med Devices* 2018; 15:323–336. doi: 10.1080/17434440.2018.1462697
2. Geremia I, et al. In vitro assessment of mixed matrix hemodialysis membrane for achieving endotoxin-free dialysate combined with high removal of uremic toxins from human plasma. *Acta Biomater* 2019; 90:100–111. doi: 10.1016/j.actbio.2019.04.009

Continued on page 14 >

Figure. Intelligent extracorporeal therapy framework



Conceptual schematic showing the transition from passive membrane-based filtration to adaptive EBP. Multimodal clinical and device-derived data are integrated through an AI-enabled "intelligent membrane" layer that links real-time sensing and predictive analytics to clinician-constrained modulation of clearance and ultrafiltration. This framework illustrates how selective biomaterials, embedded biosensors, and closed-loop control may enable personalized, dynamically adjusted extracorporeal therapy while maintaining human oversight and safety.

Next-Generation Extracorporeal Blood Purification in Critical Care

Continued from page 13

3. Rodrigues FSC, Faria M. Adsorption- and displacement-based approaches for the removal of protein-bound uremic toxins. *Toxins (Basel)* 2023; 15:110. doi: 10.3390/toxins15020110
4. Raharjo Y, et al. Selectively mixed matrix hemodialysis membrane for adequate clearance of *p*-cresol by the incorporation of imprinted zeolite. *RSC Adv* 2023; 13:2972–2983. doi: 10.1039/d2ra07557a
5. Dong Z, et al. Closed loop ultrafiltration feedback control in hemodialysis: A narrative review. *Toxins (Basel)* 2024; 16:351. doi: 10.3390/toxins16080351
6. Paats J, et al. Optical method and biochemical source for the assessment of the middle-molecule uremic toxin β2-microglobulin in spent dialysate. *Toxins (Basel)* 2021; 13:255. doi: 10.3390/toxins13040255
7. Uhlin F, et al. Optical estimation of beta 2 microglobulin during hemodiafiltration—does it work? *Blood Purif* 2015; 40:113–119. doi: 10.1159/000381797
8. Lee H, et al. Prediction of intradialytic hypotension using pre-dialysis features—a deep learning-based artificial intelligence model. *Nephrol Dial Transplant* 2023; 38:2310–2320. doi: 10.1093/ndt/gfad064
9. van Gelder MK, et al. Safety of electrooxidation for urea removal in a wearable artificial kidney is compromised by formation of glucose degradation products. *Artif Organs* 2021; 45:1422–1428. doi: 10.1111/aor.14040
10. Cheungpasitporn W, et al. Artificial intelligence in critical care nephrology: Current applications, emerging techniques, and challenges to clinical integration. *Kidney360* 2026; 7:664–677. doi: 10.34067/KID.0000001037

Restoring Immune Balance in Sepsis: The Emerging Role of Blood Purification

By Victor Ortiz-Soriano and Javier A. Neyra

https://doi.org/10.62716/kn.003392026

Sepsis remains a major cause of critical illness worldwide and is characterized by life-threatening organ dysfunction resulting from a dysregulated host response to infection. Despite the standardization of early sepsis management through the Surviving Sepsis Campaign guidelines, mortality from sepsis and septic shock remains high (1). Current standard-of-care interventions in sepsis are primarily supportive rather than disease-modifying (2). Continuous kidney replacement therapy (CKRT) is commonly used in patients with sepsis-associated acute kidney injury (SA-AKI), severe electrolyte and acid-base derangements, and fluid overload. However, conventional CKRT membranes are limited by pore size and therefore have a restricted ability to modulate the inflammatory processes that drive sepsis pathophysiology (1). Increasingly, the field is moving toward a paradigm of precision critical care nephrology, in which extracorporeal blood purification (EBP) therapies, often integrated into CKRT platforms, are used not only for organ support but also to restore immune homeostasis. These technologies aim to reduce circulating pathogen-associated molecular patterns (PAMPs), damage-associated molecular patterns (DAMPs) released from injured cells, and inflammatory cytokines that contribute to the pathobiology of sepsis (3).

Pathophysiologic and therapeutic targets

The pathobiology of Multiple Organ Dysfunction Syndrome (MODS) in sepsis reflects a complex interaction between pathogen-related factors (such as type, virulence, and microbial burden) and host features, including innate immune activation, inflammation, complement activation, mitochondrial dysfunction, and vascular dysregulation. Together, these processes contribute to a maladaptive immune response to infection. This response is characterized by the release of PAMPs, DAMPs, and both pro- and anti-inflammatory cytokines, including interleukin (IL)-6, IL-10, and tumor necrosis factor (TNF)-α (4). These soluble mediators contribute to MODS through systemic inflammation and organ cross talk, including the development of SA-AKI.

Mechanisms of adsorption

Adsorption through sorbents differs from filtration through dialysis membranes. In adsorption, molecules accumulate on the surface of a solid sorbent rather than crossing a membrane through diffusion or convection (5). The effectiveness of adsorption devices relies on physicochemical interactions and the Vroman effect, in which solutes compete for binding sites. In this process, proteins that bind quickly may later be displaced by proteins with higher surface affinity. This mechanism enables the clearance of middle molecular-weight solutes that are not effectively removed by diffusion-based therapies.

Current technologies and devices

Several EBP platforms are currently being investigated in sepsis.

- Pathogen removal: Devices such as the Seraph 100 (ExThera Medical) use biomimetic heparin-coated beads to bind circulating pathogens and DAMPs, mimicking the endothelial glycocalyx (3).
- Endotoxin removal: Polymyxin B hemoadsorption (PMX-HA) removes the circulating endotoxin (lipopolysaccharide) through direct binding to columns containing immobilized polymyxin B fibers on a hemoadsorption cartridge (2).
- oXiris: The oXiris membrane (Vantive) is a heparin-grafted membrane that uses a polyethylenimine surface that adsorbs endotoxins and cytokines from the bloodstream while simultaneously providing CKRT (2).
- Cytokine removal: CytoSorb (CytoSorbents) uses highly porous polystyrene-divinylbenzene beads to remove hydrophobic cytokines and myoglobin via concentration-dependent adsorption (5).

Relevant clinical trial data

The potential role of EBP as part of standard care in septic shock has been evaluated in several clinical studies, particularly in patients with endotoxemic septic shock. A post hoc analysis of the EUPHRATES trial (NCT01046669) identified a "target PMX-HA responder" phenotype, defined as patients with endotoxin activity assay (EAA) levels between 0.60 and 0.90, who demonstrated a reduction in 28-day mortality when treated with two sessions of PMX-HA (90–120 minutes) in addition to standard therapy. These findings were recently validated in the TIGRIS trial (NCT03901807) using a Bayesian framework that incorporated an a prior treatment effect based on this target PMX-HA responder subgroup from the earlier EUPHRATES trial (1, 6, 7).

In the context of cytokine adsorption (i.e., IL-8, IL-6, TNF-α, IL-4, and IL-10), much of the available evidence in sepsis derives from registry and observational data. Kogelmann et al. demonstrated that early initiation of therapy, defined as starting within 12 hours of septic shock onset, was associated with improved survival, especially in patients with moderate-to-high disease severity (8). Schultz et al. described a dose-response relationship with larger volumes of purified blood associated with improved survival rates (9). Some observational studies evaluating oXiris have reported improvements in hemodynamic stability in patients with sepsis, although effects on mortality have been variable. These findings highlight the need for improved precision phenotyping and patient selection to better understand heterogeneity of treatment effects (2).

Clinical application: The "right" patient and timing

The variability in treatment effects observed in the literature suggests that EBP should not be applied universally. Instead, optimal utilization depends on both prognostic and predictive enrichment strategies to identify patient phenotypes that are high risk and that are most likely to benefit from therapy. Some practical considerations follow.

- In endotoxic septic shock, patients with EAA levels between 0.60 and 0.90 appear to derive the greatest benefit from PMX-HA therapy, establishing EAA as an important biomarker for patient identification (1).
- Timing is crucial, as several studies have shown that early initiation of EBP (within 12 to 24 hours of septic shock onset) has been associated with improved survival (2).
- Recent EBP data suggest a dose-dependent relationship, in which processing more than 6 L/kg of blood during cytokine adsorption therapy was associated with reduced mortality (2).

SETS

The sequential extracorporeal therapy in sepsis (SETS) concept proposes a dynamic treatment strategy tailored to the evolving pathophysiology of sepsis. SETS includes three main phases: trigger removal, mediator clearance, and organ support (1, 2).

1) Trigger removal focuses on rapid elimination of pathogens and endotoxins to mitigate the initial sepsis insult.
2) Mediator clearance involves removal of circulating cytokines to help attenuate the dysregulated inflammatory response.
3) Organ support entails transitioning to standard CKRT to manage fluid balance and maintain metabolic control once the patient stabilizes.

Safety and limitations

Although adsorption technologies are generally biocompatible, nonselective sorbents may unintentionally remove therapeutic agents and nutrients. For example, CytoSorb has been shown to remove lipophilic antibiotics, such as linezolid, necessitating rigorous therapeutic drug monitoring and dose adjustments (1).

Conclusion and future directions

EBP represents a promising adjunct to standard critical care nephrology and may help interrupt key pathobiological pathways in septic shock. However, translating biological plausibility into improvement in patient-centered outcomes requires a systematic shift toward precision medicine. Future studies and real-world implementation initiatives should incorporate biomarker-guided (and/or artificial intelligence-assisted) phenotyping and clinical decision support tools to ensure that the most appropriate EBP therapy is administered to the right patient at the optimal time (1). ■

Victor Ortiz-Soriano, MD, and Javier A. Neyra, MD, MS, FASN, are with the Division of Nephrology, Department of Medicine, The University of Alabama at Birmingham.

The authors report no conflicts of interest.

References

1. Bellomo R, et al. Hemoadsorption: Consensus report of the 30th Acute Disease Quality Initiative Workgroup. *Nephrol Dial Transplant* 2024; 39:1945–1964. doi: 10.1093/ndt/gfae089
2. Teixeira JP, et al. Proceedings of the 2022 UAB CRRT Academy: Non-invasive hemodynamic monitoring to guide fluid removal with CRRT and proliferation of extracorporeal blood purification devices. *Blood Purif* 2023; 52:857–879. doi: 10.1159/000533573
3. Bellomo R, Ronco C, eds. *Contributions to Nephrology. Adsorption: The New Frontier in Extracorporeal Blood Purification*. S. Karger AG; 2023.
4. Chousterman BG, et al. Cytokine storm and sepsis disease pathogenesis. *Semin Immunopathol* 2017; 39:517–528. doi: 10.1007/s00281-017-0639-8
5. Reis T, et al. Basic mechanisms of hemoadsorption: Incumbency for better clinical utility. *Blood Purif* 2025; 1–14. doi: 10.1159/000548120
6. Dellinger RP, et al. Effect of targeted polymyxin B hemoperfusion on 28-day mortality in patients with septic shock and elevated endotoxin level: The EUPHRATES randomized clinical trial. *JAMA* 2018; 320:1455–1463. doi: 10.1001/jama.2018.14618
7. Neyra JA, et al. Polymyxin B haemoadsorption in endotoxic septic shock (Tigris): A multicentre, open-label, Bayesian, randomised, controlled, phase 3 trial. *Lancet Respir Med* (published online March 23, 2026). doi: 10.1016/S2213-2600(26)00047-0
8. Kogelmann K, et al. First evaluation of a new dynamic scoring system intended to support prescription of adjuvant CytoSorb hemoadsorption therapy in patients with septic shock. *J Clin Med* 2021; 10:2939. doi: 10.3390/jcm10132939
9. Schultz P, et al. High-dose CytoSorb hemoadsorption is associated with improved survival in patients with septic shock: A retrospective cohort study. *J Crit Care* 2021; 64:184–192. doi: 10.1016/j.jcrc.2021.04.011

Hemoadsorption in CRS and HLH: Expanding the Role of Blood Purification in Hematologic Emergencies

By Thiago Reis, Karina Z. C. Eid, Sabine Karam, and Phillip Scheinberg

https://doi.org/10.62716/kn.003092026

Hemoadsorption is an extracorporeal blood purification technique aimed at removing solutes (e.g., bilirubin, cytokines, and myoglobin), endotoxin, antibodies, cells, or pathogens, which, due to their physicochemical features, are not amenable to diffusive or convective clearance (1, 2). Different hemoadsorption devices target different compounds using filters or cartridges (3). Therefore, when mentioning hemoadsorption, it is paramount to cite which device was used. The term hemoperfusion is a synonym of hemoadsorption and is often used interchangeably with hemoadsorption in clinical reports.

When filters are used, adsorption occurs when blood is exposed to synthetic hollow fibers that are similar to those used in traditional hemodialysis (HD) and are functionalized, conferring additional chemical properties. Therefore, these filters allow three simultaneous mechanisms of mass transfer: diffusion, convection, and adsorption. For cartridges, blood interacts with porous polymers in the form of beads, powder, flakes, granules, or a mesh of solid fibers, packed in a plastic cylinder. The terms column, sorbent, adsorber, and resin are equivalent to cartridges (3).

The rationale for using hemoadsorption in hematology lies in its capacity to remove toxic cytokines in hyperinflammatory states, grouped under the overarching terms of cytokine release syndrome (CRS) and hemophagocytic lymphohistiocytosis (HLH) (4). CRS occurs in 40% to 95% of patients receiving chimeric antigen receptor T (CAR-T) cell therapy, depending on the CAR-T cell product (e.g., tisagenlecleucel or axicabtagene ciloleucel) (5). This treatment is currently applied against hematologic malignancies such as lymphomas, leukemias, and multiple myeloma. T Cells from the patient are collected with apheresis and re-engineered to express CARs. After the cell population is expanded, the cells are infused into the patient. The chimeric receptors will bind specific antigens on the surface of cancer cells, triggering T-cell activation and ultimately killing tumor cells but also potentially triggering an overwhelming inflammatory response from the host (6). When CRS occurs, it is usually given one of four grades according to severity. In grades 2 and 3 CRS, treatment with an interleukin (IL)-6 receptor blocker (tocilizumab) and intravenous steroids is recommended. In grade 4, higher doses of steroids are warranted, along with tocilizumab and an IL-1 receptor blocker (anakinra), and empiric antimicrobials (5). There is a strong rationale for deploying hemoadsorption in grades 3 and 4 CRS because immediate cytokine removal could limit the progression of the condition, whereas the effect of pharmacologic interventions has not yet blunted the hyperinflammatory response. Notably, no thresholds for cytokine concentrations have been established or validated for starting hemoadsorption.

HLH is another disorder, in which immunoadsorption could be beneficial, and is characterized by inappropriate activation of natural killer cells, T cells, and macrophages. Primary HLH is caused by mutations, whereas secondary HLH is triggered by infections, medications, autoimmune disorders, hematologic malignancies (e.g., lymphomas), and also hematologic therapies (7). HLH can mimic sepsis and septic shock because it may cause multiorgan dysfunction. The current first-line approach for the management of HLH is based on the association of immunosuppressants, including dexamethasone, etoposide, and cyclosporin, in parallel with the treatment of the underlying disease.

The use of hemoadsorption devices capable of removing cytokines as a rescue therapy has been addressed in a statement manuscript by the Histiocyte Society (4). The only US Food and Drug Administration (FDA)-approved adsorption filter, to our knowledge, is the acrylonitrile 69 surface-treated (AN69-ST [Vantive]) filter, designed for continuous kidney replacement therapy (CKRT) machines and not compatible with intermittent HD equipment (Table). A randomized clinical trial that used a filter with similar properties (the oXiris filter [Vantive]) during cardiac surgery demonstrated a reduction in the concentrations of tumor necrosis factor (TNF)-α and IL-8. This was not the case for IL-2, IL-6, IL-10, or interferon-γ (8). The oXiris filter is approved by regulatory agencies in the Americas, Europe, and most Asian countries.

Cartridges can easily be connected to CKRT or intermittent HD circuits (Figure). If the patient does not require KRT, the machines can be set to an isolated ultrafiltration mode and ultrafiltration flow adjusted to zero. In this configuration, blood circulates through the extracorporeal circuit containing the cartridge, without altering the patient's electrolyte, acid-base, or volume status. As of early 2026, adsorption cartridges have not been routinely available for clinical use in the United States outside specific authorizations. In contrast, CytoSorb (CytoSorbents) and HA380 (Jafron Biomedical) are approved in many countries, and the bulk of scientific evidence is based on these two devices (Table), both containing beads of styrene-divinylbenzene (2). Of note, during the COVID-19 pandemic, CytoSorb received an Emergency Use Authorization from FDA.

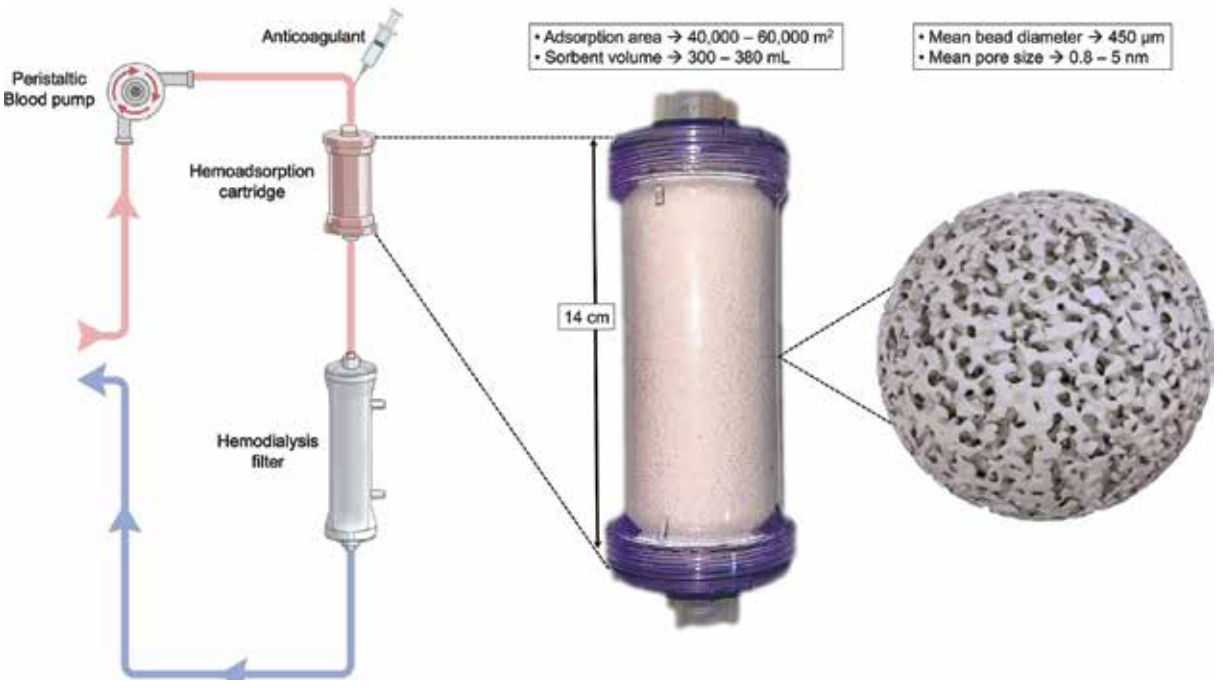
However, the clinical evidence for their usefulness in hematology emergencies remains at the proof-of-concept stage. In a 2024 case series that included 13 patients who developed HLH following CAR-T cell therapy, one individual was treated with CytoSorb. This patient survived HLH but presented post–CAR-T cell relapse and died after 330 days (9). Pickkers and colleagues conducted a randomized clinical trial using CytoSorb in 24 healthy volunteers after CRS induced by intravenous exogenous endotoxin infusion. The serum concentrations of TNF-α, IL-6, IL-8, and IL-10 in the hemoadsorption arm were lower than in the sham arm (10). These signals support biologic plausibility but do not yet define clinical applicability or outcomes.

Relative contraindications for hemoadsorption include thrombocytopenia (<20,000/μL) and hypersensitivity reactions (1). A relevant issue is the undesirable removal of protein-bound medications. Examples include removal of ticagrelor and apixaban, which could lead to thrombotic events; removal of anticonvulsants, which could precipitate seizures; and removal of antimicrobials, which could result in pathogen treatment failure. These risks can be mitigated with pre-emptive medication reconciliation, therapeutic drug monitoring when available, and dose adaptation based on exposure and bedside response.

In conclusion, nephrologists and hematologists should be familiar with hemoadsorption, as proof-of-concept data show that it could potentially be useful as an adjunctive therapy in hematologic emergencies. A multidisciplinary collaboration is needed to design and execute clinical trials that will further define the role of extracorporeal blood purification treatments. ■

Thiago Reis, MD, PhD, is an attending nephrologist in the Division of Nephrology, University of São Paulo School of

Figure. Hemoadsorption with HD



The left part of the figure depicts the schematic configuration of the extracorporeal circuit. The blood inflow segment is represented in the upper limb of the extracorporeal circuit. The cartridge is interposed between the peristaltic blood pump and the regular HD filter, the so-called HD filter, the so-called "pre-filter" configuration. After passing through the cartridge, blood enters the hollow fibers of the filter and returns to the patient via the outflow section, represented in the lower limb of the circuit. Blood flow ranges from 100 mL/minute up to 450 mL/minute, depending on the desired HD prescription. This circuit configuration is the same for both intermittent HD and CKRT machines. Anticoagulation protocols remain the same as for HD stand-alone. As such, heparin, bivalirudin, fondaparinux, and nafamostat can be used. The center of the figure displays a plastic cartridge packed with polystyrene-divinylbenzene beads. In the right part of the figure, a bead is represented. The bulk of adsorption occurs inside the trabecular structure of beads, not on their outer surface. In each cartridge, the available adsorption area ranges from 40,000 to 60,000 m^2.

Medicine; a scientific clinical researcher with the CPQuali Clinical Research Center; and with the Hospital Beneficência Portuguesa, São Paulo, Brazil. Karina Z. C. Eid, MD, is with the Division of Nephrology, University of São Paulo School of Medicine; Sabine Karam, MD, is with the Division of Nephrology and Hypertension, Department of Medicine, University of Minnesota, Minneapolis, and the Division of Nephrology and Hypertension, Department of Internal Medicine, American University of Beirut, Lebanon. Phillip Scheinberg, MD, is with the Hospital Beneficência Portuguesa.

Dr. Reis reports receiving funding for lectures and being a consultant or advisory board member for Alexion, AstraZeneca, B. Braun, Baxter, bioMérieux, Boehringer Ingelheim, Eurofarma, George Clinical, Jafron, Medcorp, Nipro, and Nova Biomedical. Drs. Eid and Karam report no conflicts of interest. Dr. Scheinberg reports being a consultant for AbbVie, Alexion, AstraZeneca, BioCryst, F. Hoffmann-La Roche Ltd., Janssen, and Pfizer; receiving research funding from Alnylam and Pfizer; and participating in speakers bureaus for Alexion, Amgen, AstraZeneca, Bristol Myers Squibb, Novartis, and Pfizer.

Table. Commercially available filters and cartridges

Material	Commercial name (manufacturer)	Target of removal via adsorption	FDA approval
Filters (hollow fibers)			
AN69-PEI-heparin	oXiris (Vantive)	Middle molecules (0.5–58.0 kDa), including cytokines and medications (e.g., caspofungin, linezolid) and endotoxin	No
AN69-ST	ST series/sepXiris (Vantive)	Middle molecules (0.5–58.0 kDa), including cytokines and medications	Yes
Cartridges (beads)			
Porous polymer beads–polystyrene-divinylbenzene	BS80, BS330, HA60, HA130, HA230, HA330, HA330-II, HA380, and CA330 (Jafron); CytoSorb and DrugSorb (CytoSorbents); MediaSorb (Medtronic); MG150, MG250, and MG350 (Biosun); and Plasorba BR-350(L) (Asahi)	Protein-bound compounds (e.g., bilirubin, bile acids, and medications), middle molecules, iodinated contrast, ticagrelor (i.e., platelet $P2Y_{12}$ inhibitor), factor Xa inhibitors, and myoglobin	No

PEI, polyethylenimine.

References

1. Reis T, et al. Basic mechanisms of hemoadsorption: Incumbency for better clinical utility. *Blood Purif* 2025; 1–14. doi: 10.1159/000548120
2. Bellomo R, et al.; Acute Disease Quality Initiative Hemoadsorption Working Group. Hemoadsorption. *Clin J Am Soc Nephrol* 2024; 19:803–806. doi: 10.2215/CJN.0000000000000433
3. Reis T, et al.; Nomenclature Standardization Faculty. Standardization of nomenclature for the mechanisms and materials utilized for extracorporeal blood purification. *Blood Purif* 2024; 53:329–342. doi: 10.1159/000533330
4. La Rosée P, et al. Recommendations for the management of hemophagocytic lymphohistiocytosis in adults. *Blood* 2019; 133:2465–2477. doi: 10.1182/blood.2018894618
5. Schroeder T, et al. Management of chimeric antigen receptor T (CAR-T) cell-associated toxicities. *Intensive Care Med* 2024; 50:1459–1469. doi: 10.1007/s00134-024-07576-4
6. Jhaveri KD, Rosner MH. Chimeric antigen receptor T cell therapy and the kidney: What the nephrologist needs to know. *Clin J Am Soc Nephrol* 2018; 13:796–798. doi: 10.2215/CJN.12871117
7. Gumber L, et al. Trends in mortality due to haemophagocytic lymphohistiocytosis across 29 European countries from 2011 to 2021: A retrospective, international, population-based study. *Lancet Rheumatol* 2026; 8:e108–e115. doi: 10.1016/S2665-9913(25)00292-9
8. Pérez-Fernández X, et al.; SIRAKI02 Study Group. Extracorporeal blood purification and acute kidney injury in cardiac surgery: The SIRAKI02 randomized clinical trial. *JAMA* 2024; 332:1446–1454. doi: 10.1001/jama.2024.20630
9. Khurana A, et al. Chimeric antigen receptor T-cell therapy associated hemophagocytic lymphohistiocytosis syndrome: Clinical presentation, outcomes, and management. *Blood Cancer J* 2024; 14:136. doi: 10.1038/s41408-024-01119-2
10. Jansen A, et al. CytoSorb hemoperfusion markedly attenuates circulating cytokine concentrations during systemic inflammation in humans in vivo. *Crit Care* 2023; 27:117. doi: 10.1186/s13054-023-04391-z

Targeting Dysregulated Inflammation in AKI: The Promise of the Selective Cytopheretic Device

By Lenar Yessayan and Ashita Tolwani

https://doi.org/10.62716/kn.003012026

Acute kidney injury (AKI) in critical illness often arises from dysregulated immune activation triggered by infection or tissue injury. Neutrophils are essential first responders in sepsis, but when excessively activated, they drive inflammation, microvascular dysfunction, and tissue injury that contribute to organ failure. The selective cytopheretic device (SCD) is an extracorporeal cartridge designed to modulate activated neutrophils and monocytes. Early studies suggest a role in inflammation-mediated AKI. Its promise, however, must be weighed against pending clinical trial results, regulatory uncertainty, and real-world implementation challenges.

How SCD works

SCD is placed in series with a continuous kidney replacement therapy (CKRT) circuit (Figure). The cartridge consists of biomimetic membrane fibers, around which blood flows under low shear conditions. These dynamics approximate microvascular flow and favor interaction between the device surface and activated circulating neutrophils and monocytes expressing CD11. A low-circuit blood ionized calcium (<0.40 mmol/L), achieved with citrate anticoagulation, appears central to modulating leukocyte behavior. Under these conditions, bound, activated neutrophils undergo degranulation and are marked for apoptosis, released back into circulation, and subsequently cleared by bone marrow and tissue macrophages (1). Selective sequestration of proinflammatory monocyte subsets may enrich reparative nonclassical monocytes, promoting tissue repair through differentiation into M2 macrophages (2).

Clinical experience in people with AKI

Clinical evaluation has evolved from early pilot work to clinical trials and pragmatic application in both adult and pediatric AKI (Table). To our knowledge, the largest randomized trial until recently, SCD-003 (NCT01400893), enrolled adults with AKI and with presumed acute tubular necrosis who were critically ill, but the study was terminated prematurely because of a national calcium shortage, an essential component for regional citrate anticoagulation. In the intention-to-treat analysis, SCD did not confer a survival advantage. However, in a prespecified per-protocol cohort, in which target postfilter ionized calcium levels were consistently achieved, mortality and dialysis dependence were lower (3). Whether this reflects true biologic efficacy or rigorous protocol adherence is difficult to disentangle; any benefit appears contingent on precise execution. This dependence on execution raises practical questions about reproducibility across centers with variable citrate experience.

Pediatric experience, although limited to single-arm studies, has been particularly encouraging. Two prospective trials in children with AKI and multiorgan dysfunction demonstrated a favorable safety profile and efficacy signals that compared favorably with historical controls, forming the basis for US Food and Drug Administration approval of SCD under a humanitarian device exemption for children weighing 10 kg or more with AKI and sepsis or a septic condition requiring CKRT (4, 5). Reported survival approached 77%—higher than that historically reported in pediatric CKRT cohorts and large registries (~50%)—whereas cross-study comparisons are limited by differences in case mix and era (5). Although these results must be interpreted cautiously in the absence of randomized controls, they suggest that immune modulation may be particularly relevant in pediatric critical illness, in which inflammatory phenotypes may be more homogeneous and protocol adherence more tightly controlled. Whether similar outcomes can be reproduced broadly, particularly outside highly specialized centers, remains an important question.

Future directions and ongoing investigation

Recognition of the device's potential has led to larger randomized evaluation. NEUTRALIZE-AKI (NCT-05758077), currently the largest trial, to our knowledge, is testing whether SCD therapy reduces death or dialysis dependence at 90 days in adults who are critically ill with multiple organ failure (6). Interim analyses have revealed no safety concerns and suggest potential benefit; completion of the trial will be essential to determine whether earlier signals translate into reproducible benefit across a broad population in intensive care units and within key subgroups. Importantly, these studies should also clarify how tightly postfilter ionized calcium targets must be maintained to realize benefit.

Case reports have also described use in cardiorenal syndrome and hepatorenal syndrome, in which immune dysregulation coexists with hemodynamic compromise (7, 8). Future studies are being designed to formally evaluate the device in these populations.

Promise balanced by implementation considerations

Targeting cellular drivers of inflammation, rather than simply removing cytokines, is conceptually attractive. For clinicians, however, implementation considerations remain. The therapy depends on reliably sustaining a low-circuit ionized calcium environment, requiring institutional expertise with citrate anticoagulation, frequent monitoring, and protocols that support safe delivery. Integration into intensive care unit workflows is also nontrivial, adding hardware, nursing tasks, and operational oversight to CKRT. Finally, definitive evidence from adequately powered randomized trials remains limited, and economic and logistical factors will influence adoption alongside regulatory approval.

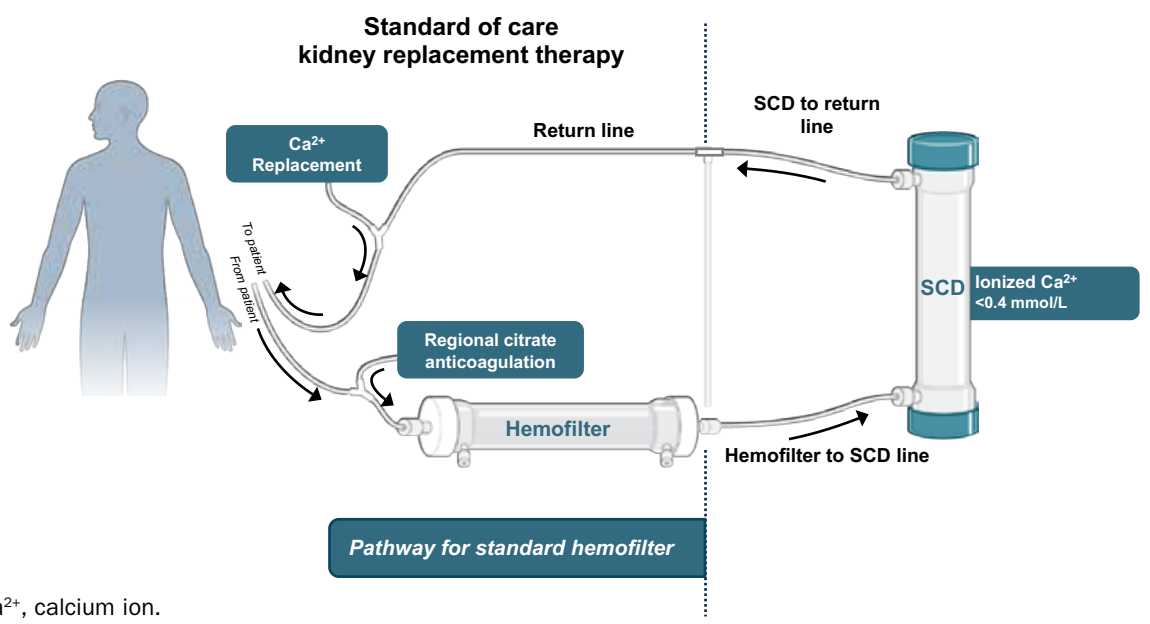
Conclusion

SCD has carved out a credible niche as a targeted, autologous cell-directed immunomodulator for inflammation-associated AKI. Early clinical work justifies cautious enthusiasm. The coming trials will determine whether its biological promise translates into consistent patient benefit across a broad range of clinical settings. If successful, the next phase will involve extending this therapy at scale while preserving the key conditions that appear necessary for its benefit. ■

Lenar Yessayan, MD, MS, is with the Division of Nephrology at the University of Michigan, Ann Arbor. Ashita Tolwani, MD, MS, MSc, FASN, is with the Division of Nephrology at The University of Alabama at Birmingham.

Dr. Yessayan reports receiving consulting fees from Vantive and serving on the Medical Advisory Board for Fresenius Medical Care. Dr. Tolwani reports receiving consulting fees from Vantive and serving on the Scientific Advisory Board for SeaStar Medical.

Figure. The SCD CKRT circuit



Ca^{2+}, calcium ion.

References

1. Westover AJ, et al. Immunomodulatory effects of a cell processing device to ameliorate dysregulated hyperinflammatory disease states. *Sci Rep* 2024; 14:12747. doi: 10.1038/s41598-024-63121-9
2. Szamosfalvi B, et al. Immunomodulatory device promotes a shift of circulating monocytes to a less inflammatory phenotype in chronic hemodialysis patients. *ASAIO J* 2016; 62:623–630. doi: 10.1097/MAT.0000000000000400
3. Tumlin JA, et al.; SCD Investigator Group. A multicenter, randomized, controlled, pivotal study to assess the safety and efficacy of a selective cytopheretic device in patients with acute kidney injury. *PLoS One* 2015; 10:e0132482. doi: 10.1371/journal.pone.0132482
4. Goldstein SL, et al. Use of the selective cytopheretic device in critically ill children. *Kidney Int Rep* 2020; 6:775–784. doi: 10.1016/j.ekir.2020.12.010

Table. Key clinical trials with SCD in patients with sepsis: mortality and dialysis outcomes

Study (year)	Population	Design	Key endpoints	Results
SCD-003 (2015) (3)	Adults who are critically ill with AKI due to ATN on CKRT and one or more nonkidney organ failure or presence of sepsis	Randomized controlled trial (N = 131); 21 centers	60-Day mortality; dialysis dependence	· Terminated early (N = 131 versus planned N = 344) due to national calcium shortages · ITT; no statistical difference between groups · Per-protocol analysis (circuit iCa <0.4 mmol/L); 60-day composite endpoint of either death or dialysis dependence: SCD 16% versus control 58%; p = 0.01
SCD-PED 1 (2020) (4)	Children who are critically ill; weight ≥15 kg; up to aged 22 years with AKI and one or more nonkidney organ failure	Single-arm clinical trial (N = 16); four centers	60-Day mortality; dialysis dependence	· 60-Day survival (secondary): SCD 12/16 (75%) · 60-Day dialysis independence: SCD 12/12 (100%) · Combined 60-day survival of SCD-PED 1 and SCD-PED 2 pediatric trials: SCD 77.3% versus controls 54.8%; p = 0.04 · Controls (N = 210) from the Prospective Pediatric (ppCRRT) Registry with similar inclusion criteria
SCD-005 (2022) (9)	Adults who are critically ill with AKI or ARDS associated with COVID-19 infection	Single-arm clinical trial (N = 22); two centers	60-Day mortality	· 60-Day mortality (secondary): SCD 50% versus control 81%; p = 0.10; 60-day mortality treated for ≥96 hours: SCD 31% versus control 81%; p = 0.01 · Controls (N = 16) from the CRRTnet Registry
SCD-PED 2 (2024) (5)	Children who are critically ill; weight 10–20 kg; up to aged 17 years with AKI on CKRT and one or more nonkidney organ failure	Single-arm clinical trial (N = 6); four centers	60-Day mortality; dialysis dependence	· 60-Day survival (secondary): SCD five of six (83%) · 60-Day dialysis independence: SCD five of five (100%) · Combined 60-day survival of SCD-PED 1 and SCD-PED 2 pediatric trials: SCD 77.3% versus controls 54.8%: p = 0.04 · Controls (N = 210) from the ppCRRT Registry with similar inclusion criteria
NEUTRALIZE-AKI (ongoing) (6)	Adults who are critically ill with AKI on CKRT and one or more nonkidney organ failure and CRP >3.5 mg/dL	Randomized controlled trial (N = 340); 20 centers	90-Day mortality; dialysis dependence	· Largest current randomized control trial (target N = 340); interim analysis; suggests possible benefit; completion anticipated ~2027

ARDS, acute respiratory distress syndrome; ATN, acute tubular necrosis; CRP, C-reactive protein; iCa, ionized calcium; ITT, intention to treat.

5. Goldstein SL, et al. Selective cytopheretic device use in continuous kidney replacement therapy in children: A cohort study with a historical comparator. *Kidney Med* 2024; 6:100792. doi: 10.1016/j.xkme.2024.100792
6. Yessayan L, et al. Rationale and design of NEUTRALIZE-AKI: A multicenter, randomized, controlled, pivotal study to assess the safety and efficacy of a selective cytopheretic device in patients with acute kidney injury requiring continuous kidney replacement therapy. *Nephron* 2024; 148:43–53. doi: 10.1159/000531880
7. Yessayan LT, et al. Extracorporeal immunomodulation therapy in acute chronic liver failure with multiorgan failure: First in human use. *ASAIO J* 2024; 70:e53–e56. doi: 10.1097/MAT.0000000000002033
8. Humes HD, et al. Translation of immunomodulatory therapy to treat chronic heart failure: Preclinical studies to first in human. *PLoS One* 2023; 18:e0273138. doi: 10.1371/journal.pone.0273138
9. Yessayan LT, et al. Extracorporeal immunomodulation treatment and clinical outcomes in ICU COVID-19 patients. *Crit Care Explor* 2022; 4:e0694. doi: 10.1097/CCE.0000000000000694

Biofilter-Based Continuous Kidney Replacement Therapy in Pediatric Acute Kidney Injury: Tailoring Technology for Small Patients

By Pranav Sivaram and Rupesh Raina

https://doi.org/10.62716/kn.003202026

Pediatric acute kidney injury (AKI) affects approximately 30% of neonates in intensive care units and independently increases mortality risk nearly fivefold (1). For decades, peritoneal dialysis served as first-line kidney replacement therapy (KRT) in this population. Yet its limitations, slow ultrafiltration (UF), suboptimal solute clearance, and contraindications in patients after surgery or with sepsis restricted its effectiveness in infants with more severe illnesses. Traditional adult-adapted continuous KRT (CKRT) platforms proved inadequate for children under 15 kg due to extracorporeal circuit volumes exceeding 15% of neonatal blood volume, creating prohibitive hemodynamic risks (2).

Technologic evolution: From adaptation to miniaturization

Over the past decade, the field has shifted from modifying adult platforms to engineering devices specifically for infants. The Cardio-Renal Pediatric Dialysis Emergency Machine (CARPEDIEM), designed for infants 2.5 to 10.0 kg, represents the most significant advance. With extracorporeal circuit volume under 30 mL, precision roller pumps enabling blood flows of 5 to 50 mL per minute, and UF accuracy within 1 g per hour, CARPEDIEM addresses fundamental physiologic constraints in neonates (2, 3).

Similarly, the Prismaflex HF20 filter set bridges the gap between adapted adult technology and dedicated neonatal devices for infants 4 to 20 kg. With a reduced extracorporeal blood volume of 60 mL and a polyarylethersulfone membrane, the HF20 has demonstrated safety and efficacy in infants as small as 2.3 kg who are hemodynamically unstable (4). Alternative approaches, including gravity-assisted continuous flow peritoneal dialysis (CFPD), the Newcastle Infant Dialysis and UF System (NIDUS), and the Aquadex UF device, have expanded the therapeutic armamentarium for small infants, each offering distinct advantages in specific clinical scenarios (3, 5, 6) (Figure and Table).

This technologic evolution has rapidly translated into practice change. The Contemporary Infant and Neonatal Dialysis cohort reported that between 2017 and 2022, CKRT surpassed peritoneal dialysis as the most common initial dialysis modality in US neonates (71% versus 26%) (7). These data demonstrate a clear shift in neonatal dialysis practice, positioning CKRT as the predominant first-line modality in contemporary US centers.

Which patients benefit most?

The greatest benefit is seen in neonates and infants under 15 kg who are critically ill, particularly those under 5 kg (2). These include patients postcardiac surgery requiring precise UF, neonates on extracorporeal membrane oxygenation, children who are hemodynamically unstable with multiorgan dysfunction, and infants with severe fluid overload unresponsive to peritoneal dialysis (2).

Protocol differences in infants younger than 12 months

Neonatal CKRT is not simply "small adult CKRT"; it requires fundamentally different assumptions about blood volume, access, and solute clearance. Blood priming strategies must account for circuit volumes representing 10% to 15% of circulating blood volume; saline priming is preferred, with packed red blood cells reserved for the smallest patients (11%) (8). Blood flow rates are reduced to 3 to 9 mL/kg per minute. Vascular access typically requires 4.0 to 6.5 French dual-lumen catheters, with umbilical venous access as an alternative. Continuous veno-venous hemofiltration or hemodiafiltration is preferred, with effluent flow rates of 28 to 125 mL/kg per hour (8).

Ongoing challenges

Despite these advances, extracorporeal therapies in pediatric patients present unique challenges related to the extracorporeal circuit volume, which can represent a significant proportion of a child's total blood volume and lead to hemodynamic instability and hemodilution (9). Anticoagulation management is particularly complex in children due to age-dependent variations in coagulation factor levels, smaller therapeutic windows, and increased bleeding risk (9). Additionally, cytokine removal or modulation strategies face obstacles, including the lack of pediatric-specific dosing data, variable pharmacokinetics across different age groups, and uncertainty about optimal timing and targets for intervention in the developing immune system (9). In one prospective observational study, the most frequent complications of biofilter-based CKRT in pediatric patients were reported to be hypotension at connection, electrolyte disturbances, and thrombocytopenia, with relatively rare catheterization-related problems occurring in infants younger than 12 months and those weighing under 10 kg (10).

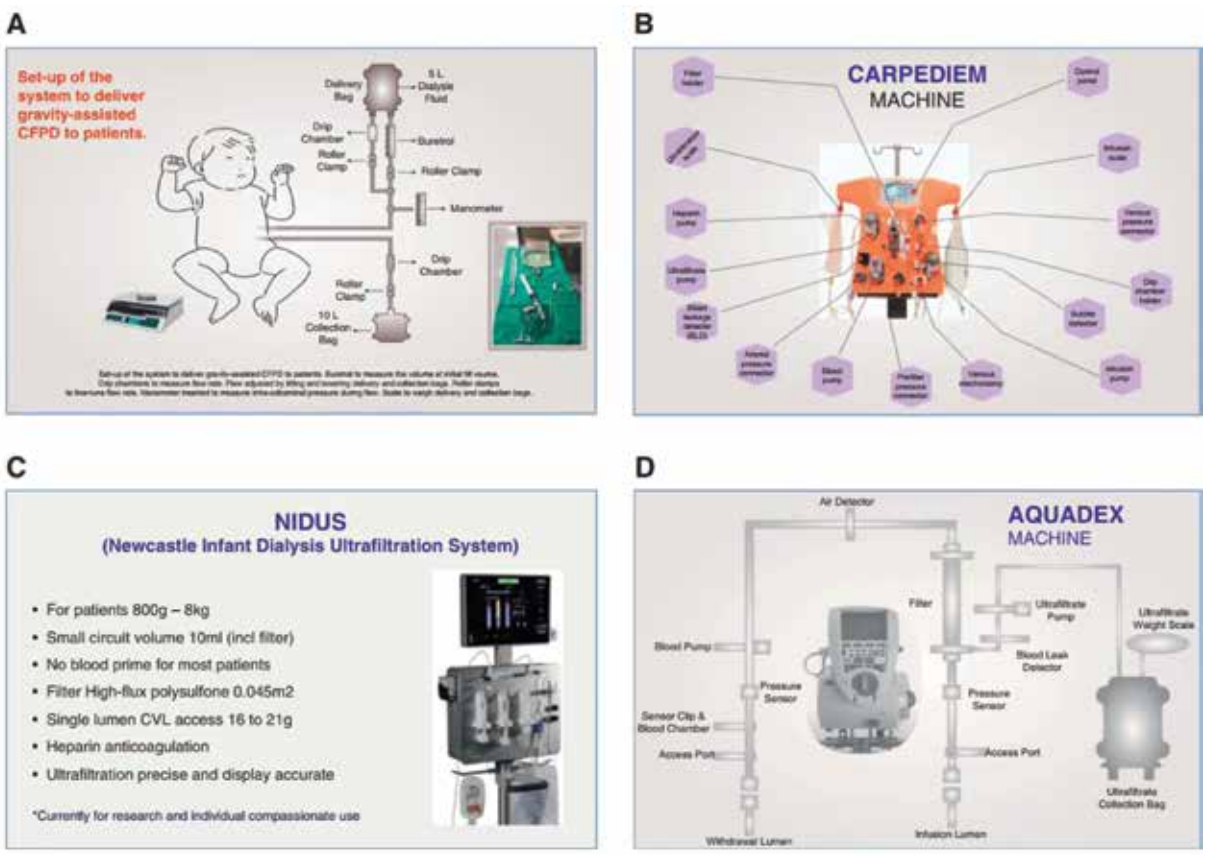
Emerging outcome data

Comparative analysis suggests that dedicated neonatal platforms versus adapted adult machines may improve survival in infants under 5 kg (97% versus 44% survival to CKRT discontinuation) (11). The Improving CRRT [Continuous Renal Replacement Therapy] Outcomes in Neonates and Infants Through Interdisciplinary Collaboration Learning Network reports 60% to 67% survival to hospital discharge (12). Similarly, the Pediatrix neonatal dialysis registry found that over 70% of infants survived to neonatal intensive care unit discharge, with greater mortality among infants without kidney anomalies and those with greater severity of illness at dialysis initiation (13).

Forward view

Dedicated neonatal CKRT platforms represent a shift in the management of infants with AKI who are critically ill, redefining KRT from an extraordinary intervention to become a viable component of routine neonatal critical care. Future efforts must prioritize protocol harmonization, earlier AKI detection using validated biomarkers, standardized anticoagulation approaches, and systematic long-term kidney outcome assessment. As these technologies mature, the central challenge will shift the focus from engineering feasibility to widespread clinical implementation, training, and dissemination. The success of neonatal CKRT will ultimately be measured, not by device innovation alone but also by its consistent integration into everyday practice for the patients who need it most. ■

Figure. Neonatal dialysis systems



(A) Gravity-assisted CFPD, (B) CARPEDIEM, (C) NIDUS, and (D) Aquadex UF circuits. CVL, central venous line. Reused with permission from Govindan et al. (6).

Table. Summary of neonatal KRT devices, including priming volume, key features, and FDA approval status

Clinical parameter	CARPEDIEM	Aquadex	NIDUS	HF20
Target weight range (US)	2.5–10.0 kg	>20 kg (SCUF indication)	Not FDA approved	8–20 kg
Regulatory status (US)	FDA cleared (2020)	FDA cleared (2020)	Not FDA cleared	FDA cleared (2021)
Extracorporeal circuit volume	26–41 mL (cartridge-dependent)	33 mL	<10 mL	60 mL
Membrane surface area	0.075–0.290 m^2	0.12 m^2	0.045 m^2	0.2 m^2
Blood flow capability	2–50 mL/minute	10–40 mL/minute	20–45 mL/minute	20–100 mL/minute
Dialysate flow rate	0–10 mL/minute	Not applicable	Not applicable	50–2500 mL/hour
UF limits	Up to 2000 mL/24 hours (10-mL increments)	Up to 500 mL/hour (10-mL increments)	0–60 mL/hour (3.2-µL steps)	Up to 500 mL/hour (5-mL increments)
Fluid balance accuracy	±1 g; up to 30 g/24-hour variance	±10% of UF rate	<0.25% error	<1% error
Supported modalities	CVVH, CVVHD, SCUF	CVVH, SCUF	CVVHD, SCUF	CVVH, CVVHD, CVVHDF, SCUF
Anticoagulation options	Heparin or none	Heparin or none	Heparin	Heparin or citrate

Data summarized and reformatted from Slagle et al. (5). CVVH, continuous veno-venous hemofiltration; CVVHD, continuous veno-venous hemodialysis; CVVHDF, continuous veno-venous hemodiafiltration; FDA, US Food and Drug Administration; SCUF, slow continuous UF.

Pranav Sivaram, BS, is with the College of Medicine, Northeast Ohio Medical University, Rootstown. Rupesh Raina, MD, FASN, is with the Department of Nephrology at Akron Nephrology Associates/Cleveland Clinic Akron General and the Department of Nephrology at Akron Children's Hospital, Akron, OH.

The authors report no conflicts of interest.

References

1. Meena J, et al. Acute kidney injury in neonates: A meta-analysis. *Pediatrics* 2024; 154:e2023065182. doi: 10.1542/peds.2023-065182
2. Ronco C, et al. Continuous renal replacement therapy in neonates and small infants: Development and first-in-human use of a miniaturised machine (CARPEDIEM). *Lancet* 2014; 383:1807–1813. doi: 10.1016/S0140-6736(14)60799-6
3. Raina R, et al. Advances in kidney replacement therapy in infants. *Adv Chronic Kidney Dis* 2021; 28:91–104. doi: 10.1053/j.ackd.2021.05.002
4. Liu ID, et al. Use of HF20 membrane in critically ill unstable low-body-weight infants on inotropic support. *Pediatr Nephrol* 2013; 28:819–822. doi: 10.1007/s00467-012-2394-3
5. Slagle C, et al. Recent advances in kidney replacement therapy in infants: A review. *Am J Kidney Dis* 2024; 83:519–530. doi: 10.1053/j.ajkd.2023.10.012
6. Govindan S, et al. KRT designed for infants: A game changer. *Kidney360* 2024; 5:1041–1043. doi: 10.34067/KID.0000000000000484
7. Muff-Luett M, et al. Dialysis modality and mortality of the Contemporary Infant and Neonatal Dialysis (COINED) cohort: A Pediatric Nephrology Research Consortium (PNRC) study. *Pediatr Nephrol* (published online January 13, 2026). doi: 10.1007/s00467-025-07082-9
8. Garzotto F, et al. Continuous kidney replacement therapy in critically ill neonates and infants: A retrospective analysis of clinical results with a dedicated device. *Pediatr Nephrol* 2020; 35:1699–1705. doi: 10.1007/s00467-020-04562-y
9. Bottari G, et al. Extracorporeal blood purification in European pediatric intensive care units: A consensus statement. *JAMA Netw Open* 2025; 8:e2457657. doi: 10.1001/jamanetworkopen.2024.57657
10. Santiago MJ, et al. Complications of continuous renal replacement therapy in critically ill children: A prospective observational evaluation study. *Crit Care* 2009; 13:R184. doi: 10.1186/cc8172
11. Goldstein SL, et al. Survival of infants treated with CKRT: Comparing adapted adult platforms with the Carpediem™. *Pediatr Nephrol* 2022; 37:667–675. doi: 10.1007/s00467-021-05180-y
12. Slagle CL, et al. Infant renal replacement therapy using Carpediem: A multicenter observational cohort study from the ICONIIC Learning Network. *J Pediatr* 2026; 288:114838. doi: 10.1016/j.jpeds.2025.114838
13. Sanderson KR, et al. Mortality risk factors among infants receiving dialysis in the neonatal intensive care unit. *J Pediatr* 2022; 242:159–165. doi: 10.1016/j.jpeds.2021.11.025

Hybrid Extracorporeal Organ Support: Understanding Advances in Filter Characteristics

By Pramod K. Guru, Srivatsa Nagachandan, and Himanshi Banker

https://doi.org/10.62716/kn.003212026

Multiorgan failure represents a terminal pathophysiologic process frequently seen in patients in intensive care units and is often linked to elevated mortality rates. It is well established that organ systems can experience failure concurrently through intricate interorgan cross talk and that isolated single-organ support may not adequately address this complexity (1). The failed organ requires protection from additional harm and rest to recover, whereas definitive strategies address the underlying illness. In recent years, the concept of extracorporeal organ support (ECOS) or multiple organ support therapy (MOST) has emerged to address this need (2). Instead of siloed systems like ventilators and dialysis machines, ECOS envisions integrated platforms that deliver gas exchange, kidney support, liver detoxification, and acid-base balance within a single unit, helping to maintain optimal hemodynamic stability. This multidisciplinary strategy, first articulated over a decade ago, challenges the "compartmentalized" approach of treating each organ in isolation.These integrated systems can be classified into three primary categories: Type 1 encompasses clearance-dominant systems such as kidney replacement, type 2 consists of gas exchange-integrated systems like extracorporeal membrane oxygenation (ECMO), and type 3 contains multicompartment detoxifying systems such as Advanced Organ Support (ADVOS) (1, 3). The integration of these hybrid systems is made possible by distinct filter technologies that combine traditional blood purification with extracorporeal gas exchange (Figure).

Filter characteristics

Integrated ECOS systems use fundamentally different membrane strategies compared with conventional kidney replacement therapy (KRT). A comparative overview of different filters currently in use that can be clubbed into three categories is provided in the Table.

Composition and selectivity of membranes

The development of continuous KRT (CKRT) established biocompatible high-flux synthetic membranes (polyethersulfone, polysulfone, and polymethylmethacrylate) with ultrafiltration coefficients greater than 20 mL/hour per mm Hg to efficiently remove small solutes by diffusion and convection without albumin loss (4). However, these membranes cannot eliminate protein-bound uremic toxins (PBUTs). The deficiency in traditional KRT was compensated by the establishment of albumin dialysis or the molecular adsorbent recirculating system (MARS), which used albumin-impregnated membranes to remove PBUTs. The blood is dialyzed across an albumin-impregnated membrane against 20% albumin dialysate to create a concentration gradient that permits protein-bound compounds to move from plasma albumin to dialysate albumin. The key innovation of MARS is albumin regeneration via charcoal and anion exchange resin columns in the dialysate cleansing circuit (2). Subsequently, there was a tandem shift in ECMO membranes from traditional silicone membrane ECMO to a mesh-like polymethylpentene (PMP) membrane, which provided efficient gas diffusion with protein preservation, particularly albumin loss and plasma leakage. The extracorporeal carbon dioxide removal (ECCO$_2$R)-CKRT system aimed to combine gas exchange membranes for CO_2 removal and high-flux synthetic membranes for kidney support. These membranes, however, cannot eliminate PBUTs because they rely on gas-phase membrane diffusion (4). ADVOS fundamentally advances beyond MARS by regenerating albumin's toxin-binding capacity through biochemical (pH) and physical (temperature) modulation of the dialysate in dual purification circuits, rather than through external charcoal columns (5). Emerging technologies, including mixed matrix membranes and medium cutoff membranes, further expand selectivity by incorporating adsorptive elements or enhancing middle molecule clearance (5–50 kDa) while preserving albumin, enabling "expanded hemodialysis" (4).

Acid-base engineering

Traditional extracorporeal systems such as KRT and ECMO were not designed with active acid-base engineering in mind. In MARS, acid-base correction occurs indirectly through its integrated hemodialysis component, which clears water-soluble solutes and delivers bicarbonate-buffered dialysate. The system does not manipulate dialysate pH for albumin regeneration, nor does it remove CO_2; any improvement in acid-base status reflects conventional dialysis effects rather than targeted modulation (6). Similarly, the Prometheus system focuses on protein-bound toxin clearance: Albumin-bound toxins cross an albumin-permeable membrane, undergo adsorption via resin columns, and are returned to the circuit, while standard hemodialysis provides metabolic and acid-base control (2).

In contrast, ECCO$_2$R-CKRT platforms use hollow-fiber gas exchangers to directly remove CO_2, thereby correcting respiratory acidosis, whereas the CKRT component manages bicarbonate balance and metabolic acidosis. ADVOS adopts a distinct fluid-based approach, enabling direct removal of acid and CO_2 without a membrane oxygenator. By generating an alkaline dialysate environment (approximately pH 10), ADVOS shifts the carbonic acid-bicarbonate equilibrium toward CO_2 formation, which then diffuses into the dialysate, while hydrogen ions are simultaneously extracted into the alkaline circuit (1, 6).

Cytokine removal capacity and mechanisms

Adsorptive membranes such as oXiris and CytoSorb integrate cytokine and endotoxin removal with CKRT using specialized materials capable of binding inflammatory mediators. High cutoff membranes (e.g., SepteX [60 kDa molecular weight cutoff]) can clear large toxins such as myoglobin and light chains. Although these facilitate the nonselective extraction of inflammatory mediators straight from whole blood, in vitro investigations indicate a reduction above 50% in several cytokines, damage-associated molecular patterns, pathogen-associated molecular patterns, and mycotoxins, with the significant exception of the tumor necrosis factor-α trimer (7). This size-selective adsorption focuses on middle molecular weight mediators, facilitating the concurrent reduction of various inflammatory pathways.

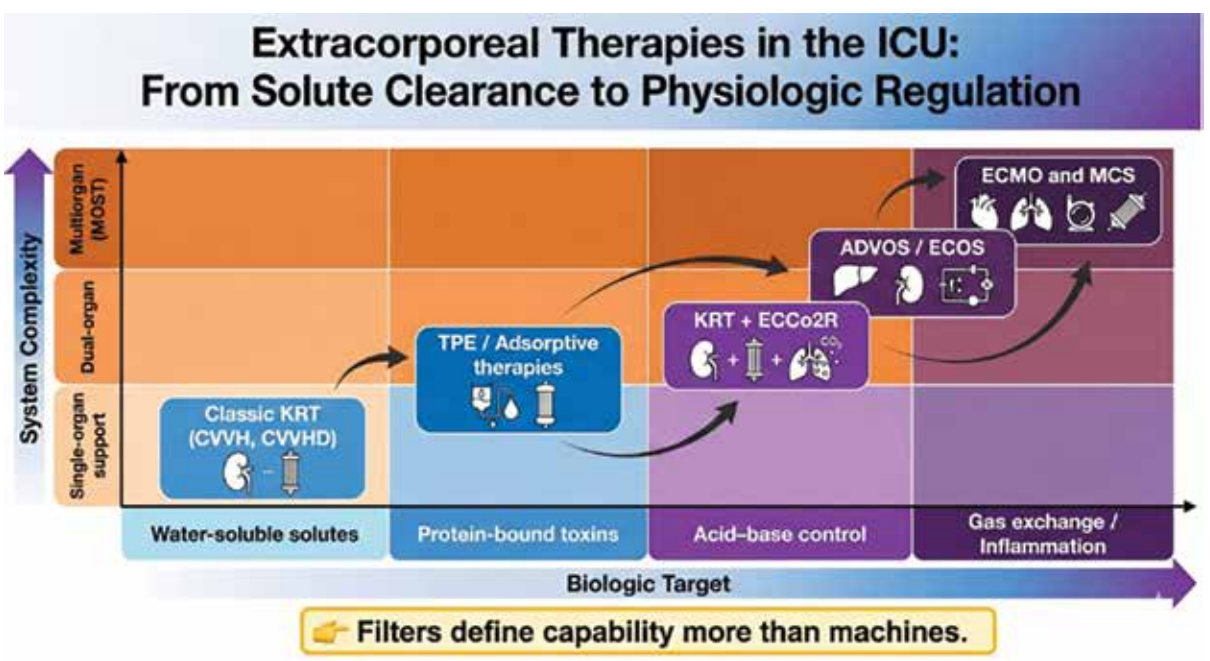
Current evidence

Clinical evidence supporting MOST remains promising but largely observational. The largest ADVOS data from the Extracorporeal Multiple Organ Support Registry (N = 282) suggests favorable physiologic trends like improved bilirubin, creatinine, blood urea nitrogen, and rapid acidosis correction, with better hemodynamic stability and reduced vasopressor needs, although randomized evidence is lacking (8).

For hemoadsorption, registry data for CytoSorb (N = 1434) show observed mortality lower than the Acute Physiology and Chronic Health Evaluation II-predicted rates, although not statistically significant. Meta-analytic data demonstrate no mortality benefit, despite consistent reductions in vasopressor requirements, inflammatory markers, and modest improvements in Sequential Organ Failure Assessment subscores (9). It is prudent to note that the removal may affect both proinflammatory and anti-inflammatory mediators equally, raising concerns about whether this might paradoxically worsen immune dysregulation. ECOS effectively reduces partial pressure of CO_2 and enables ultra–lung-protective ventilation, yet outcome data remain modest, with filter clotting remaining a persistent limitation (10).

To our knowledge, no randomized or prospective trials have yet demonstrated mortality benefit for combined lung–kidney ECOS therapies, so they remain as rescue strategies for refractory multiorgan failure. Future randomized trials are required to determine whether these integrated approaches translate into improved survival (8). ■

Figure. The progressive evolution of filter functionality enabling the development of hybrid extracorporeal support systems



CVVH, continuous veno-venous hemofiltration; CVVHD, continous veno-venous hemodialysis; ICU, intensive care unit; MCS, mechanical circulatory support; TPE, therapeutic plasma exchange.

Table. Comparative overview of characteristics between various conventional and integrated systems

Characteristic	Conventional CKRT (CVVH/CVVHD/CVVHDF)	Albumin dialysis (MARS/Prometheus)	$ECCO_2R$ systems/respiratory dialysis	ECMO	ADVOS
Primary indication	Dialysis requiring kidney injury with hemodynamic instability	Live failure with organ dysfunction	Respiratory decompensation	Refractory cardio-respiratory failure	Multiorgan failure (kidney, liver, lung dysfunction)
Membrane type	Polyethersulfone, polysulfone, polymethylmethacrylate (~1.0–1.8 m^2); high flux/ low flux	MARS: polysulfone membrane (~1.0–2.1 m^2); albumin: impregnation; Prometheus: high-flux polysulfone (~2.0 m^2)	PMP (~0.5–0.8 m^2); hollow-fiber gas exchange membrane	PMP (~1.5–4.5 m^2); hollow-fiber gas exchange membrane	Polysulfone-based (~1.4–1.8 m^2); albumin-impermeable membrane
Blood flow rate	100–300 mL/minute	150–250 mL/minute	200–500 mL/minute (low-flow $ECCO_2R$)	2000–7000 mL/minute	Up to 300 mL/minute
Small solute clearance (urea, creatinine)	Excellent	Moderate to good	Not primary function	None	Excellent
Middle molecule clearance (β_2-microglobulin)	Moderate (8–20 mL/minute, better with convection)	Good (albumin-bound middle molecules)	Not primary function	Not applicable	Good (combined diffusion-convection-adsorption)
Protein-bound toxin removal	Poor (40%–55% reduction ratio for PBUTs)	Excellent (bilirubin, bile acids via albumin binding)	Not applicable	Not applicable	Excellent (bilirubin: 1.9 mg/ dL through albumin dialysis)
CO_2 removal capacity	None	None	80–160 mL/minute via membrane oxygenator	High (150–300+ mL/minute depending on sweep gas flow and blood flow rate)	26–160 mL/minute (median, 49.2 mL/minute) fluid-based
Oxygenation capacity	None	None	Minimal to negligible	High (up to 200–400 mL O_2/minute depending on blood flow and membrane surface area)	None
Acid-base correction mechanism	Bicarbonate-buffered replacement fluid/dialysate (diffusion/convection)	Indirect via toxin removal and kidney function improvement	Indirect via CO_2 removal and ventilator adjustment	Indirect via CO_2 removal and oxygenation	Direct removal of acid and CO_2 via alkaline dialysate (~pH 10)
Albumin regeneration	Not applicable	Yes, charcoal and anion exchange columns (MARS) or direct adsorption (Prometheus)	Not applicable	Not applicable	Yes, pH and temperature modulation in dual purification circuits
Treatment duration	Continuous (24 hours/day)	Intermittent sessions (6–8 hours)	Continuous or intermittent (hours to days)	Continuous support (days to weeks)	Median, 17.0–17.5 hours per session
Vascular access	Dual-lumen central venous catheter (11.5–16.0 Fr)	Dual-lumen central venous catheter (11.5–16.0 Fr)	Dual-lumen catheter or single 15.5 Fr or larger venous catheter	Large-bore venous and/or arterial cannulas (15–31 Fr for veno-venous; 15–31 Fr venous + 15–21 Fr arterial for VA)	Conventional hemodialysis venous catheter (11.5–16.0 Fr)
Anticoagulation requirements	Regional citrate or systemic heparin	Regional citrate or systemic heparin	Systemic anticoagulation (despite heparin-bonded circuits)	Systemic anticoagulation with heparin or direct thrombin inhibitors (despite heparin-bonded circuits)	Standard dialysis anticoagulation
Complications	Circuit clotting (most frequent), electrolyte disturbances, hypothermia; rare: hypertriglyceridemia-related circuit failure, euglycemic ketoacidosis, cold agglutinin-mediated filter clotting	Rare circuit/filter clotting, minimal bleeding events; citrate-related toxicity	Circuit-related complications such as clotting, bleeding complications, hemodynamic effects from rapid CO_2 removal	Common: bleeding, thrombosis, hemolysis, limb ischemia (VA-ECMO), infection, oxygenator failure, acute kidney injury	Minimal device-related complications, minor clotting events resolving spontaneously

CVVHDF, continous veno-venous hemodiafiltration; VA, veno-arterial.

Pramod K. Guru, MD, MBBS, FASN, is with the Mayo Clinic, Jacksonville, FL. Srivatsa Nagachandan, MD, is with the Apollo Adlux Hospital, Kochi, India. Himanshi Banker, MBBS, is with Tucson Medical Center, Tucson, AZ.

The authors report no conflicts of interest.

References

1. Acharya M, et al. The role of the ADVanced Organ Support (ADVOS) system in critically ill patients with multiple organ failure. *Artif Organs* 2022; 46:735–746. doi: 10.1111/aor.14188
2. Huber W, Ruiz de Garibay AP. Options in extracorporeal support of multiple organ failure. *Med Klin Intensivmed Notfmed* 2020; 115(Suppl 1):28–36. doi: 10.1007/s00063-020-00658-3
3. Allardet-Servent J, et al. Safety and efficacy of combined extracorporeal CO2 removal and renal replacement therapy in patients with acute respiratory distress syndrome and acute kidney injury: The pulmonary and renal support in acute respiratory distress syndrome study. *Crit Care Med* 2015; 43:2570–2581. doi: 10.1097/CCM.0000000000001296
4. Leypoldt JK. Solute fluxes in different treatment modalities. *Nephrol Dial Transplant* 2000; 15(Suppl 1):3–9. doi: 10.1093/oxfordjournals.ndt.a027961
5. Rodrigues FSC, Faria M. Adsorption- and displacement-based approaches for the removal of protein-bound uremic toxins. *Toxins (Basel)* 2023; 15:110. doi: 10.3390/toxins15020110
6. Perez Ruiz de Garibay A, et al. Respiratory and metabolic acidosis correction with the ADVanced Organ Support system. *Intensive Care Med Exp* 2019; 7:56. doi: 10.1186/s40635-019-0269-7
7. Gruda MC, et al. Broad adsorption of sepsis-related PAMP and DAMP molecules, mycotoxins, and cytokines from whole blood using CytoSorb® sorbent porous polymer beads. *PLoS One* 2018; 13:e0191676. doi: 10.1371/journal.pone.0191676
8. Fuhrmann V, et al. The Advanced Organ Support (ADVOS) hemodialysis system fulfills its intended purpose: Analysis of data from 282 patients from the Registry on Extracorporeal Multiple Organ Support (EMOS). *PLoS One* 2025; 20:e0318917. doi: 10.1371/journal.pone.0318917
9. Schönfelder K, et al. Artificial liver support with CytoSorb and continuous veno-venous hemodiafiltration versus advanced organ support (ADVOS) for critically ill patients with hyperbilirubinemia and acute-on-chronic liver failure (ACLF). *BMC Nephrol* 2025; 26:432. doi: 10.1186/s12882-025-04342-6
10. Stommel AM, et al. Effects of extracorporeal CO_2 removal on gas exchange and ventilator settings: A systematic review and meta-analysis. *Crit Care* 2024; 28:146. doi: 10.1186/s13054-024-04927-x

Core Interventions for the Prevention of Peritoneal Dialysis–Related Infections

By Jeffrey Perl, Kerry Leigh, and Joseph Kessler

https://doi.org/10.62716/kn.003512026

"Core Interventions for the Prevention of Peritoneal Dialysis–Related Infections," recently published in *CJASN*, represents a major coordinated effort to improve outcomes for individuals receiving peritoneal dialysis (PD) by standardizing infection-prevention practices across dialysis programs in the United States (1). The work provides a unique North American perspective and is led by the ASN PD Core Interventions Workgroup, a multidisciplinary panel of experts with the overarching goal of reducing preventable infections, improving patient safety, and supporting the broader adoption of home dialysis therapies.

PD offers important advantages for people with kidney failure, including greater independence and quality of life. However, PD-related infections (peritonitis and exit-site and tunnel infections) remain a major barrier to the broader adoption and long-term use of PD. These complications are associated with significant morbidity and are a leading cause of technique failure and subsequent transition to hemodialysis.

To address the prevalence of PD-related infections, the manuscript outlines a set of core interventions (evidence-informed practical strategies) that dialysis programs can implement. These interventions are not entirely new; rather, they synthesize existing international guidelines and research into a standardized framework for clinical practice.

The core interventions focus on six key domains:

1. Routine surveillance and feedback on PD infection rates ensure that dialysis programs continuously monitor outcomes and identify areas for improvement.
2. Standardized staff training and competency assessment help ensure that all members of the care team are consistently applying best practices.
3. Structured patient and caregiver education reinforces proper technique and empowers patients to actively participate in infection prevention.
4. Regular infection-prevention assessments (including technique checks and retraining) help identify and correct lapses in practice.
5. Use of antimicrobial prophylaxis at the catheter exit site reduces the risk of bacterial colonization and infection.
6. Prophylactic antibiotics for select procedures and clinical scenarios help mitigate infection risk during high-risk periods.

A central theme of the manuscript is that infection prevention in PD is a team-based, systems-level responsibility. Success depends not only on individual clinician or patient behavior but also on coordinated processes, standardized protocols, and a culture of continuous quality improvement. The authors emphasize the importance of multidisciplinary collaboration, including nephrologists, nurses, patients, and caregivers, as well as the need for ongoing evaluation through quality-improvement initiatives and data-driven feedback.

This publication is part of a broader, coordinated initiative to advance infection prevention in PD through education, dissemination, and engagement with the nephrology community. Several complementary activities are underway to support implementation of the PD core interventions.

- An ASN podcast, launched in April, provides an in-depth discussion of the manuscript and its development. Tushar Chopra, MD, FASN, professor of medicine in the Division of Nephrology at the University of Virginia School of Medicine, Charlottesville, interviews the study's lead author (J.P.), offering insights on the development of the manuscript and practical considerations for implementing the interventions in clinical practice. (To listen to the podcast, please visit www.asn-online.org/media/podcast.aspx?s=1.)
- A journal club–style webinar, scheduled for June 16, 2026, at 11 a.m. Eastern Daylight Time, will further promote discussion and dissemination of the work. This session will be co-hosted with the International Society for Peritoneal Dialysis North American Chapter and conducted in cooperation with the American Nephrology Nurses Association. The webinar will bring together multidisciplinary perspectives, including physicians and nurses, to review the manuscript, discuss real-world applications, and share best practices. Participants can submit questions at the time of registration and in the chat during the webinar. (To register for the webinar, please visit www.asn-online.org/PDCoreInterventionsJournalClub.)
- The initiative will be supported by the ASN Excellence in Patient Care website (epc.asn-online.org/), which will serve as a centralized resource hub. The website will soon host the core interventions, frequently asked questions, and curated references, providing dialysis programs with accessible tools to support implementation.

Collectively, the "Core Interventions for the Prevention of Peritoneal Dialysis–Related Infections" marks an important multidisciplinary step toward standardized, high-quality infection prevention in PD (1). The manuscript highlights that, although these interventions are grounded in the best available evidence, there remain important gaps in knowledge. Ongoing research is needed to refine strategies, address emerging challenges (such as antimicrobial resistance), and further reduce infection risk. ■

ASN PD Core Interventions Workgroup.

Jeffrey Perl, MD, is a staff nephrologist at St. Michael's Hospital and professor of medicine at the University of Toronto, Ontario, Canada. He co-chairs the ASN Home Dialysis Steering Committee. Kerry Leigh, RN, and Joseph Kessler, RN, are with ASN's Excellence in Patient Care.

Dr. Perl reports being a consultant for Sobi, US Renal Care, iRen Medical, and Vantive Health; receiving research funding from Vantive Health; being a speaker for US Renal Care; and serving on speakers bureaus for Vantive Health and Fresenius Medical Care. Ms. Leigh and Mr. Kessler report no conflicts of interest.

Reference

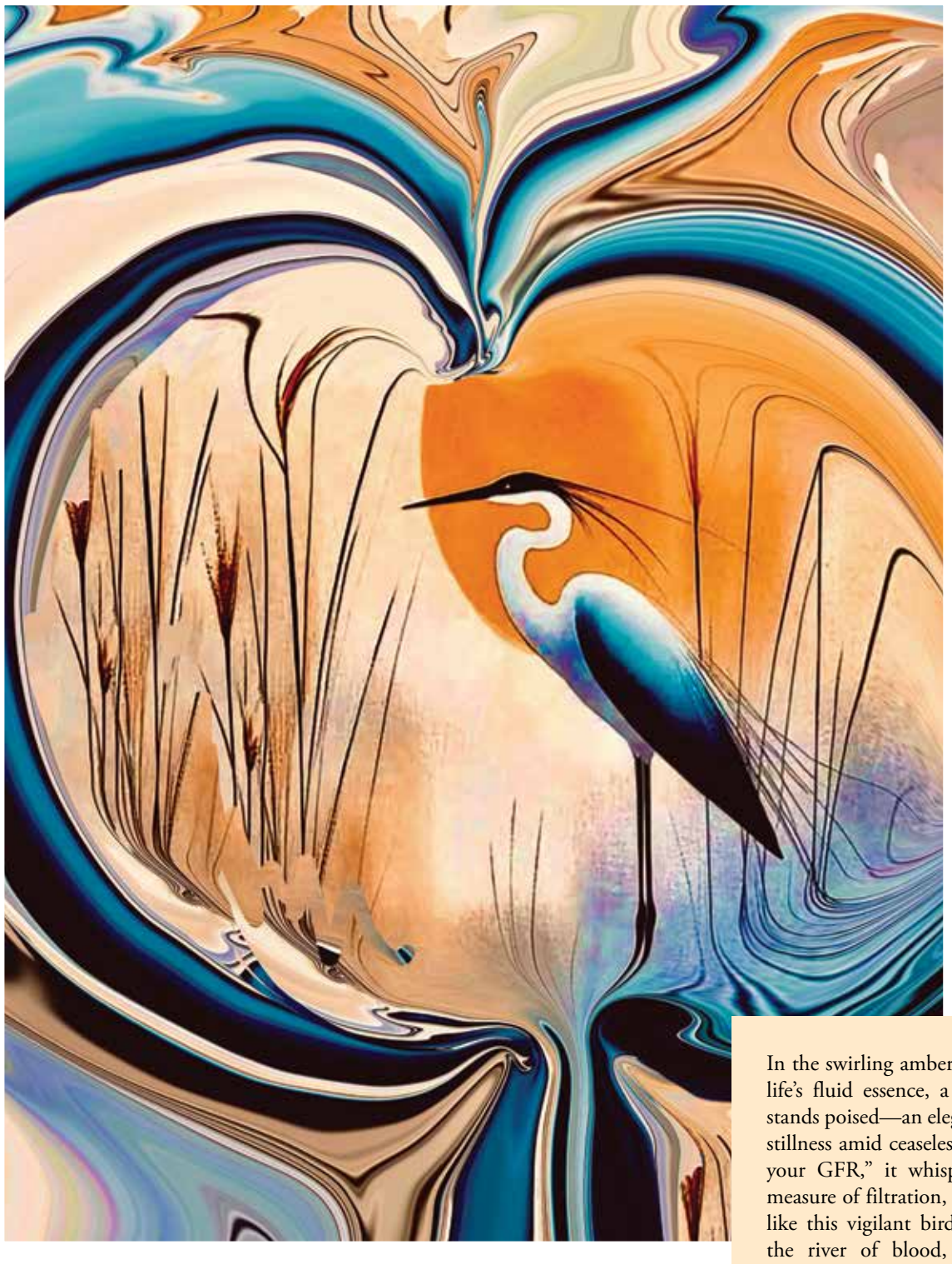
1. Perl J, et al. Core interventions for the prevention of peritoneal dialysis–related infections. *Clin J Am Soc Nephrol* (published online December 5, 2025). doi: 10.2215/CJN.0000000976

CREATIVE CORTEX

Watch Your GFR

By Anil Saxena

https://doi.org/10.62716/kn.003132026



Artwork by AnilzArt. Anil Saxena, MD, FASN, is a digital artist based in Dubai, United Arab Emirates. His abstract artwork blends trained medical expertise with vibrant color palettes, creating visually captivating landscapes of human identity and transformation. Saxena's work has been exhibited internationally and featured on the covers of medical journals. GFR, glomerular filtration rate.

In the swirling amber-blue vortex of life's fluid essence, a solitary heron stands poised—an elegant sentinel of stillness amid ceaseless flow. "Watch your GFR," it whispers: the quiet measure of filtration, where kidneys, like this vigilant bird, patiently sift the river of blood, culling waste while preserving vital clarity. In its graceful vigil lies profound philosophy—patience in observation, precision in release—guarding the balance that sustains the soul's serene flight through turbulent currents. ■

KidneyX Launches Its Next Prize Competition to EMPOWER Living Kidney Donation

By Suzanne Watnick

https://doi.org/10.62716/kn.003272026

The Kidney Innovation Accelerator (KidneyX), a public–private partnership between the US Department of Health and Human Services (HHS) and ASN to accelerate innovation in the prevention, diagnosis, and treatment of kidney diseases, has launched its next prize competition to EMPOWER living kidney donation. Since its inception in 2018, KidneyX has awarded over $25 million to innovators across more than 70 awards. The program has continued to receive bipartisan, bicameral support during the annual appropriations process, and ASN plans to advocate for continued funding in fiscal year 2027.

KidneyX prizes have traditionally addressed some of the most promising innovations in kidney care, including challenges on redesigning dialysis and developing an artificial kidney. In doing so, KidneyX has aimed to de-risk commercialization by attracting outside investment, creating a sense of urgency for people living with kidney diseases, coordinating regulatory and payment pathways across HHS, and offering streamlined funding opportunities through a series of prize competitions.

The newest KidneyX prize will address barriers to living kidney donation. Kidney failure is a significant public health challenge. Mortality rates for those on dialysis range from 15% to 20% per year and cost Medicare over $50 billion annually. Although kidney transplantation is the optimal therapy to improve survival and quality of life for those with kidney failure who are eligible (and yields about $500,000 in savings to the American taxpayer per kidney), very few receive a kidney transplant, as demand far exceeds organ supply. The kidney transplant waitlist is nearing 100,000 people, with over 10 individuals on the waitlist dying per day. Addressing a small portion of this gap, deceased kidney donation has slowly increased over the last 10 years from approximately 12,000 to over 21,000. However, living kidney donation has remained relatively stagnant during this period of time—under 7000 transplants per year.

The KidneyX EMPOWER: Living Link Prize aims to address barriers to living kidney donation. A large gap exists in living donation, in which the medical, logistic, and financial hurdles for donors often halt the process before it can begin. This single-phase competition will award a total of $4 million to address one or more of the following five focus areas:

1. **Public Awareness & Mentorship:** Interventions that connect candidates with trained donor mentors to normalize living donation
2. **Donor Readiness & Eligibility:** Digital tools that assist candidates in safely meeting clinical criteria, such as blood pressure stabilization, to qualify for surgery
3. **Donor Interventions:** Deployed models illustrating behavioral or economic interventions such as automated reimbursement of lost wages that increase living donation rates

4. **Center Practices & Decision Support:** Evidence-based, transparent protocols designed to reduce unnecessary variability and logistical delays at transplant centers
5. **Patient-Centered Outcomes:** Tracking systems and support models that prioritize long-term donor satisfaction, health, and psychological well-being

By focusing on living kidney donation, this KidneyX prize aims to catalyze several vital outcomes, including streamlined evaluation, equitable access, and economic neutrality for those donating the gift of life. Through this continued public–private partnership, KidneyX is not just funding science, it is building a permanent ecosystem of innovation that aims to transform kidney care from a burden of survival into a path toward a better quality of life for people living with kidney diseases. ■

For more information about the KidneyX EMPOWER prize, please visit https://www.kidneyx.org/prize-competitions/empower-prize-challenge/. For further questions or comments, you can also contact Dr. Suzanne Watnick at swatnick@asn-online.org.

Suzanne Watnick, MD, FASN, is a professor of medicine in the Division of Nephrology at the University of Washington in Seattle and the ASN Health Policy Scholar.

The author reports no conflicts of interest.

Timing of Reductions in Kidney Function Helps Predict Outcomes in Heart Failure

https://doi.org/10.62716/kn.003582026

For patients who are hospitalized with heart failure, data on the timing of acute declines in kidney function can aid in prediction of adverse cardiovascular outcomes, including mortality, suggests a study in the *American Journal of Kidney Diseases*.

The researchers analyzed data on 3931 patients who were hospitalized with acute heart failure (AHF), enrolled in the EVEREST trial (NCT00071331). Declines in kidney function were assessed, defined as creatinine increases of 0.3 mg/dL or greater, 50% or greater, or percentage of creatinine change. Timing of acute reductions in kidney function—3, 7, or 14 days after randomization—was evaluated for an association with outcomes, including mortality, a composite of cardiovascular mortality or heart failure hospitalization, and declines in the estimated glomerular filtration rate (eGFR).

Median follow-up was 9.9 months. Acute decline in kidney function at 3 days was not associated with mortality or with

the composite of cardiovascular mortality or heart failure hospitalization. However, kidney function decline at 7 days was associated with increases in adverse outcomes: Hazard ratios (HRs) per 30% increase in creatinine were 1.19 for mortality and 1.10 for the composite outcome.

For patients with acute kidney function decline at 14 days, risks were even higher: HRs, 1.27 for mortality and 1.15 for the composite outcome. At all three times, acute declines in kidney function were associated with increased risk of an eGFR decline to less than 30 mL/min/1.73 m^2 and with an eGFR decline of greater than 40%.

Acute declines in kidney function are common in patients with AHF, but their effects on clinical outcomes remain unclear. The new findings suggest that the timing of reductions in kidney function is a significant factor: Declines occurring early after admission appear to have little impact on mortality or cardiovascular outcomes, whereas declines at 7 to 14 days are associated with worse outcomes.

Regardless of timing, patients with acute declines in kidney function consistently have worse long-term kidney function. The timing of declines in kidney function "provides a potential definition to be evaluated and tested for applications as a kidney safety endpoint in future studies of AHF," the investigators conclude [McCallum W, et al. Association of the timing of acute declines in kidney function in acute heart failure with cardiovascular and kidney outcomes. *Am J Kidney Dis*, published online March 23, 2026. doi: 10.1053/j.ajkd.2025.12.005]. ■

Iptacopan for IgA Nephropathy

https://doi.org/10.62716/kn.003592026

The complement factor B inhibitor iptacopan effectively slows decline in kidney function in patients with immunoglobulin A nephropathy (IgAN), according to final results of a randomized trial in *The New England Journal of Medicine*.

The phase 3 APPLAUSE-IgAN trial (NCT04578834) enrolled 478 adult patients with IgAN, all with an estimated glomerular filtration rate (eGFR) of 30 mL/min/1.73 m^2 or higher and a 24-hour urine protein-to-creatinine ratio (UPCR) of 1 or higher, despite supportive care. Patients were randomly assigned to treatment with oral iptacopan (200 mg) or placebo twice daily.

An interim analysis at 9 months found a significant 38.3% reduction in UPCR for patients assigned to iptacopan. The current report presents the final results for eGFR and secondary outcomes at 2 years' follow-up in 477 patients.

Patients receiving iptacopan had a significantly slower decline in kidney function: an annualized total eGFR slope of –3.10 mL/min/1.73 m^2 per year versus –6.12 mL/min/1.73 m^2 per year with placebo. This benefit appeared similar across prespecified patient subgroups. Iptacopan was also associated with improvement compared with placebo on a composite kidney failure endpoint: 21.4% versus 33.5%.

Adverse event rates were similar between iptacopan (87.0%) and placebo (89.1%) groups. Serious adverse events occurred in 12.2% (iptacopan group) and 11.7% (placebo group) of patients. Serious infections, mainly pneumonia, were more frequent with iptacopan (6.7%) versus placebo (2.1%). There were no deaths in either group.

Iptacopan targets overactivation of the alternative complement pathway, which contributes to glomerular inflammation and kidney injury in IgAN. Based on the interim reductions in proteinuria, iptacopan received accelerated approval from the US Food and Drug Administration for treatment of primary IgAN.

Two-year follow-up findings from APPLAUSE-IgAN show that iptacopan slows the decline in eGFR among patients with IgAN at high risk of progression. "[I]ptacopan can reduce the rate of kidney-function decline in a broad range of patients with IgA nephropathy," the researchers write [Barratt J, et al.; APPLAUSE-IgAN Study Group. Iptacopan in IgA nephropathy—final 24-month data. *N Engl J Med*, published online March 29, 2026. doi: 10.1056/NEJMoa2600743]. ■

The Emotional Realities of Life After Kidney Transplant

By Lisa Schwartz

https://doi.org/10.62716/kn.003462026

For individuals living with chronic kidney disease or kidney failure, kidney transplantation offers a second chance at life. For many transplant recipients, the emotional weight of the second chance can be just as profound as the physical recovery.

But often, patients do not speak of the challenges of post-transplant life, feeling conflicted by the duality of living in gratitude while also struggling with the emotional load. Double organ transplant recipient Valen Keefer calls these the "quiet burdens" of transplantation.

Diagnosed with polycystic kidney disease as a child, Keefer received a kidney transplant more than 2 decades ago, followed by a liver transplant in 2018. She knows firsthand the experience of juggling the unspoken challenges of post-transplant life—from uncertainty to feelings of guilt, mixed with immense gratitude. "With so much attention on labs, medications, and clinical goals, there's often little room to explore what life actually *feels* like after transplant," says Keefer, who, as a patient advocacy leader, travels the country to elevate the patient experience in kidney care and transplantation. "People who have gone through the multifaceted transplant experience balance living a full life alongside the highs and lows of the emotional journey."

Coexisting in gratitude, guilt, and everything in between

Doug S., who received a living donor kidney from his sister in 2024, understands well the emotional complexity of the experience. Although he was elated that his sister was a match and more than willing to be his living donor, he felt a constant sense of guilt throughout the process. "If anything happened to her because she chose to give me a kidney, I would not have been able to live with myself," he says. "That feeling, and knowing she gave up a part of herself for me, is something I'll always carry, along with being eternally thankful that she saved my life."

David Singer, LCSW, LICSW, a clinical social worker with Legacy Transplant Services at Legacy Good Samaritan Medical Center in Portland, OR, says that this type of survivor's guilt is real. "Some patients find themselves thinking, 'Someone had to die for me to live.' Or, they worry that they won't live up to the gift they have been given," he explains. The emotional impact of this gift often takes hold after the surgery, when there is finally space to process the enormity of the experience. "That is when the questions begin," Singer says: "Am I doing enough? What if something goes wrong? What if I don't make the most of this second chance?"

Singer helps people understand that those feelings are valid, but they do not have to define what comes next. "It's about reframing these thoughts," he says: "A donor family chose to create meaning from loss. A living kidney donor understood the risks and chose to give. I let my patients know that they can honor that gift by living their life fully."

Dealing with uncertainty

After a transplant, lingering in the back of people's minds are concerns, such as, "How long will my transplant last?" "Why did my estimated glomerular filtration rate go down this month?" "What will my future look like?"

Even decades after her kidney transplant, Keefer says that she still holds her breath every time she undergoes labs. "If the numbers are stable, I exhale. If not, the questions begin." She adds that "Uncertainty isn't just part of the medical journey; it can reshape how we live. For me personally, it influences how I plan for the future. I weigh the risks versus the benefits in the things I do to help ensure I stay healthy."

Singer sees this consistently in his practice. His response is to be present early in the journey. "Part of our transplant center's protocol is to see every patient within the first 15 days of their transplant," he says. "I let them know I am available. The early post-transplant period can be overwhelming, traumatic, for some people. Patients do not have to navigate this experience alone."

Similarly, at the University of Maryland Medical Center in Baltimore, patients undergo both pre- and post-transplant psychosocial assessments to ensure that the care team understands where each person is physically and emotionally throughout the transplant process. Larissa Dichard, LCSW-C, LICSW, team lead clinical supervisor for the medical center's transplant social workers, describes the post-transplant touchpoint as a key opportunity to normalize the emotional healing process and connect patients with additional support resources. "Our team approaches every patient individually and with curiosity," she says. "Understanding their personal experiences and feelings, without judgment, helps validate their emotions, fears, and anxieties. Letting people know they are not alone in what they are feeling is itself a form of care."

Living in the new normal

There is a common belief that once surgery is complete, a patient is simply "all better." Life after transplant, however, is rarely that straightforward.

Recipients still face dietary constraints, strict medication regimens, and heightened susceptibility to illness due to the immunosuppressants that prevent organ rejection. Follow-up appointments and lab work become a regular part of life. Medication side effects, including weight gain from steroids, tremors from anti-rejection drugs, fatigue, and gastrointestinal issues, can be unexpected and sometimes difficult to manage.

"In the first 6 months after my kidney transplant, I was constantly battling infections," Keefer recalls. "It was my first glimpse at the tradeoffs these medications demand." Yet, she has come to view these lifesaving protocols from a perspective of gratitude, adding, "Taking my medications is one of the most tangible ways I can honor my donors."

Isolation is another piece of this new normal that often surprises people. Singer, who began his career as a dialysis technician, watched patients build real connections in the dialysis center. "Post-transplant, that camaraderie and support system [are] suddenly gone," he says. His approach is to help patients build new sources of community. "Some people re-enter the workforce. Some start volunteering or spend more time with their [children or grandchildren]. Whatever it is, we encourage patients to make it meaningful. A transplant opens up possibilities for people to create a new life."

Dichard and her team draw on acceptance and commitment therapeutic frameworks and emphasize the importance of normalization and validation, helping patients accept their new reality, focusing on what they can control, and celebrating each milestone as it comes. "The transplant journey is a process, and every person experiences it uniquely. When people understand that others have walked this path, it can be incredibly reassuring."

Moving forward with gratitude

Dichard says many of the patients whom she counsels view their post-transplant life as a sort of rebirth, and she encourages them to live fully. Singer, too, offers reassurance, stating, "For a short period after transplant, life can feel unpredictable. But as time progresses, we let patients know: 'You are going to have more energy; you are going to find joy again. There is a light at the end of the tunnel.'"

For Keefer, that light has become a guiding force in her patient advocacy work and personal life. She credits the partnership with kidney care clinicians and caregivers, stating, "Because of their support, transplant recipients go on to do extraordinary things." After more than 2 decades since her kidney transplant, Keefer has found that the burdens and the gratitude often live side by side. "Living with a transplant reminds us to live purposely, care deeply, and find meaning in this life entrusted to us." ■

Are you a fellow with a tip or idea you'd like to share with your fellow peers and the broader kidney community?

Send your idea to the *ASN Kidney News* Fellows First column at kidneynews@asn-online.org

KidneyNews

Free Subscriber Service Request Card

☐ I wish to start/renew a FREE subscription to *Kidney News*

7-digit number label (Required for change of name/address only)

Name

Address

City State Zip

Phone Email Address

Signature Date

Sign up for eTOC alerts at www.kidneynews.org/magazine and never miss an issue.

Please Check Degree(s)

☐ MD ☐ DO ☐ PhD ☐ MBA ☐ RN ☐ MS ☐ BS

☐ Other_____

ASN American Society of Nephrology

Submit your request via QR code, email bhenkel@asn-online.org, or mail to Bob Henkel, 1401 H St NW, #900, Washington, DC 20005.

Index to Advertisers

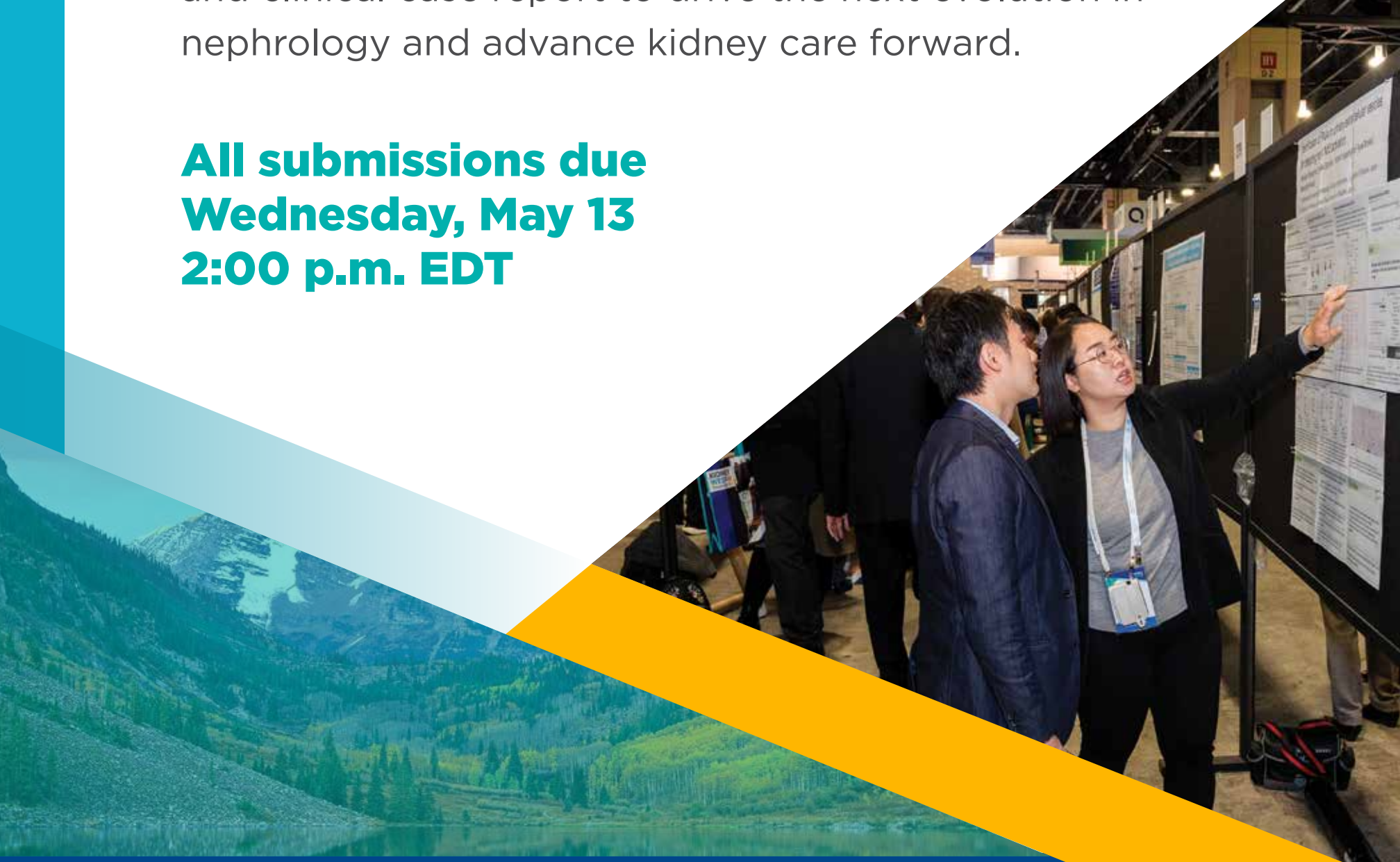
KIDNEY WEEK 2026

Where Research Meets Global Impact: Submit Your Abstract

Share your cutting-edge research with **over 12,000 kidney health professionals** at ASN Kidney Week 2026 in Denver, CO.

From clinical advancements, breakthrough diagnostics, or transformative studies, submit your research abstract and clinical case report to drive the next evolution in nephrology and advance kidney care forward.

All submissions due Wednesday, May 13 2:00 p.m. EDT



Explore submission guidelines and submit your abstract at www.asn-online.org/kidneyweek.