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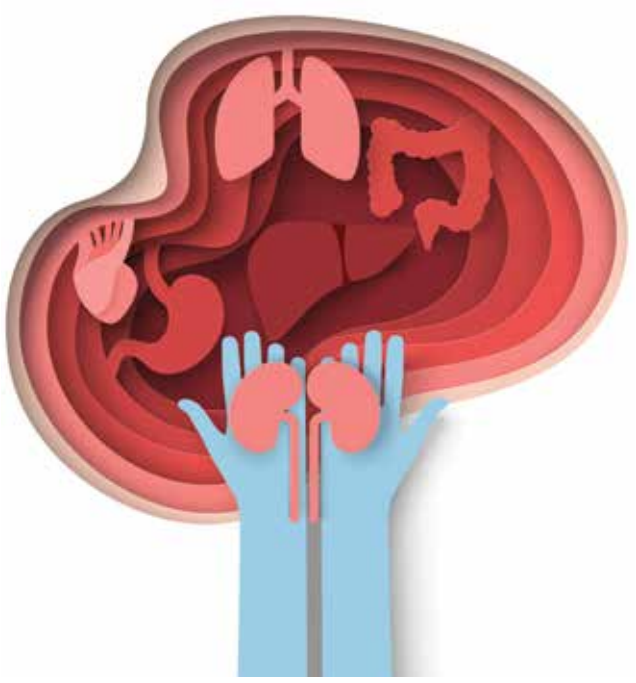
Legislation Clears the Path for Transplant System Reform

By Bridget M. Kuehn



A July Capitol Hill visit from an ASN delegation highlighted the need to fast-track passage of legislation to reform and modernize the U.S. transplant system. The visit was the latest in years of advocacy by patient and clinician organizations seeking to improve the nation's transplant system and make transplantation more accessible.

The Securing the U.S. Organ Procurement and Transplantation Network (SUS OPTN) Act passed the U.S. House of Representatives and the Senate with bipartisan support in late July (1, 2), 1 week after ASN advocates visited their members of Congress asking for swift enactment of the legislation. ASN and 29 other organizations representing patients with kidney diseases and their clinicians supported the legislation (3). The passage of the SUS OPTN Act provides the Health Resources & Services Administration (HRSA) the ability to fully implement its "OPTN Modernization Initiative," which aims to increase transparency, accountability, competition, and efficiency in the OPTN.

"It just gives HRSA the green light to go ahead with the Modernization Initiative," said ASN President Michelle Josephson, MD, FASN, professor of medicine and surgery at The University of Chicago Pritzker School of Medicine, IL. "This is step one."

Need for modernization

Roslyn Mannon, MD, chair of ASN's Policy and Advocacy Committee and professor of medicine in the Division of Nephrology and vice chair of research in the Department of Medicine at the University of Nebraska Medical Center in Omaha, remembers that early in her career, many transplant programs were small "mom and pop" operations driven by trailblazers at local hospitals. The National Organ Transplant Act of 1984 established the first national organ recovery and allocation system, and the United Network for Organ Sharing (UNOS) received the first federal contract to operate the OPTN and has operated it ever since (4). Mannon noted the remarkable accomplishments in the field of transplant since then. There are now 56 organ

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Heat, Diet, and Antibiotics Implicated in Rising Pediatric Kidney Stones

By Bridget M. Kuehn

A complex mix of factors, including extreme heat exposure, consumption of processed foods, and antibiotic use, may contribute to rising kidney stone rates in children and adolescents.

A study in *CJASN* identified a 26% increase in kidney stones per 5-year period among 15- to 19-year-olds in South Carolina between 1997 and 2012 (1). This finding was the "canary in the coal mine," alerting scientists to the alarming trend of rising pediatric kidney stones, said Gregory Tasian, MD, MSc, MSCE, a pediatric nephrologist at the Children's Hospital of Philadelphia, PA. The data showed that girls, Black children, and adolescents were disproportionately affected. Since then, data from children's hospitals indicate a nationwide increase of approximately 6% to 10% per year over the past several decades, according to a recent review of the data by Tasian and colleagues (2).

"There is convincing evidence it is still happening," Tasian said. "If we can understand what is driving these trends, then you can develop interventions that can work on the causal pathway." The cause is likely multifactorial, he continued. About half of an individual's vulnerability to developing kidney stones is genetic, Tasian noted. Additionally, diet and hydration play a role, as do environmental factors, such as heat exposure or other exposures like antibiotics that may alter mineral metabolism by altering the gut microbiome.

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procurement organizations and 250 transplant centers in the United States, and by 2022, the system had completed 1 million organ transplants. But Mannon acknowledged room to continue to progress and address shortcomings in the system.

"I recognize the incredible work our field has done," she said. "But it also feels like our field is lagging."

Mannon shared that concerns from transplant teams and patients have not been addressed in some cases. For example, archaic technology and hardships for transplant centers not located near a major transportation hub can lead to delays in receiving organs. Additionally, it has been difficult to track organs in transit. That has been incredibly frustrating considering how easy it is to track far less valuable online purchases from retail sites, she noted.

"These are precious commodities," Mannon said. "These are people's organs helping other people."

A 2022 Senate hearing outlined the results of a Senate investigation into the U.S. transplant system and its contractors (5). Investigators alleged inadequate system oversight, a lack of technical expertise, and mismanagement leading to excessive numbers of unused organs. Additionally, the White House Digital Service recommended breaking up UNOS' "monopoly" on the transplant system to help address problems with outdated software, system failures, and overreliance on manual data entry (6).

Vineeta Kumar, MD, a transplant nephrologist at The University of Alabama at Birmingham, said the system is not necessarily working poorly now, but she noted that much has changed in the last four decades. For example, the complexity and volume of patients have increased.

"We've learned over decades of experience that we want to be able to do more better," she said. "We need a new set of tools that are different than [what] we needed four decades ago."

The U.S. transplant system is the largest in the world but also has the highest rate of discarded organs, said Sumit Mohan, MD, MPH, professor of medicine and epidemiology at Columbia University and medical director of the kidney transplant program at Columbia University Irving Medical Center in New York. The system discards one in four donated kidneys, and most are transplantable, said Mohan, who also serves on ASN's Quality Committee. The number of discards is also growing, he noted.

"That is simply unacceptable," he said. "The majority of those kidneys would have been used in another system."

The exact reasons for the high discard rate are unclear, partly because there are inadequate data to understand what caused a kidney discard, Mohan explained. But there are likely multiple contributing factors. Some possible contributors are previous performance measures that rewarded centers for the transplanted organ's performance, which incentivized cherry-picking the best organs available and putting patients on the waiting list most likely to have a successful transplant, he said. Kumar agreed that the current quality metrics for transplant centers, which are used by payors like Medicare, may inadvertently incentivize centers to keep their local waitlist small.

"In that process, you can really limit access," Kumar said. She noted that having more granular data might allow more meaningful quality metrics. But doing that requires both more sophisticated data systems and appropriate resources for good data entry into the system—both stated goals of the OPTN Modernization Initiative.

Kidney allocation procedures may also lead to kidney discards, Mohan noted. For example, if multiple transplant centers are offered and turn down an organ, the organ may spend too much time on ice to be transplanted.

"Transplant is a team sport," Kumar said. "Every cog in the wheel has to function in rhythm with the other wheel to turn, but not everything in transplant is aligned for that."

There are about 100,000 people on the kidney waiting list and about 25,000 kidney transplants each year, a disparity that discarded kidneys may exacerbate, Mannon noted. About 6000 patients on the waiting list die each year. Additionally, about half a million people are on dialysis, but it is not clear why more of them are not on the transplant waiting list, Mohan said. He said nephrologists believe most would be good transplant candidates. There have also been persistent racial, ethnic, and socioeconomic disparities in which patients receive transplants, Mohan highlighted.

"We need a more patient-centered, more transparent system," he said. "As a system, we are not doing well from an access-to-care standpoint."

Policy fixes

HRSA's OPTN Modernization Initiative aims to address some of the shortcomings of the current system, focusing on upgrading information technology systems and making transplant more transparent, opening competition for contracts, and increasing accountability (7). Specifically, the initiative is focused on five key tasks: technology, data transparency, governance, operations, and quality improvement and innovation. HRSA has also created a dashboard highlighting de-identified information on organ donors, procurement, transplant waitlists, and wait time (8).

"At HRSA, our stewardship and oversight of this vital work [are] a top priority," said HRSA Administrator Carole Johnson in a statement from the agency (9). "That is why we are taking action to both bring greater transparency to the system and to reform and modernize the OPTN. The individuals and families that depend on this life-saving work deserve no less."

Statutory restrictions on HRSA's administration of the transplant system needed to be lifted to fully implement the Modernization Initiative. Mohan explained that the previous law required the OPTN contractor to be a nonprofit and have experience overseeing the OPTN. Since UNOS has run the OPTN for 40 years, it was effectively the only contractor eligible to apply.

"It [the SUS OPTN Act] gives HRSA a lot more flexibility to do the things we think it needs to do," Mohan said.

"The notion of modernization is something to embrace," Mannon said. "This is a great opportunity to move the field forward."

The SUS OPTN Act lifts the restriction that the contractor be a nonprofit with experience and opens the possibility of creating multiple contracts for individual tasks such as governance or technology. Mohan said this would allow HRSA to award contracts to vendors with the right technology, logistics, or governance expertise. It also requires separate contracts for

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OPTN's Board of Directors and its operations. Currently, the OPTN and UNOS are so closely aligned that many of the same people serve on the two organizations' Boards of Directors and as officers in the organizations. But HRSA wishes to separate the two organizations, create independent governance boards, and spread some of the tasks of the OPTN among multiple contractors.

The SUS OPTN Act and Modernization Initiative open a national conversation on how to improve the transplant system and a discussion about new ways to achieve the system's goals, said Kumar. She noted that, currently, many dialogues about how to improve the system are occurring in silos—the modernization process can bring people together to develop meaningful improvements and help break down those silos that hinder communication and patient care.

"It's a step forward to making things better for our patients and the transplant enterprise in general," she said.

Josephson emphasized that greater investment in the transplant system is needed to help upgrade its information technology and ensure independent oversight of the system. The Biden administration's fiscal year 2024 budget proposed doubling federal investment in organ transplantation and procurement, from $36 million to $67 million. Securing the additional funding will require Congressional approval of the budget request.

"It puts into place the opportunity to make structural improvements," Josephson said. "That is an exciting thing."

Mohan said that upgrading the system's information technology and increasing the amount of data it tracks is essential. The entire system relies on technology and accurate data to support the allocation of organs and monitor the transplant system's performance.

"We need a lot more data than we currently collect to be able to do all those tasks in a meaningful, robust, and accurate way," he said.

Mannon noted that having a competitive contracting process brings the U.S. transplant system more in line with other U.S. government functions and that the prospect of losing a contract for poor performance may incentivize contractors to perform better. "Competition has always been an important aspect of how this country has moved forward," she said.

Mohan noted that HRSA's OPTN Modernization Initiative includes a preference for a nonprofit organization to be the contractor for the governance tasks, which he says makes sense. The key to success will be strong oversight from HRSA, he said.

"The onus falls to HRSA to do a better job of managing the contracts," he said. "They must do a much better job of ensuring the contractors are delivering. If HRSA does that well, it won't matter whether the contractor is for-profit or nonprofit."

Ongoing advocacy from ASN and other organizations dedicated to the needs of patients with kidney diseases and their caregivers is also essential.

"What we all have to do is to help HRSA succeed," Josephson said. "If they succeed, we succeed. We have to be honest with them about what's good and bad [in the system] and focus on improving areas that need improvement and keeping things that work." ■

Disclaimer: The views of Drs. Kumar, Mannon, and Mohan are their own and do not represent the official views of their institutions or ASN.

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Heat, Diet, and Antibiotics Implicated in Rising Pediatric Kidney Stones

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Effect moderator

There is growing recognition that climate change and more frequent extreme heat episodes are driving increasing rates of kidney diseases in some populations. Emerging evidence demonstrates increased rates of admission for kidney diseases during heat waves (3) and elevated rates of kidney stones (4).

Additionally, scientists have implicated chronic heat exposure in rising rates of kidney disease of unknown origin in young agricultural workers in Central America and other parts of the world (5). Some studies suggest that the roots of the condition may be traced back to childhood (6). Nathan Raines, MD, MPH, an instructor of medicine at Beth Israel Deaconess Medical Center and Harvard Medical School in Boston, MA, and a researcher studying the trend, said that heat is an "effect moderator" in kidney diseases. He described that it likely interacts with genetic factors, agricultural chemical exposures, infections, or other not-yet-identified contributors.

"Heat exposure drives dehydration," Raines explained. He said dehydration may lead to reduced urine output, which could contribute to stone formation in children, but it is unlikely to cause the condition on its own. Instead, he added, it likely makes the body less able to compensate for other factors that may contribute to stone formation. Rising temperatures may also contribute to drought, reducing water access, said Kari Nadeau, MD, PhD, interim director of the Center for Climate, Health, and the Global Environment and professor and chair of the Department of Environmental Health at the Harvard T.H. Chan School of Public Health, Boston.

Children are especially vulnerable to dehydration, Nadeau said. She explained that children have a faster metabolism than adults and need more water per unit of weight than adults. Their kidneys are also more vulnerable to injury because they are still developing and do not have as much buffer against damage as adult kidneys do. Children also may be less aware of the importance of hydration or the dangers of high temperatures, Nadeau added. "Kids don't necessarily know to go under a tree right away or go into a cooling room, and they will keep exercising unless someone stops them," she said.

In addition to driving dehydration, heat stress can cause proteins in the body to degrade, Nadeau explained. Filtering out large amounts of degraded proteins can tax kidneys already struggling with limited water. "It becomes hard for [the kidneys] to function, and you can get kidney stones," she said. That kind of stress on kidneys early in life may contribute to chronic kidney disease later in life.

Multiplicative effects

Other trends, such as growing consumption of highly processed foods and greater exposure to antibiotics, may interact with factors like heat exposure to propel kidney stone risk in children.

Consuming foods or beverages with very high concentrations of sugar or salt, which is common in many readily available, processed foods, is associated with a higher risk of developing kidney stones, said Kamyar Kalantar-Zadeh, MD, MPH, PhD, professor of medicine at the University of California, Los Angeles (UCLA), and chief of nephrology and hypertension at Harbor-UCLA Medical Center. He explained that diets high in protein, especially processed meats; low in calcium; or high in sugary drinks, may also contribute to kidney stone risk.

Nadeau noted that communities disproportionately affected by food insecurity or scarcity might have less access to affordable, nutritious foods that can help buffer the body against heat stress. For example, she described that some inexpensive foods, such as potato chips and cookies, might be widely available in stores in California's Central Valley communities, but the fresh produce grown by workers in the Central Valley may be less accessible. "We need to enable communities to have good, healthy choices," she said.

The same communities may also be disproportionately affected by climate change-related heat exposure, pollution, and conditions, such as diabetes, that also affect kidney health, she noted. As a result, improving equitable access to social determinants of health is essential. "Climate change is like an X-ray that exposes health inequity," she added.

Antibiotics may be another potential contributor to pediatric kidney stones. Studies have found that five commonly prescribed antibiotics are associated with an increased risk of kidney stones (7) and that individuals with stones are missing gut bacteria key to human health (8). "Things that change the composition of the microbiome increase the likelihood of forming stones because your gut handles minerals in a different way," Tasian said.

A complex mix of factors, including extreme heat exposure, consumption of processed foods, and antibiotic use, may contribute to rising kidney stone rates in children and adolescents.

Diagnosis and treatment

One of the challenges of treating kidney stones in children is that they may often go undiagnosed. Physicians may not be expecting to see kidney stones in children or adolescents, Tasian said. Pre-adolescent children may also present with diffuse belly pain instead of the excruciating flank pain, nausea, and vomiting, as experienced by adults during an acute kidney stone event, he explained. "Stones are something you often don't recognize until you have one of these incredibly painful events; it could be going on for months or years before it's recognized," he added.

Physicians typically use computed tomography (CT) scans to diagnose kidney stones in adults. But ultrasound is first used for diagnosing children with kidney stones because it does not expose them to radiation, Tasian said. Ultrasound is not as good at detecting stones as CT, so sometimes a follow-up CT is needed, he expressed.

Two medications—one diuretic and another drug that raises urine pH—have been the frontline therapies for kidney stones for decades, Tasian explained. Both focus on treating the incredibly painful incidence of stones. If a blockage is detected, and surgery is required, a pediatric urologist or surgeon who specializes in treating stones in children is needed because there are unique considerations for treating stones in children, Tasian said.

New therapies are needed to treat stone disease as an ongoing disorder of mineral metabolism, Tasian said. He noted that in children and adolescents, the recurrence rate of kidney stones is 50% (2), and individuals who develop kidney stones also have lower bone density and a higher risk of fracture, hypertension, and heart disease. "We need to shift the paradigm from [the] stone as something that causes episodic events to something that has a continuous and long-term impact on human health," he continued.

Prevention and policy

Kalantar-Zadeh emphasized the importance of children drinking water and eating fresh fruits and vegetables in reducing the risks of kidney stones. He stressed avoiding processed foods or meats high in salt or other additives. Tasian agreed: "A well-balanced diet high in vegetables and low in sodium—a heart-healthy diet—is helpful for preventing kidney stones and is good for you in general. The more water you drink, the more the urine is dilute, and the less likely stones can form." Nadeau also recommends rehydrating drinks with electrolytes, such as Gatorade or even milk, to help children who have become dehydrated recover.

Individuals with a history of kidney stones should also seek evaluation and treatment from a urologist or nephrologist to prevent future stones and to help decrease the risk of kidney stones becoming a chronic problem, Tasian said.

Public health measures may also help reverse the trend of rising kidney stones in children and adolescents. Tasian noted that some European countries limit the amount of sodium in processed foods (9). Kalantar-Zadeh recommended that schools restrict access to salty or processed foods or sugary drinks in cafeterias and school vending machines. Raines said schools might also need to implement heat protections for students, for example, ensuring adequate hydration and time for rest, similar to heat protections for workers. Education to help parents understand how heat exposure may contribute to disease mechanisms and how they can prevent it is also essential, Raines continued. Nadeau also recommended more education for physicians and health care professionals on climate change mitigation and adaptation to help them guide patients toward protective measures.

Policies that mitigate rising global temperatures are also urgently needed, Tasian said. "The risk is going to increase as the climate warms," he added. "More people will be exposed to extreme heat, which we know dramatically increases the risk of presenting with a stone." ■

Disclaimer: Dr. Raines' views do not represent the official views of Beth Israel Deaconess Medical Center or Harvard Medical School or of the La Isla Network, a nonprofit organization for which Dr. Raines serves as an advisor.

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USPSTF Releases Final Research Plan for Chronic Kidney Disease Screening

By Lauren Ahearn

The best treatment for chronic kidney disease (CKD) is early intervention. However, 90% of Americans with kidney diseases are unaware (1). For nearly a decade, ASN along with the broader kidney care community, has advocated for federal support of routine screening to identify kidney diseases and intervene earlier to stop or slow progression. One of the main goals of these advocacy efforts has been for the U.S. Preventive Services Task Force (USPSTF) to release official screening guidelines for CKD.

An independent, volunteer panel of physicians that offers evidence-based recommendations about clinical preventive guidelines, USPSTF first proposed a research plan for CKD screening in 2012 but ultimately recommended against the formation of official guidelines (2). But advocacy efforts continued, and, in 2022, USPSTF decided to reconsider its 2012 decision with the release of a new proposed evidence review for CKD screening with an open public comment period (3).

Following a rigorous development process including public comment, USPSTF released its Final Research Plan for Chronic Kidney Disease Screening (4) on June 12, 2023. Among the changes made to the final plan were clarifications of the targeted screening population and the addition of a sub-key question on the effectiveness of repeat screening for CKD.

Evidence shows that the greatest opportunity for CKD screening comes from targeting those with CKD risk factors such as hypertension and diabetes. Despite this evidence, USPSTF insisted on the exclusion of studies in which patients were selected due to preexisting conditions in both the Draft and Final Research Plans. ASN maintains that the exclusion of such studies would lead to an incomplete and misleading assessment of CKD.

Shortly after its release of the Final Research Plan, ASN and the National Kidney Foundation (NKF) released a joint statement acknowledging the plan as a step in the right direction while reiterating concern that the proposed research plan continues to focus on the screening of asymptomatic, low-risk individuals (5). ASN and NKF expressed concern that USPSTF overstates current clinical practice guidelines for screening in hypertensive populations, which list albuminuria testing as optional. In the case of individuals with diabetes, the statement also documents that only 40% of those individuals receive annual albuminuria screening (6).

While ASN is confident that the evidence will ultimately demonstrate the value of CKD screening, ASN continues to urge USPSTF to expand its approach and ultimately increase the diagnosis of those with or at most risk of CKD.

Recommendation development process

USPSTF follows a multistep process to develop its recommendations, starting with a research plan that guides the review of existing evidence, resulting in a recommendation based on that evidence. Throughout the process, USPSTF solicits and considers public and expert input to improve its work. The 2023 plan released for public comment included a proposed analytic framework, key and contextual questions, an approach to accessing health equity and variation in evidence across populations, and a research approach.

ASN was pleased to comment on the proposed plan and applauded USPSTF for undertaking the important review. ASN's comments addressed both the individual elements and questions posed by USPSTF in the research plan (7). ASN also identified several flaws with the proposed evidence review, raising concern that the study would meet the same fate seen in 2012. ASN expressed concern over the scope of the evidence review—particularly the exclusion of studies in which patients were selected due to preexisting conditions such as hypertension and diabetes.

A call to action

ASN and NKF remain committed to ensuring access to preventive care for all individuals living with and at risk of CKD in the United States and are jointly considering options for focusing attention on this development with multiple target audiences (5). In the meantime, an upcoming Clinical Practice Session at Kidney Week 2023 in Philadelphia, PA, titled "Screening for Kidney Diseases: A Call to Action" will be held on Thursday, November 2, 2023, from 10:30 AM EDT–12:30 PM EDT and will highlight opportunities to implement screening for kidney diseases, including collaborative care models, health and economic consequences, and special populations.

More information on Kidney Week 2023 can be found here: https://www.asn-online.org/education/kidneyweek/. ASN will update its membership and the community as it continues to advocate for earlier intervention in kidney care.

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ASN Executive Vice President's Update

The Kidney Health Initiative Has Surpassed Every Expectation

By Tod Ibrahim

This month, the Kidney Health Initiative (KHI) celebrates its first decade, showcases current activities, and articulates a vision for the future. Such an important milestone provides an opportunity to assess KHI's efforts to meet its mission of catalyzing "innovation and the development of safe and effective patient-centered therapies for people living with kidney diseases" (1).

KHI is the most successful public-private partnership in the history of the kidney community (Figure 1). Having participated in KHI from the initial discussion with nephrology leaders at the U.S. Food and Drug Administration (FDA) on World Kidney Day 2012, I would like to highlight KHI's achievements by describing seven themes that have emerged since its inception.

1. KHI engages living people with kidney diseases meaningfully, equally, and consistently. Diagnosed as a freshman in college, the late Celeste Castillo Lee lived with kidney diseases for more than 30 years (2). Ms. Lee's life experience sparked a passion for activism, a desire for innovation, and a commitment to collaboration. As one of two patient representatives on the inaugural KHI Board of Directors (with Sam Pederson), she insisted that people with kidney diseases contribute throughout KHI.

With leadership from Ms. Lee and Mr. Pederson, KHI established a Patient and Family Partnership Council (PFPC) in 2015. Serving as Founding PFPC chair, Ms. Lee helped guarantee that KHI workgroups include patients or care partners, that the KHI Board of Directors has three patient representatives, and that the Annual KHI Stakeholders Meeting spotlights real-life experiences of people living with kidney diseases.

Since KHI established PFPC, FDA has held a Patient-Led Drug Development Meeting on kidney diseases, and there have been seven externally led Patient-Focused Drug Development Meetings hosted by patient organizations, such as the Alport Syndrome Foundation, IgA Nephropathy Foundation, National Kidney Foundation (NKF), NephCure Kidney International, and Polycystic Kidney Disease (PKD) Foundation. The success of these interactions helped result in FDA forming the Center for Drug Evaluation and Research (CDER) Patient Engagement Collaborative in 2017 and the Center for Devices and Radiological Health (CDRH) Patient Engagement Advisory Committee in 2018.

PFPC's influence was instrumental at the U.S. Department of Health and Human Services (HHS) when the Kidney Innovation Accelerator (KidneyX) was established in 2018, helping to ensure patient representation on the KidneyX Steering Committee and in the review of all submissions. To date, KidneyX has awarded 25 prizes to people with kidney diseases who developed "ideas and fixes" through "their own everyday experiences and ingenuity" (3). Influenced by PFPC, ASN now includes people with kidney diseases in the planning process and as faculty for Kidney Week, as editors and authors for ASN's peer-reviewed journals, and in initiatives focused on excellence in kidney care. Last year, ASN launched Cele's Champions: Cele Fogarty Travel Support Program for Patients to help people with kidney diseases attend Kidney Week.

2. KHI transforms the lexicon and shifts the focus to kidney health. From 1972 to 2012, the kidney community focused on dialysis, which the U.S. government made available to every American in 1972, regardless of age, income, or disability. When FDA and ASN discussed KHI as a new public-private partnership 40 years later in March 2012, we knew we needed to build on this commitment to access while prioritizing the protection of kidney health rather than focusing on kidney failure.

Because of this vision, patients are now referred to as people. Chronic kidney disease is now referred to as kidney diseases. End stage renal disease (ESRD) and end stage kidney disease are now referred to as kidney failure (4). In 10 years, the kidney community has moved from acronym-filled, confusing lexicon to language that raises awareness and promotes an understanding of kidney diseases by the public, the media, and policymakers. Ten years later, we now devote ourselves to protecting kidney health—instead of waiting until kidney failure—for people to start to receive treatment.

3. KHI fosters clinical development by standardizing endpoints in kidney diseases to improve trial design. Developing new therapies is a long, circuitous, and difficult process. Historically, doubling of serum creatinine, dialysis, and death were the standard endpoints for clinical trials in nephrology. In his ASN President's Address in 2012, Ronald J. Falk, MD, FASN, asserted, "It is this reality that has filled our vernacular with words that overflow with negative connotations: 'end-stage,' 'chronic,' 'progressive,' 'inexorable' and the 'three Ds' of doubling of the serum creatinine, dialysis, and death" (5).

Before 2012, many commercial entities (like biotechnology, medical device, and pharmaceutical companies) were hesitant to invest in clinical development for kidney diseases, partly because these endpoints were nonuniform or insufficient for evaluating the efficacy and safety of novel therapies. Not surprisingly, nephrology trailed other specialties in clinical trials in the decades before 2012 (6).

Employing a data-driven approach, KHI workgroups published endpoints for vascular access and lupus nephritis that were defined by consensus across stakeholders. KHI also led efforts to establish surrogate endpoints for primary hyperoxaluria and immunoglobulin A (IgA) nephropathy, prompting the use of the FDA Accelerated Approval Program for these rare diseases, thereby getting therapies to patients sooner. According to FDA, this program allows "for earlier approval of drugs that treat serious conditions, and [to] fill an unmet medical need based on a surrogate endpoint" (7).

In addition to these efforts by KHI, NKF worked with FDA and the European Medicines Agency on changes in albuminuria and estimated glomerular filtration rate slope as surrogate endpoints (8, 9). As a result, the kidney community now has more uniform and appropriate endpoints for clinical trials in kidney diseases.

4. KHI speeds the development of devices and biologics by advancing artificial kidneys and xenotransplantation. In 2014, then-ASN President Sharon M. Moe, MD, FASN, testified at a U.S. House of Representatives Science, Space, and Technology Committee hearing on the role of prize competitions in promoting innovation. Citing KHI in her testimony, Dr. Moe stated, "If Congress signals to the private sector that you want alternatives to the forms of dialysis currently covered by the [Medicare] ESRD program, then I believe companies, investors, and inventors will produce life-changing and cost-saving technologies" (10). Explaining that "dialysis was thought of as a bridge to kidney transplantation," Dr. Moe emphasized that "the increase in the number of patients with kidney disease without an increase in the number of available organs has left patients waiting for a transplant for years."

In 2016, the White House convened a summit to address the shortage of organs available for transplantation. There, then-ASN President Raymond C. Harris, MD, FASN (who chaired the KHI Board of Directors from 2019 to 2022); current ASN President Michelle A. Josephson, MD, FASN; and then-ASN Secretary-Treasurer John R. Sedor, MD, FASN, announced three initiatives: the first $7 million toward a kidney disease prize competition, a partnership with the U.S. Department of Veterans Affairs (VA), and "a commitment to developing a roadmap to achieve the goal of creating a bio-artificial or bioengineered alternative to dialysis" (11).

Working with FDA CDRH—which shared ASN's concern about both the transplant waitlist and lack of innovation in dialysis—KHI published the Technology Roadmap for Innovative Approaches to Renal Replacement Therapy in 2018. Defining the pathway to an artificial kidney, this foundational work was agnostic to the approach (cellular, mechanical, or biohybrid) (12). Led by former ASN President Joseph V. Bonventre, MD, PhD, FASN, the roadmap (updated in 2022 with a Human Centered Design Toolkit for Kidney Failure) stimulated interest from multiple fields and new researchers to solve technical challenges while keeping patient goals front and center.

Since the Technology Roadmap's publication, FDA approved new home hemodialysis machines, funded efforts to evaluate patient-reported outcome measures (PROMS), and developed a patient preference survey about wearable kidney devices. Building on this momentum, the Executive Order on Advancing American Kidney Health in 2019 also committed the federal government to developing "an artificial kidney" and producing "a strategy for encouraging innovation in new therapies" (13). In June 2023, the second phase of the KidneyX Artificial Kidney Prize awarded innovators working in regenerative medicine, cellular engineering, and xenotransplantation (14).

5. KHI promotes investment from commercial entities focused on treating kidney diseases. By engaging people with kidney diseases; transforming the lexicon to shift the focus to kidney health; increasing the development of drugs to treat kidney diseases by securing surrogate endpoints; and speeding the development of artificial kidneys and xenotransplantation through the development of devices and biologics, KHI has made a case for investing in nephrology and for encouraging politicians and policymakers to value the importance of kidney health.

Advancing this case, KHI participated in several Capital Markets Days for Kidney Health organized by ASN. Starting in 2019 at the London Stock Exchange, capital markets days have brought investors and companies interested in kidney health together with nephrologists, people with kidney diseases, innovators, and government officials from FDA and HHS. Besides changing the narrative and raising awareness about opportunities across nephrology—including prevention, screening, diagnosis, and treatment—capital markets days help emphasize that the kidney community is "open for business."

Rather than summarizing all the recent—and considerable—investment in kidney health, three recent examples illustrate the progress KHI helps facilitate. This year, Novartis agreed to acquire Chinook Therapeutics, "a biopharmaceu-

tical company with two high-value, late-stage medicines in development" to treat IgA nephropathy and proteinuric glomerular diseases for $3.2 billion (15). In 2020, Outset Medical's initial public offering generated more than $275 million. Since 2016, investors committed more than $1 billion for companies (such as Evergreen Nephrology, Interwell Health, Monogram Health, Somatus, and Strive Health) to pursue varied strategies for partnering with nephrologists to provide integrated kidney care.

6. KHI convenes the kidney community, federal leaders, and other stakeholders for precompetitive discussions that improve care for people with kidney diseases. Since 2012, KHI has brought together ASN, FDA, and 156 member organizations representing people with kidney diseases (and other patient advocates); health professionals; biotechnology, medical device, and pharmaceutical companies; research organizations; the dialysis industry; and representatives from other government agencies, including the Centers for Disease Control and Prevention (CDC), Centers for Medicare & Medicaid Services (CMS), National Institutes of Health (NIH), and VA (Figure 1).

This remarkable collaboration exists because KHI was founded on a key value: precompetitive inclusivity. From day one, the KHI leadership, staff, and I have fundamentally opposed any effort to play favorites among KHI members, shift to a model that embraces "pay to play," or indicate that some members of the kidney community are more important than others. KHI's members, leadership, staff, and I have remained focused on overcoming barriers at a precompetitive level.

KHI is the only precompetitive collaboration focused on kidney diseases that works throughout FDA, including CDRH, CDER, the Center for Biologics Evaluation and Research, and the Center for Food Safety and Applied Nutrition. Prior to KHI, the kidney community interacted within FDA and across federal agencies in a reactive, one-off manner. Because representatives from FDA, CDC, CMS, NIH, and VA participate in KHI, the kidney community can focus on accelerating innovation and helping the 37 million Americans with kidney diseases proactively, strategically, and holistically.

7. KHI produces leaders throughout the kidney community. When ASN leadership and staff met with FDA representatives on World Kidney Day 2012, every participant recognized that the nephrology workforce was struggling. Over time, KHI identified precompetitive barriers to bringing new products to market, advanced the use of PROMS and surrogate endpoints for clinical trials in kidney diseases, and engaged in roadmapping to coordinate a multi-stakeholder community. The therapies and products these gains helped catalyze have also helped renew interest in nephrology as a career and brought new hope to the scientists and health professionals already dedicated to kidney medicine.

Serving on a KHI workgroup or in the leadership requires significant time and effort. Everyone is volunteering their expertise, and the knowledge gap among FDA medical officers, sponsors, nephrologists, and people with kidney diseases has, at times, seemed wide. ASN's members, leadership, staff, and I applaud the many nephrologists who joined commercial entities to better advise about opportunities in treating kidney diseases or to design appropriate clinical trials. ASN also thanks the many nephrologists who have embraced the regulatory arena to guide KHI projects and educate the greater kidney community on the science, governing framework, or strategies to engage people living with kidney diseases.

More recently, commercial entities have included people with kidney diseases in their efforts. ASN's members, leadership, staff, and I commend these individuals for their remarkable contributions as well. While Ms. Lee and Mr. Pederson deserve considerable credit for this exciting reality, at least four additional leaders are responsible for KHI's inclusivity and for setting the overall initiative on a path to exceeding expectations:

- Dr. Falk, who first articulated the need for KHI, dedicated his ASN presidency to making KHI a reality, and served on its inaugural Board of Directors as ASN Council Liaison.
- Patrick Archdeacon, MD, who is currently Deputy Director, Office of New Drugs, Division of Diabetes, Lipid Disorders, and Obesity, at FDA CDER. Dr. Archdeacon facilitated the meeting in March 2012, helped broker KHI's establishing Memorandum of Understanding, served as the founding co-chair of its Board of Directors, and positioned KHI for success.
- Prabir Roy-Chaudhury, MD, PhD, FASN, who served as the founding co-chair of the KHI Board of Directors with Dr. Archdeacon, was then elected to the ASN Council, and served as the ASN Council Liaison to the KHI Board of Directors through 2022. He will become ASN President on January 1, 2025.
- Melissa R. West, who served as the chief staff executive for KHI for its first 8 years. In 2020, she became ASN Senior Director for Strategic Relations and Patient Engagement and continues to contribute significantly to ASN, KHI, and the broader kidney community. (I sincerely appreciate her considerable help with this editorial.)

Besides highlighting KHI's achievements, these seven themes summarize how nephrology and the kidney community have changed during the last decade. For example, nephrologists now have powerful, new drugs to treat kidney diseases, FDA recently approved the first de novo prognostic test to predict kidney disease progression, and KidneyX has awarded more than $18 million (and counting) to innovators.

In his 2012 ASN President's Address, Dr. Falk announced, "This summer, the US Food and Drug Administration (FDA) commissioner Dr. Margaret Hamburg and I signed a Memorandum of Understanding between the ASN and the FDA that seeks to develop a platform for constructive collaborations between the FDA, academia, patient support groups, and multiple members of industry" (5). Dr. Falk then predicted that KHI would "help write a new and exciting chapter in our fight against kidney disease."

At the Annual KHI Stakeholders Meeting this month, KHI Board of Directors Chair Uptal D. Patel, MD, will articulate his vision for the next chapter of the initiative. If the second chapter is anything like KHI's first decade, none of us will recognize nephrology in 2033.

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Figure 1. KHI's first decade by the numbers

Toward an International Goal of "Pragmatic" Perfection in Blood Pressure Measurement

By Jordana Cohen

Blood pressure measurement often gets deprioritized as a mundane step in clinic office visits that is little more than an afterthought. In direct opposition to this common false heuristic, an international working group, comprised of many of the world's top clinical hypertension researchers, recently published a consensus statement and call to action to improve the quality of office blood pressure measurement worldwide (1). The authors cited dozens of randomized trials that supported that lowering blood pressure reduces the risk of major cardiovascular events (2), all of which relied on standardized (i.e., systematically performed, high-quality) office blood pressure measurements. Data collected by Drawz et al. (3) revealed that routine office blood pressure measurements yielded systolic blood pressure readings as much as 45 mm Hg above and 30 mm Hg below research study measurements among participants of the Systolic Blood Pressure Intervention Trial (SPRINT). Accordingly, the majority of routine office blood pressure measurements fail to address key steps. These missteps in measurement can easily result in pronounced over- and undertreatment of hypertension.

The consensus statement (1) stresses the importance of working toward standardized office blood pressure measurements as standard of care for the diagnosis and management of hypertension. Standardized office blood pressure measurements require several factors to be in place (Table 1), including appropriate facility, equipment, personnel, patient preparation, and measurement technique. These conditions can be very challenging to achieve in a typical clinical setting. Nonetheless, the authors emphasize the importance of being as pragmatic as possible in implementing these key steps and in avoiding dogmatic assertions about aspects of blood pressure measurement that are not evidence based. Although the U.S. Preventive Services Task Force (4) and several other guidelines recommend out-of-office blood pressure monitoring for the diagnosis of hypertension to overcome many of the limitations of routine office blood pressure measurements, the authors of the consensus statement argue that home and ambulatory blood pressure goals are not yet supported by randomized trial evidence (5) and that standardized office blood pressure measurements remain paramount. The authors acknowledge that there are several barriers to obtaining standardized office blood pressure measurements, most notably, a lack of sufficient time during a typical clinic visit. They argue that these barriers can be readily overcome if health care institutions and payers begin to prioritize accurate blood pressure assessment and point to large-scale success stories that benefited from such support (6, 7).

Many clinicians may argue that standardized office blood pressure measurements are far from pragmatic. Nonetheless, growing evidence supports that we do a poor job of measuring blood pressure and may unwittingly be causing harm (3, 8). We owe it to our patients to do better. ■

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Table 1. Necessary conditions to obtain standardized blood pressure measurements

Facility	• Quiet room • With or without a clinician present
Equipment	• Clinically validated, automated blood pressure device (9) • Appropriate upper-arm cuff size
Personnel	• Trained health care clinician • Annual retraining
Patient preparation	• Abstinence from alcohol, nicotine, caffeine, and exercise for ≥30 minutes before the measurement • Empty bladder • 3- to 5-Minute rest • No conversation during measurement
Measurement technique	• Correct cuff placement (bare upper arm, 2–3 cm above the antecubital space) • Correct patient positioning (mid-arm at the level of the heart, back supported, feet flat on the ground) • Use of the arm with the higher blood pressure • Two or more measurements obtained ≥30 seconds apart

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Who Owns Hypertension?

Tina Turner's Death Turns Spotlight on Nephrologists' Role in Treating High Blood Pressure

By Eric Seaborg

When rock icon Tina Turner died on May 24, 2023, at age 83, many obituaries highlighted her status as a patient with kidney disease. Her death brought new attention to her widely read blog post on a website for patients with kidney diseases, titled "My kidneys are victims of my elevated blood pressure" (1). Turner was diagnosed with hypertension in 1978 at approximately age 40, but said she "didn't care much about it. I can't remember ever getting an explanation about what high blood pressure means or how it affects the body."

In a plea for other patients to take the condition seriously, Turner wrote that had she known more about the deleterious effects of hypertension on her kidneys, she would have taken it more seriously, noting, "My kidneys are victims of me denying the fact that my hypertension needed therapy with conventional medicine."

Taking ownership

Turner's story invigorated an ongoing debate in the kidney community about nephrologists' role in treating hypertension. "[W]e need to continue to take ownership of hypertension as nephrologists," Kenar D. Jhaveri, MD, FASN, professor of medicine at the Donald and Barbara Zucker School of Medicine at Hofstra/Northwell in Hempstead, NY, and editor-in-chief of *Kidney News*, wrote in these pages last year (2).

Jhaveri says that in recent years, "There has been more interest in the nephrology community to be in charge of treating hypertension. A lot of the divisions of kidney disease[s] include hypertension in their name. Cardiologists, internists, and nephrologists can take on these patients, but out of experience and interest, I think nephrologists can do a better job. When the patient's regular doctor can't handle it, instead of going through other specialists, maybe the first referral should be to a nephrologist."

"Nephrology already owns hypertension," according to Aldo Peixoto, MD, professor of medicine in nephrology at Yale School of Medicine, New Haven, CT. He says that hypertension was formerly "a sort of subspecialty" of cardiology, but over the past 20–30 years, more cardiologists have focused their attention on interventional cardiology and other procedure-based approaches and paid less attention to preventive cardiology. His sense from his involvement with the former American Society of Hypertension (ASH) and with the American Heart Association's (AHA's) Hypertension Council is that nephrologists outnumber cardiologists in these groups.

Peixoto says that hypertension is so common among the general population that it needs to be handled "in general internal medicine," and most cases can be handled with a simple drug regimen. But for the 15%–20% of patients who need to see a subspecialist for resistant hypertension, nephrologists "are very good at treating" these complicated, more difficult cases.

"It's important not to have turf wars about who should do what," says Swapnil Hiremath, MD, MPH, associate professor at the University of Ottawa and staff nephrologist at The Ottawa Hospital in Ontario, Canada. "Whoever does it the best should do it. I have seen all sorts of people doing hypertension work: a family doctor, internist, nephrologist, cardiologist, clinical pharmacologist, and endocrinologist. But they need to know what they are doing."

Hypertension certification

Hiremath worries that some nephrologists think hypertension is simple—as he did when he began practicing—and do not take an adequate interest in learning about it. When a colleague recruited Hiremath to help with research projects, he found that his nephrology fellowship had not prepared him adequately for the level of hypertension knowledge he needed. Hiremath studied and pursued specialist certification from the former ASH.

The former ASH established that certification program in 1998, but the society dissolved 6 years ago. However, a group of physicians carried on the American Hypertension Specialist Certification Program (AHSCP) (3), which is currently governed by a board of directors of nine physicians, of whom three of its five officers are nephrologists. The certification exam is administered by the Professional Testing Corporation, a company headquartered in New York City.

The AHA absorbed another project of the former ASH: certification of hypertension centers. One requirement for certification as a center is that the director must be certified by the AHSCP. The AHA website lists fewer than 20 centers that have been certified nationwide. (The AHA certifies hypertension centers, not people.) The AHA also established the Hypertension Council among its many scientific councils. The Hypertension Council holds annual hypertension scientific sessions in conjunction with the AHA's Council on the Kidney in Cardiovascular Disease.

In another area reflecting its influence, the AHA and the American College of Cardiology published the influential, general "2017 Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults" (4), explains Peixoto, who contributed to the guideline as a reviewer representing the former ASH. (ASN was not among the 11 organizations listed as official collaborators.)

Consequences of hypertension

AHA's interest in hypertension reflects that stroke and heart failure top the list of the condition's most serious risks. "Most patients die of cardiovascular disease or stroke before they reach end stage kidney disease," says Matthew Sparks, MD, FASN, associate professor of medicine in the Division of Nephrology at Duke University, Durham, NC, noting it is relatively rare to see a patient with end stage kidney disease compared with cardiovascular problems. "It is an independent risk factor for cardiovascular disease. When you have kidney disease, you have cardiovascular disease. The kidney plays a really important role in the long-term management of blood pressure. Perturbations in the kidney cause high blood pressure, and high blood pressure causes perturbations in the kidney. It is kind of a chicken and the egg."

This interplay illustrates how hypertension cuts across disciplines—and a sampling of the leadership of a few hypertension centers around the country reveals the diversity of specialties involved in treatment. The University of Chicago's AHA-certified center is led by a nephrologist, as is the center at Hiremath's institution. The Center for Resistant Hypertension at Johns Hopkins Medicine in Baltimore, MD, is led by a cardiologist. The clinical director of the AHA-certified center at Beth Israel Deaconess Medical Center in Boston, MA, is an internist. All six of the physicians at the Brigham and Women's Hospital Hypertension Clinic in Boston are endocrinologists. This diversity can lead to a lack of clarity about which discipline should take charge in cases of hypertension, but nephrologists are perfectly positioned to do so, Hiremath says.

"If you look at what causes hypertension, in most cases, the kidney is involved in one way or the other, so who else but us [nephrologists] should know about it?" Hiremath asks. "We need to know how to treat blood pressure well because our patients very commonly have high [blood] pressure." Hiremath believes that nephrologists who did not get enough exposure to treating hypertension during their fellowship should pursue training, which can be done in a variety of ways. "If you have people on your faculty who have expertise, and you do a rotation in that clinic or work with them, you will get good training. On the other hand, if you are [at] a center where hypertension is not a part of any nephrologist's interest, and the cardiologists or endocrinologists are managing hypertension, then you are not going to get enough exposure. You have to work with patients, even [if it means working with] someone outside of nephrology who is working in hypertension."

Sparks suggests that nephrologists should play a leadership role in hypertension in at least two ways: "One role is to disseminate best practices to be involved in clinical guidelines and research. And the other role is, because a lot of our patients have hypertension, we have to be good at treating it. If you see a patient with uncontrolled hypertension, it is not something that you punt back to primary care. One of our biggest roles is to try to uncover the reason why an individual has hypertension."

Jhaveri points out that another reason for ownership of hypertension is the opportunity it offers for finding additional cases of kidney diseases. "We do get consulted for resistant hypertension, and we often diagnose patients with kidney disease [who] might have actually triggered the hypertension," he explains.

In Tina Turner's case, it's not possible to make a diagnosis or draw definitive conclusions without access to her medical records, but in her memoirs and the blog post, she detailed a long and complicated medical history that included strokes, dialysis, and a kidney transplant. Her belief that her kidneys were the victim of her elevated blood pressure might be debatable. "It is kind of old school science that hypertension causes kidney disease," Jhaveri says. "There is actually more and more data that [it] is the other way around, that kidney disease might be the cause of hypertension." Sparks notes that getting hypertension at the age of 40 is unusual. The knowledge was not available at the time of her diagnosis so many years ago, but nephrologists have since learned about polymorphisms in the apolipoprotein L1 gene that can raise the risk for chronic kidney disease. But that might be all the more reason for nephrologists to be engaged in hypertension treatment. As Turner noted in her blog post: "The struggle for healing is always also a struggle for accurate information!" ■

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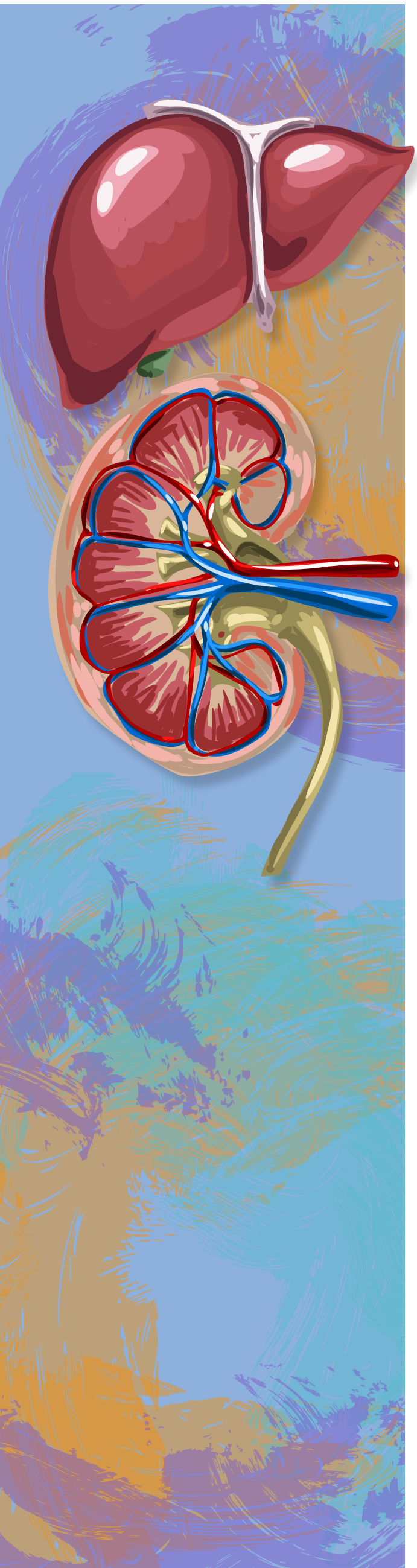

THE LIVER AND KIDNEY CONNECTION: HEPATORENAL SYNDROME AND MORE

By Kenar D. Jhaveri

Acute kidney injury (AKI) is common and can be deadly in patients with cirrhosis. There are a variety of causes of AKI in the patient population with cirrhosis. As nephrologists, we are often asked to consult on such cases to rule out hepatorenal syndrome (HRS). But how common is HRS?

A recent study published by Patidar et al. (1) in the *Journal of Hepatology* sheds light on the true incidence of this phenomenon. This was a retrospective cohort study of 11 hospital networks of consecutive adult patients admitted in 2019 with AKI and cirrhosis, totaling over 2000 patients (median age, 62 years; 38.3% female; median model for end stage liver disease-serum sodium [MELD-Na] score, 26). The etiology of AKI was adjudicated based on pre-specified clinical definitions (prerenal/hypovolemic AKI, HRS-AKI, acute tubular necrosis [ATN], and others). The study showed that hypovolemic or prerenal AKI was the most common (44%), followed by ATN (30%), and then HRS (12%). Patients with prerenal AKI had the lowest rate of death. ATN and HRS had similar outcomes (~50% mortality at 90 days).

Another study published recently by Singal et al. (2) of 2016–2019 National Inpatient Sample admissions demonstrated similar incidence of HRS as the study by Patidar et al. (1) (16.5% of admissions for AKI and cirrhosis using billing codes versus 12.1% fully adjudicated cases). They also found nearly identical outcomes in hospital mortality rates (24.5% versus 25.8%). Both studies lacked kidney biopsy data. These studies may guide us in recognizing that HRS is uncommon and that ATN may be more important to consider, as it has similar outcomes as HRS-AKI.

Content covered in this issue of *Kidney News* further highlights the liver and kidney connection. With a focus on kidney diseases in liver transplantation, we present the complexities of simultaneous liver and kidney versus liver-alone transplantation and explore prognostic biomarkers of posttransplant complications. We also review various glomerular diseases seen with hepatitis B and C, examine the role of palliative care in combined kidney and liver diseases, and discuss the impact of hyperbilirubinemia on kidney function, among other topics. We hope the readers find this special issue helpful in their care for their patients with both liver and kidney diseases.

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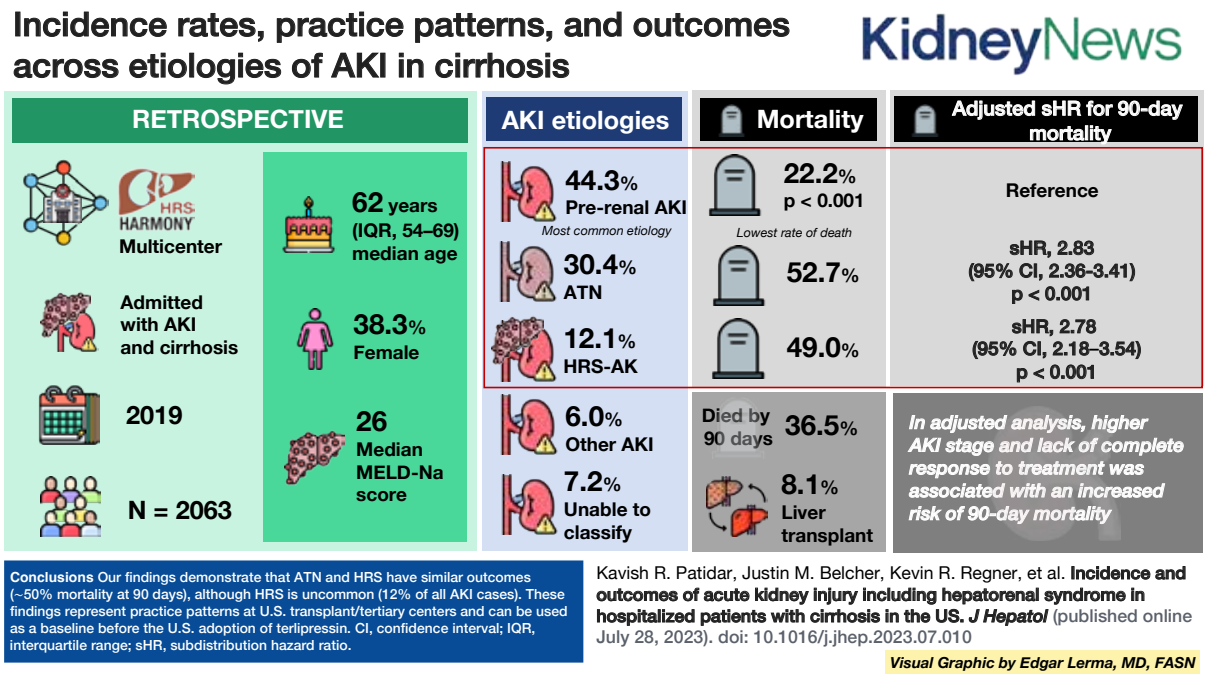

Precision Medicine in Liver Transplantation: Prognostic Biomarkers of Acute Kidney Injury and Early Allograft Dysfunction

By Jeremy Puthumana and Chirag Parikh

Liver transplantation is a complex and life-saving procedure that offers hope to patients with end stage liver disease. Despite significant advancements in surgical techniques and perioperative care, the occurrence of post-transplant complications remains a significant concern. Among these complications, acute kidney injury (AKI) and early allograft dysfunction (EAD) are particularly challenging, as they can have profound implications on both short-term and long-term outcomes. Consequently, the pursuit of robust prognostic markers to anticipate these complications and facilitate early intervention has garnered substantial scientific interest.

Serum neutrophil gelatinase-associated lipocalin (NGAL) is a promising and well-studied biomarker that has been shown to predict AKI in multiple other disease settings including after cardiac surgery (1). In addition, one study found arterial lactate concentration at the end of liver transplantation to be predictive of EAD (2).

In a recently published article in *Scientific Reports*, Cho et al. (3) aimed to build on previous work and determine whether serum NGAL, lactate, or lactate-adjusted NGAL at the end of surgery could predict AKI and EAD. In a retrospective cohort of 353 patients undergoing living donor liver transplantation at Seoul National University Hospital, the investigators found that lactate-adjusted NGAL at the end of surgery significantly increased prognostic accuracy for AKI (area under the curve [AUC], 0.89; 95% confidence interval [CI], 0.85–0.92) and EAD (AUC, 0.88; 95% CI, 0.84–0.91) compared with the individual biomarkers when added to the clinical model. Furthermore, the authors determined that the optimal cutoffs for lactate-adjusted NGAL were 191 and 125 for AKI and EAD, respectively.

Although the findings from the study by Cho et al. (3) are promising, the road to full integration into clinical practice requires additional validation and comprehensive assessment across diverse patient populations and transplantation centers. The study was a single-center, retrospective cohort study with a relatively small sample size. Notably, the study was based on patients with a low model for end stage liver disease and with mostly hepatocellular carcinoma. Therefore, it remains to be seen whether lactate-adjusted NGAL remains a good prognostic tool at the same cutoffs in the broader transplant population, of whom many are more severely ill and may have elevations in serum NGAL and lactate for a multitude of reasons.

The findings in the study by Cho et al. (3) should prompt validation studies in prospective cohorts, together with further studies to assess whether targeted interventions provided to patients with elevated, lactate-adjusted NGAL are effective in preventing and mitigating the severity of AKI and EAD. ■

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The authors report no conflicts of interest.

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Fellows First

The Goldilocks Principle on Bilirubin

By Raad Chowdhury

The impact of hyperbilirubinemia on kidney function continues to be a topic of discussion with two conflicting philosophies: whether bilirubin is nephrotoxic or nephroprotective. To understand the two perspectives, it is imperative to review the physiology behind its metabolism. Eighty-five percent of bilirubin is produced from the breakdown of red blood cells in the reticuloendothelial system as unconjugated bilirubin, and the rest is produced from myoglobin. Unconjugated bilirubin is albumin bound in the blood and delivered to the liver where it enters the sinusoidal circulation (1). There, it is taken up by hepatocytes, made water soluble by conjugation, and subsequently excreted as bile. Excessive production, impairment, or obstruction at any of these steps can lead to either conjugated or unconjugated hyperbilirubinemia and clinical jaundice. After exiting the biliary system, the conjugated bilirubin is secreted in the duodenum and converted to urobilinogen by gastric microfauna. Twenty percent of urobilinogen is reabsorbed systemically and either enters portal circulation or is renally excreted. It is worth noting that urobilinogen production will decrease if the level of defect is prior to duodenal secretion (1).

The nephrotoxic potential of hyperbilirubinemia was first proposed in 1899 after a review of autopsies from patients with jaundice and kidney failure revealed bile pigments in the glomeruli (2). In 1937, Elsom (3) showed the improvement of kidney function with clinical improvement of jaundice in a small cohort, establishing the dogma. Mechanistically, in states of elevated, conjugated hyperbilirubinemia, the glomerular filtration and tubular transport processes may be overwhelmed because of increased oxidative stress, proximal tubular dysfunction, and cast formation (4, 5). In a histological study of 44 patients, bile casts were mostly found in the distal nephron and had significantly higher levels of conjugated bilirubin (6). A large study of over 30,000 patients by Chen et al. (7) showed that higher total bilirubin levels were associated with increased all-cause mortality; of note, liver patients were not excluded, and therefore, there may be an additive effect on the findings.

On the other hand, bilirubin has also been shown to minimize oxidative stress, highlighting possible nephroprotective effects in vivo and on a population level. In an earlier study, it was shown that conjugated bilirubin can scavenge hypochlorous acid, a reactive oxygen species typically produced by neutrophils, and thus act as an antioxidant (8). Boon et al. (9) performed a more recent investigation into this using an adenine-induced animal model of chronic kidney disease (CKD) in rats. Adenine-induced CKD produced intense oxidative stress, and this study demonstrated that rats with endogenously elevated total bilirubin levels had reduced oxidative stress and less kidney damage. The authors concluded that systemic inflammation and oxidative stress may be attenuated in states of elevated total bilirubin (9). On a population level, a large, retrospective study showed that low total bilirubin levels are an independent risk factor of estimated glomerular filtration rate decline in patients with diabetes and hypertension (10). Interestingly, patients with unconjugated hyperbilirubinemia end stage kidney disease with a uridine diphosphate glucuronosyltransferase 1A1 genotype, similar to Gilbert's syndrome, had reduced cardiac events and all-cause mortality (9). Beyond the kidneys, Cao et al. (11) published a 4-year follow-up of 440 patients with previous myocardial infarction, and they concluded that higher total bilirubin levels reduced incidence of long-term cardiovascular events, providing a secondary risk prevention.

So, who is the winner between the two opposing paradigms? Like many concepts in medicine, the truth likely lies somewhere in the middle. From a basic science standpoint, there appears to be evidence for both nephrotoxic and protective mechanisms, which speaks more to the complexity of how physiology works than provides a definitive answer. Clinical studies showing the toxic effect of elevated bilirubin are inherently biased, as these studies select a highly morbid population with many confounding factors that can lead to kidney injury. Specifically, the large study by Chen et al. (7) did not exclude patients with liver disease. Interestingly, the study by Cao et al. (11) that showed positive cardiac benefits excluded supraphysiological levels of bilirubin and patients with liver, hemolytic, and gallbladder disease.

The second point requiring further clarification pertains to the specific type of bilirubin under consideration. The majority of referenced studies measure "total bilirubin," thus leaving the impact of conjugated versus unconjugated bilirubin inadequately understood. This poses a challenge when examining studies that suggest nephroprotection. For instance, Stocker and Peterhans (8) demonstrated the antioxidant properties of conjugated hyperbilirubinemia, while Boon et al. (9) discussed the positive benefits of unconjugated hyperbilirubinemia in hemodialysis patients. Consequently, there is a need for well-structured translational studies to determine the potential range at which the benefits of bilirubin become positive; this relationship might even follow a U-shaped curve. It is also possible that both unconjugated and conjugated bilirubin confer nephroprotective effects, but this association requires further investigation. Bile cast nephropathy has been compared to myeloma cast nephropathy, and similar to how light chains can surpass a threshold and induce nephrotoxicity, bilirubin may follow a comparable pattern. Keeping the literature in mind and the clinical course of liver and kidney diseases into account, this might be an example of the "Goldilocks Principle": an agonistic and antagonistic duality in how bilirubin potentially impacts the kidney. ■

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The author reports no conflicts of interest.

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The Nuts and Bolts of Simultaneous Liver-Kidney Versus Liver-Alone Transplantation in 2023

By Yousuf Kyeso, Sambhavi Krishnamoorthy, and Beatrice P. Concepcion

Patients with liver failure are at an increased risk of developing acute kidney injury and chronic kidney disease (CKD) due to various factors. Some common causes of kidney dysfunction in patients with liver failure include hepatorenal syndrome, acute tubular necrosis, infection, bilirubin cast nephropathy, hemodynamic changes, and nephrotoxic medication use. The ultimate treatment for patients with liver failure is orthotopic liver transplantation (OLT), with or without simultaneous kidney transplantation.

The decision to pursue simultaneous liver-kidney transplantation (SLK) can be challenging. For patients in need of a liver transplant and with concomitant kidney dysfunction, the argument for pursuing SLK is that it confers a survival advantage compared with liver-alone transplant (1, 2). What becomes a challenge then is distinguishing between acute and reversible kidney dysfunction—in which case, SLK may be unnecessary—versus established CKD. Several points to consider in patients with liver failure and kidney dysfunction include the following:

- Serum creatinine-based estimated glomerular filtration rate (GFR) can often overestimate true kidney function due to the low muscle mass of patients with liver failure. Using cystatin C or a nuclear GFR scan may be helpful in obtaining a better estimate of kidney function, although these processes may not be readily available at all centers.
- The presence of proteinuria/albuminuria and radiologic findings, such as kidney echogenicity and small kidney size, point toward the presence of chronic disease; however, the absence of proteinuria/albuminuria and normal echogenicity and normal kidney size do not necessarily rule this out.
- A kidney biopsy may be helpful in identifying chronic pathologic changes, such as glomerulosclerosis, interstitial fibrosis, and tubular atrophy, but the procedure likely confers a higher-than-average risk of bleeding, as patients with liver failure may be coagulopathic.

The decision to pursue [simultaneous liver-kidney transplantation] in a patient with liver failure and kidney dysfunction is complex.

In 2017, the Organ Procurement and Transplantation Network (OPTN) implemented an SLK allocation policy requiring patients being listed for SLK to meet medical eligibility criteria (Figure 1) (2). Patients who do not meet criteria can still be prioritized to receive a "safety-net" deceased donor kidney transplant if their GFR is persistently ≤20 mL/min or if they are dialysis-dependent between 60 and 365 days after OLT. The implementation of the OPTN policy has not only allowed for a standardized approach to SLK listing but has also provided assurance to clinicians that a safety-net kidney transplant would be available in cases in which kidney dysfunction persists after OLT, hopefully limiting unnecessary SLK listing in patients with potentially reversible kidney dysfunction.

Indeed, preliminary data suggest that the OPTN SLK allocation policy has allowed for more efficient use of deceased donor kidneys while ensuring early access to kidney transplantation among liver transplant recipients with CKD (3–5). Furthermore, a recently published study by Cheng et al. (6) found that among patients with liver failure who met SLK eligibility, only those with concomitant kidney failure derived a survival benefit after SLK, suggesting that more stringent criteria for SLK eligibility, along with more liberal safety-net priority criteria, should be considered.

In conclusion, the decision to pursue SLK in a patient with liver failure and kidney dysfunction is complex. A thoughtful and thorough assessment of the acuity and reversibility of kidney dysfunction is warranted while considering the medical eligibility requirements set forth by the OPTN. Decision-making should be approached in a multidisciplinary fashion in which transplant nephrologists, hepatologists, and transplant surgeons can weigh in to make the best decision for each individual patient. ■

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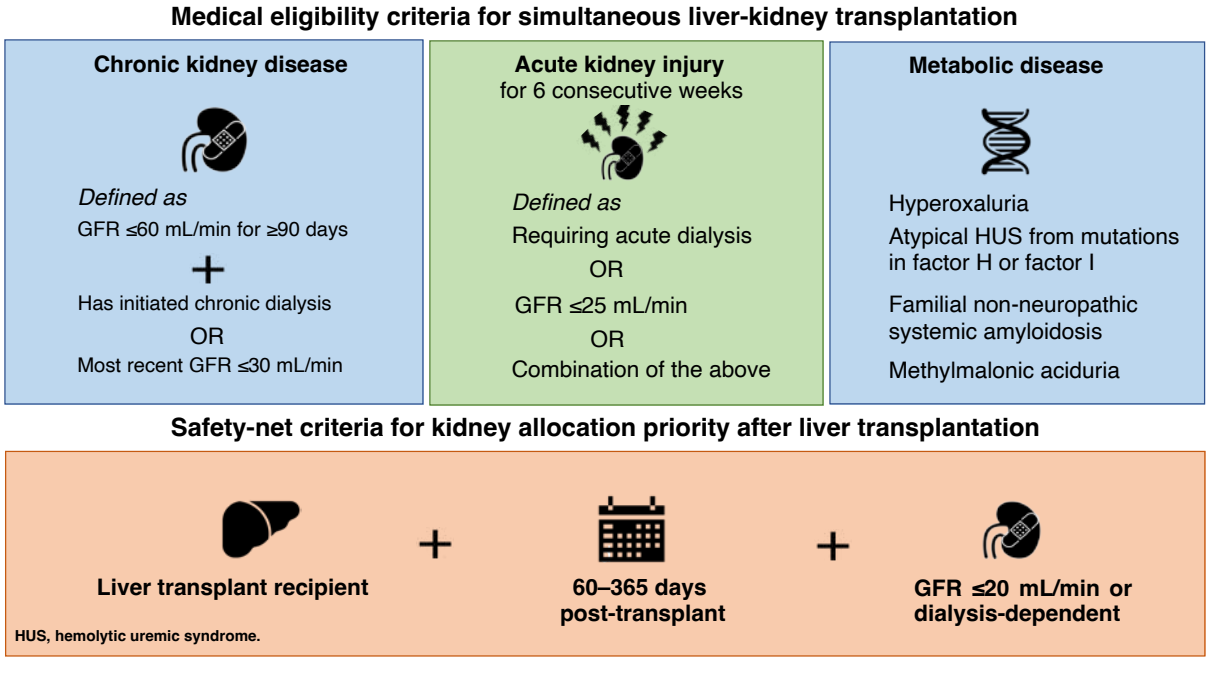
Drs. Kyeso and Krishnamoorthy report no conflicts of interest. Dr. Concepcion reports serving on the Organ Procurement and Transplantation Network Kidney Committee from July 1, 2020, to June 30, 2023, and is the medical director of the Kidney Transplant Program at the University of Chicago.

Figure 1. Eligibility criteria under the SLK Allocation Policy



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Acute Kidney Injury Risk in Liver Transplant Recipients Is Associated with Low Mean Arterial Pressure

By Naim Issa, Samy Riad, and Aleksandra Kukla

Acute kidney injury (AKI) is a common complication following liver transplantation and can have a negative impact on immediate and long-term transplant outcomes (1). Studies focusing on defining the risk and pathophysiology of AKI are critical to developing interventions to modify the incidence of AKI in this high-risk population.

In their recent work, Caragata et al. (2) investigated the relationship between the magnitude, stratified by different levels of mean arterial pressure (MAP), and the duration of hypotension (in minutes) during the liver transplant and risk of AKI in the first 2 days following surgery. The study included 1292 patients from a single center in Canada. The primary outcome, AKI, was defined as an increase in creatinine by 0.3 mg/dL or 1.5 times above the baseline value; in the secondary outcome, the authors divided AKI into stages based on the Kidney Disease: Improving Global Outcomes (KDIGO) definition (3). Forty percent of patients experienced AKI (based on the creatinine component only). Stage 1 AKI occurred in 28% of patients, whereas stages 2 and 3 were observed in 8.4% and 3.7% of patients, respectively. Fifty-two patients (4%) initiated hemodialysis. Prolonged intraoperative hypotension was independently associated with AKI. Patients who experienced MAP levels below 55 mm Hg and 50 mm Hg for 20 minutes or longer were at the highest risk for AKI (Figure 1). These results were consistent across different baseline estimated glomerular filtration rates (eGFRs), including patients with a preoperative eGFR greater than 60 mL/min/1.73 m^2. Interestingly, these patients were actually more susceptible to developing postoperative AKI. These findings are not surprising and are consistent with previous research linking intraoperative hypotension and postoperative AKI (4–6).

In the general population, hypotension is defined as a MAP below 65 mm Hg. The study by Caragata et al. (2) suggests that liver transplant recipients may be able to better tolerate low blood pressure in terms of developing AKI, unless the MAP drops below 55 mm Hg for at least 20 minutes. Experimental studies have suggested that cirrhosis is associated with disruption of renal blood flow autoregulation. These patients have low, systemic vascular resistance and, in general, have lower MAPs than other surgical patients. Therefore, they may not be as susceptible to AKI with a MAP greater than 55 mm Hg. Previous small-scale studies in liver transplant recipients have also demonstrated lower MAP thresholds for hypotension-associated kidney injury (7, 8).

Limitations in the Caragata et al. (2) study include its retrospective, single-center design and the small number of patients. Additionally, the study did not investigate the specific mechanisms underlying the association between intraoperative hypotension and AKI during liver transplant surgery. Further research involving larger prospective studies is warranted to validate this study's findings and to confirm potential benefits or harm from targeting higher or lower intraoperative MAPs during liver transplant surgery. ■

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The authors report no conflicts of interest.

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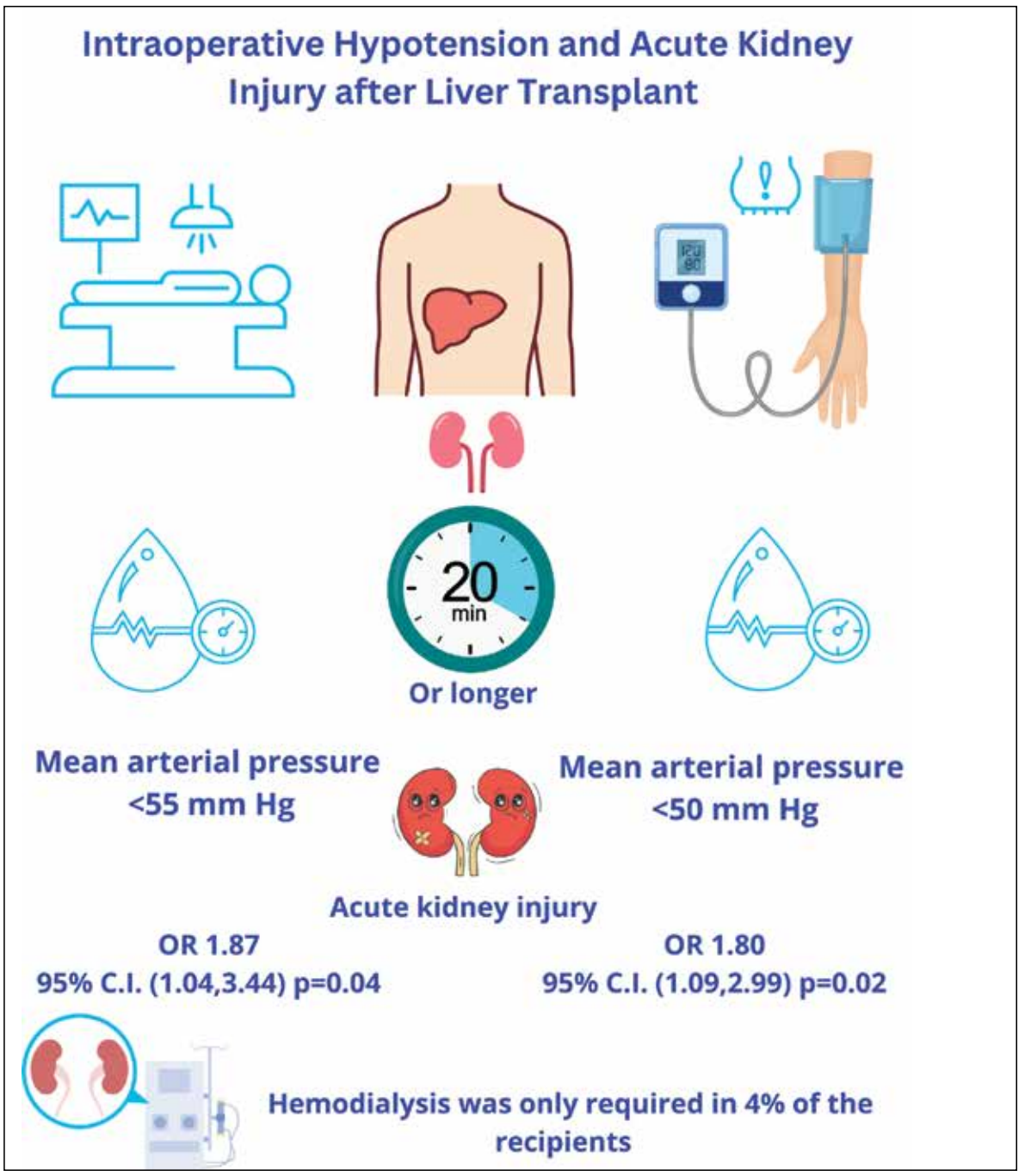
Figure 1. Infographic summary of the study findings



C.I., confidence interval; OR, odds ratio.

No Filters: Bridging the Gap Between Palliative Care and Combined Kidney and Liver Diseases

By Clara Y. Tow, Farhan A. Chowdhury, and Antonio Gabriel D. Corona

An upcoming article "Palliative care in kidney and liver diseases" (1) calls for a greater understanding of the role of palliative care in patients with combined kidney and liver diseases. The devastating cross-organ pathophysiology is invariably associated with poor outcomes, leading to a growing recognition of the need for palliative care in this population. Despite this, there remain challenges in the early integration of palliative care for the interdisciplinary care of these patients. This brief commentary discusses two frequently encountered issues—the difficulty with prognostication and the potential for transplantation—that may preclude timely referrals to palliative care for patients with kidney and liver failure.

Prognostication

While the definition of palliative care has evolved throughout the years, it remains entrenched in facilitating effective communication to determine goals of care (2). This requires accurate prognostication for multiple reasons. First and foremost, it helps medical clinicians recognize the severity of illness that the patient faces and the chances of recovery. This understanding then facilitates patient-centered care and allows for meaningful conversations regarding symptom control and management of end-of-life scenarios.

The most well-recognized predictive model, the model for end stage liver disease (MELD), incorporates international normalized ratio, creatinine, and total bilirubin into a logarithmic formula to predict 90-day mortality and has been used to prioritize patients on the liver transplant waiting list. Since its inception, the MELD score has undergone different iterations to improve mortality prediction and organ allocation. The incorporation of sodium (MELD-Na) better reflected the circulatory dysfunction and spectrum of hepatorenal syndrome manifested in patients with advanced liver disease (3). The most updated version, MELD 3.0, incorporates sex at birth and albumin (4). These variables not only improve survival prediction but more importantly, address sex-based disparities, which for a large part had been attributed to using creatinine as an estimate of glomerular filtration.

Using serum creatinine has been a constant talking point in defining kidney diseases in the setting of cirrhosis. There is realization that prototypes of kidney injury are under-diagnosed in patients with liver disease (5), which is concerning from a prognostication standpoint, as the development of kidney dysfunction is a lynchpin in the detection of cirrhotic decompensation. Literature has emerged supporting the use of cystatin C as a superior estimate of glomerular filtration (6). However, as cystatin C is not routinely available, it has yet to become the new standard.

Because of this, it is vital that palliative care referrals occur as early as possible in the illness trajectory, ideally at the time of diagnosis of cirrhosis. Without more refined and accessible diagnostics to accurately detect kidney diseases, waiting to meet traditional kidney injury criteria may prove to be too late and afford a shorter period for palliative care practitioners to establish rapport and build trust with the patient.

Transplantation

The potential for organ transplantation may also exclude patients from receiving palliative care interventions. Palliative care has a defined and well-accepted role for patients with advanced liver disease who are not on the transplant pathway. For those who are considered for transplantation, this role becomes much more complicated, as candidacy can be fluid and contingent on dynamic patient conditions (Figure 1). For example, it is not uncommon to encounter patients with cirrhosis on the transplant pathway, who suddenly develop acute decompensation, such as kidney failure. Such patients require aggressive medical care, including hemodialysis, to aid in their recovery from their critical condition in the hope of achieving transplant candidacy status. At the same time, it is acknowledged that acute kidney injury requiring dialysis carries a dismal prognosis (7). In these situations, the presence of kidney diseases, which is a defining event for the diagnosis of end stage liver disease, can be the factor that triggers the transplant pathway or the same factor that hinders transplant candidacy because of clinical deterioration. Consequently, the decision to offer dialytic therapies can be difficult to make given the uncertainties that surround these rapidly shifting landscapes.

For patients with advanced liver disease, especially those with concomitant kidney failure, palliative care should be available to them as early as possible in the disease process. They should receive symptom relief that balances quality and quantity of life, and they should have support systems in place if organ transplantation is ultimately not feasible. Transplant teams, historically, have not integrated palliative care into transplant practices, leaving a widening gap in patient care (8). Education and awareness as to how palliative care can collaborate with transplant teams are necessary to promote the physical and emotional well-being of this patient population that is extremely debilitated and unique.

As our understanding of diseases grows, so should our understanding of our patients' needs. Recognizing that the presence of kidney dysfunction in liver disease may herald a precarious disease course, often culminating in mortality, palliative care should be involved as early as the diagnosis is made and throughout the patient's clinical course, collectively and cooperatively, with organ transplant teams. ■

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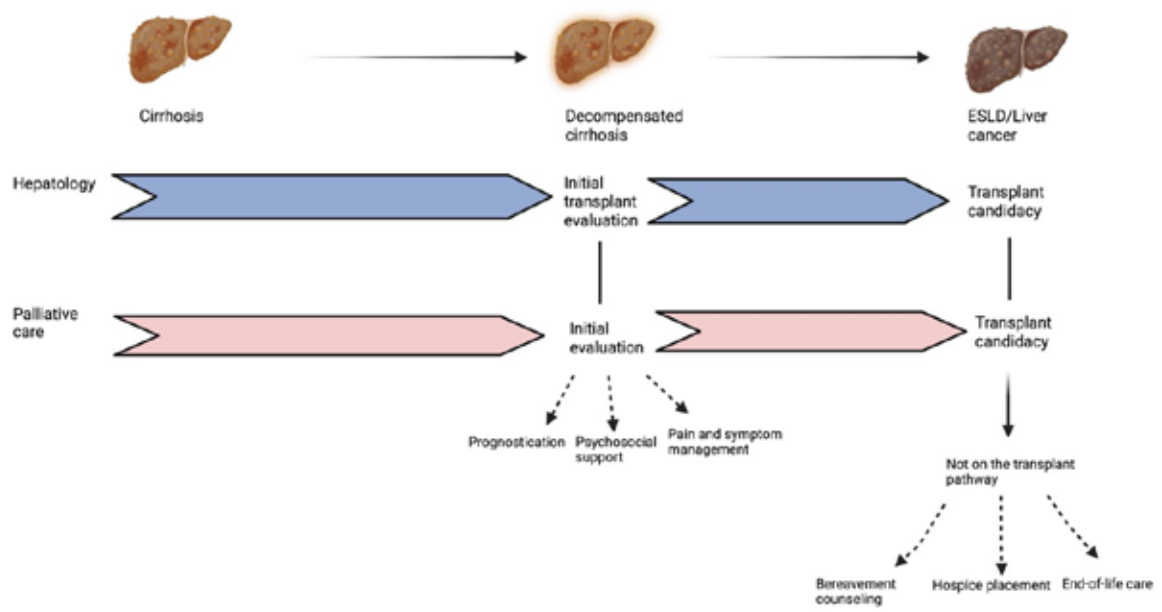
Figure 1. Palliative care integration with the transplant pathway



The temporal relationship of palliative care with the transplant pathway. Transplant evaluation usually begins at the time of cirrhosis decompensation, liver cancer, or a MELD 15 score. Palliative care referrals can be done concomitantly. Integrating palliative care early, once liver cirrhosis is diagnosed, can build a longitudinal relationship with patients. If transplantation is not deemed to be a safe option, this relationship can culminate in instituting hospice care, bereavement counseling, and services that are in line with patients' end-of-life wishes. ESLD, end stage liver disease. Images from Biorender.

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Glomerular Diseases Associated with Hepatitis B and C

By Zhabiz Solhjou, Qiyu Wang, and Alejandro Garcia-Rivera

Chronic infection with hepatitis B virus (HBV) and hepatitis C virus (HCV) is a significant global health issue and can cause a spectrum of glomerular diseases. Despite its high global burden, glomerular disease only occurs in a subset of patients (3%–5%) (1, 2). These glomerular disorders are largely mediated by the host response of antibody formation with subsequent deposition of immune complexes in the glomerulus.

Hepatitis B

Membranous nephropathy (MN) is the most common pattern of glomerular injury in chronic HBV infection, and a minority of patients may present with membranoproliferative glomerulonephritis (MPGN) (3). In addition, polyarteritis nodosa (PAN), a type of immune complex-mediated necrotizing vasculitis in small- and medium-sized vessels, may occur in the setting of high-burden hepatitis B surface antigen (HBsAg) (3). A global effort of vaccination has significantly reduced childhood MN from perinatal exposures and PAN in endemic areas (3, 4).

With a smaller molecular weight and a predilection to passage, the highly negatively charged glomerular basement membrane, hepatitis B e antigen (HBeAg), is more commonly involved in the pathogenesis of HBV-associated MN (HBV-MN). HBsAg, on the other hand, is more frequently associated with an MPGN pattern of injury, due to its larger size and anionic charge (5). Clinically, the presence of HBeAg is highly correlated with disease activity, whereas the development of anti-HBe antibodies and clearance of HBeAg are typically associated with disease remission (6). HBV-MN typically presents with nephrotic-range proteinuria and occurs more commonly in children, the majority of whom tend to resolve spontaneously. In the adult population, however, spontaneous remission is uncommon, and 30%–50% of patients develop progressive chronic kidney disease that could eventually lead to kidney failure (7, 8).

Treatment of HBV-MN remains a challenge. Historically, before antiviral therapy became widely available, there was a major concern that corticosteroids could lead to activation of viral replication and worsening liver function (7). To date, the 2021 Kidney Disease: Improving Global Outcomes (KDIGO) guideline continues to recommend against the use of immunosuppressive agents, such as rituximab or cyclophosphamide, in HBV-MN given the risk for acceleration of HBV replication (9). However, data from small cohorts suggest that when combined with antiviral therapy, corticosteroids or tacrolimus could be effective in improving proteinuria without triggering viral replication or causing worsening liver or kidney injury (10, 11). Large randomized controlled trials are needed to rigorously evaluate the efficacy and safety of combined therapy. It is important to note that the nucleoside and nucleotide analogues need to be dose adjusted, according to the estimated glomerular filtration rate (eGFR).

Hepatitis C

HCV leads to chronic B cell stimulation and is the most common cause of mixed cryoglobulinemia, which could affect small-sized blood vessels and manifest with purpuric rash, peripheral nerve involvement, arthralgia, and cryoglobulinemic glomerulonephritis (cryoGN). Proteinuria (nephrotic or non-nephrotic range), low complement level (especially C4), various degrees of kidney impairment, and monoclonal immunoglobulin (Ig; almost invariably IgM kappa [IgMk]) are classical laboratory features (12).

The high efficacy of a direct antiviral agent (DAA) for HCV has led to a shift in the management of cryoGN over the past 10 years. An abundance of data suggested the high efficacy of DAA alone (without immunosuppression) in treatment of cryoGN. Currently, DAAs are recommended as the first-line treatment for cryoGN, including those with an eGFR lower than 30 mL/min/1.73 m^2, for whom three DAA-based regimens have been recommended (9). Concurrent immunosuppression (rituximab and corticosteroids) should be considered in patients with aggressive, organ-threatening manifestations (rapid, progressive glomerulonephritis or pulmonary hemorrhage) or those who continue to have signs and symptoms of active glomerulonephritis despite achievement of a sustained virological response (~30%). Plasmapheresis may be considered as a bridge therapy for organ-threatening manifestations (13).

Finally, it is important to recognize that clinical presentation of cryoGN may be desynchronized from viral replication, and persistent, de novo, or recurrent cryoGN could occur even after viral eradication (14, 15). Persistent manifestations of cryoglobulinemia should also prompt an evaluation for B cell-proliferative disorders. ■

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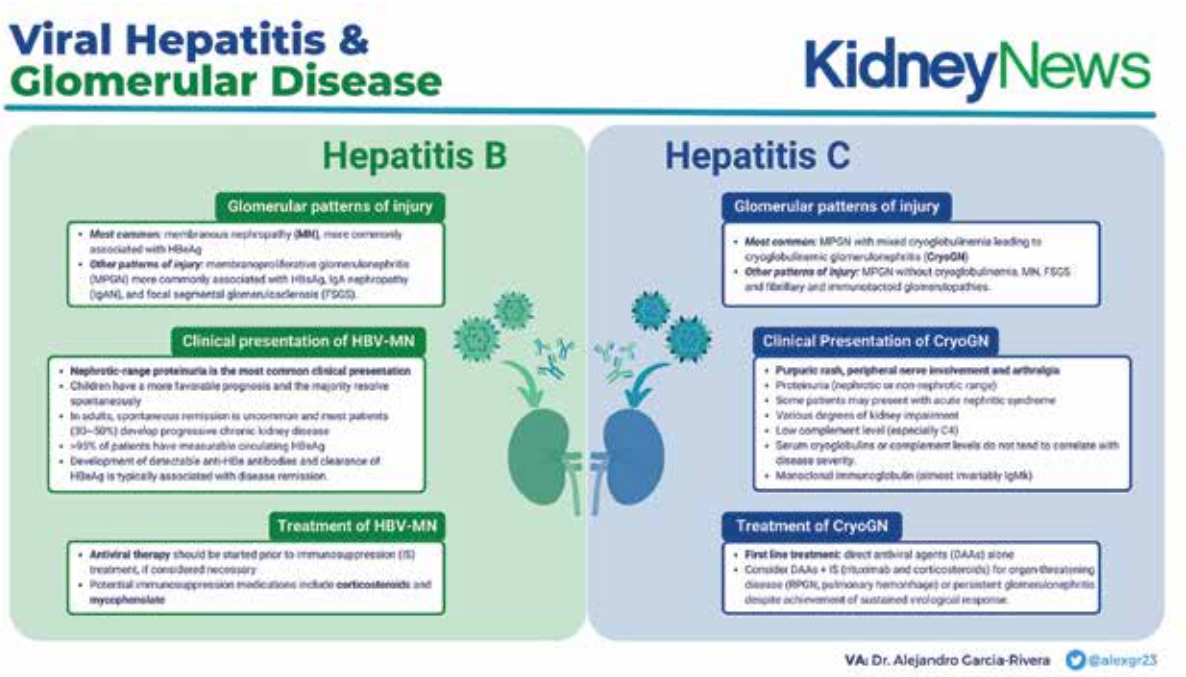


A Change in Praxis: Making the Most of Each Donated Kidney

By Abhinav Bhalla and Darshana M. Dadhania

Despite more than 90,000 patients waitlisted for a kidney transplant, 21.3% of donated kidneys were not used according to the 2020 Annual Data Report of the Scientific Registry of Transplant Recipients and Organ Procurement and Transplant Network (1). As organ demand far exceeds supply, transplant professionals strive to break barriers and improve utilization of available kidneys (2, 3). Seminal studies, such as Transplanting Hepatitis C Kidneys into Negative Kidney Recipients (THINKER) (4) and Exploring Renal Transplants Using Hepatitis C Infected Donors for HCV-Negative Recipients (EXPANDER) (5), have transformed the way we use kidneys from donors who are hepatitis C virus (HCV) positive. The combination of novel direct-acting antiviral (DAA) therapies for HCV, with cure rates approaching 100% (6), and the unfortunate rise in opioid overdose-related mortality of young individuals (7) has translated into an unanticipated opportunity for those with chronic kidney disease (CKD) who are waitlisted for a kidney transplant (8). The dramatic change in praxis as it relates to utilization of HCV-positive kidneys for transplantation is shown in Figure 1A.

In the article entitled "Kidney transplantation from hepatitis C virus-infected donors to uninfected recipients: A systematic review for the KDIGO [Kidney Disease: Improving Global Outcomes] 2022 hepatitis C clinical practice guideline update" by Gordon and colleagues (9), the authors performed a systematic review on the use of donors who are HCV viremic for kidney transplantation into recipients who are HCV naïve (donor [D]+/recipient [R]−). Sixteen investigations of HCV D+/R− kidney transplantation, comprising 557 patients, were evaluated using a specified protocol for DAAs. Sustained viral response at 12 weeks was reported in all studies and was achieved in 97.7% of patients (95% confidence interval [CI], 96.3%−98.8%). Although a shorter course of DAAs resulted in high rates of viremia, those who remained viremic after the initial treatment achieved viral clearance following retreatment. Serious adverse events were reported in 69% of the studies and were uncommon at a rate of 0.4% (95% CI, 0.1%−2.8%). Three cases of fibrosing cholestatic hepatitis were reported among 211 patients, two with a delayed start of DAA therapy; all three had complete resolution.

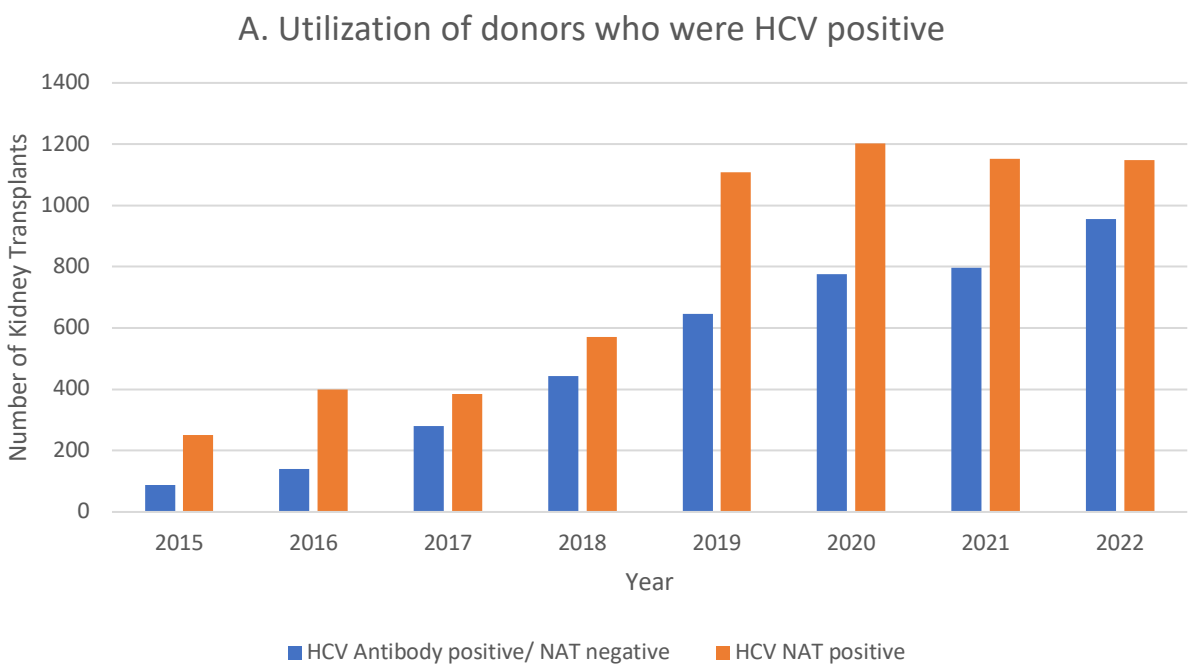
The mortality at 1-plus year was 2.1%, and the data appeared to be similar to the outcome in HCV D−/R− transplants. One-year kidney graft survival was 97.6%, similar to HCV D−/R− transplants. These data support the recently published 2022 KDIGO guidelines on management of HCV in CKD, which strongly recommend consideration of hepatitis C-positive kidneys for all recipients irrespective of their serological status (10).

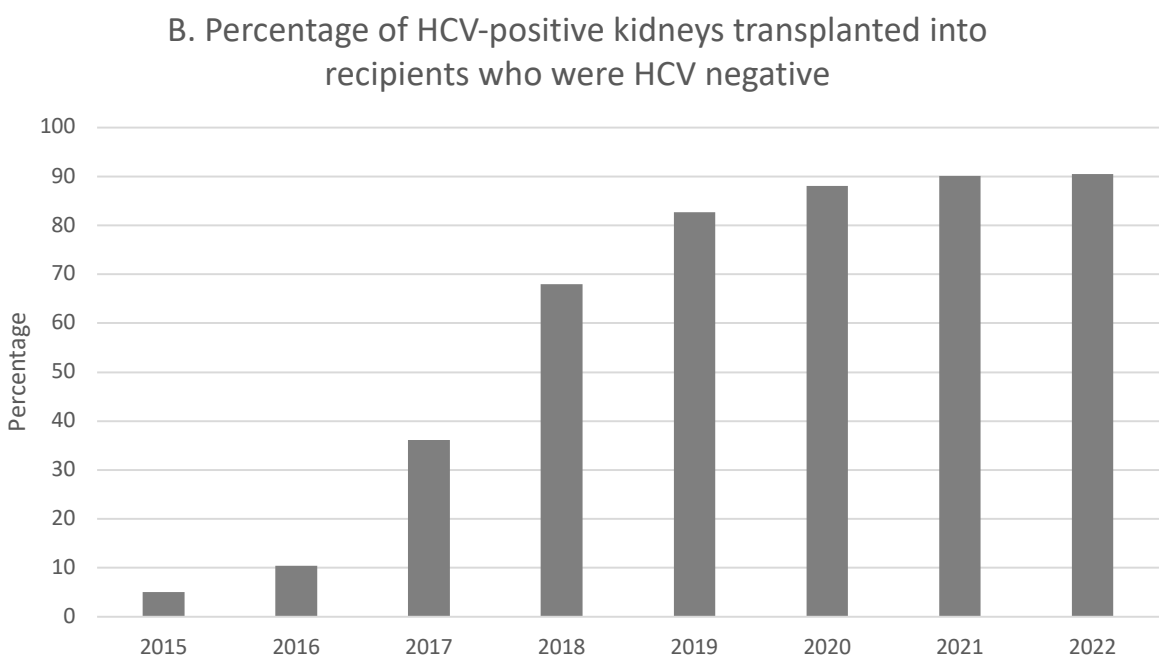
Although the results are promising, the authors caution about the lack of long-term data on the safety and graft survival in HCV D+/R− transplants. In this publication, HCV-positive kidneys were associated with 51% lower rates of delayed graft function compared with HCV D−/R−, and there was no difference in the acute rejection rates. It remains to be seen if this translates into a better long-term graft survival for HCV D+/R− transplants. Given these data, the cost of DAA therapy for HCV seems like a small price to pay for the savings gained by transitioning a patient off of dialysis to a functioning kidney allograft.

With the increase in kidney donors who are HCV positive, the transplant community will need to ensure that there is equal access to these organs. Prompt review of data and development of practice guidelines such as the KDIGO 2022 Hepatitis C Clinical Practice Guideline will facilitate education and adoption of these novel approaches by practitioners (10). Equally important are the goals of educating our patients and ensuring insurance coverage for the much-needed DAA therapies that cost more than $84,000 for a 12-week treatment (11). As noted by Gordon et al. (9), some patients did experience fibrosing cholestatic hepatitis when there was a delay in DAA therapy.

Since the gap between supply and need for kidneys remains large, it is imperative that innovative protocols are established to reduce kidney discards and optimize the long-term success of kidney transplants. Publication of the EXPANDER (5) and THINKER (4) trials in 2018 laid the foundation for transplantation of >7500 kidneys from donors who were HCV positive. The proportion of HCV-positive kidneys transplanted into recipients who are HCV negative has increased from 5% in 2015 to >90% in 2022 (Figure 1B). The systematic review by Gordon et al. (9) should further educate the transplant community and facilitate optimal utilization of the donor pool.

Figure 1. Transplantation of HCV-positive kidneys





Data are based on deceased donor kidney transplants performed in the United States between April 1, 2015, and December 31, 2022, provided by the Organ Procurement and Transplantation Network on May 10, 2023. NAT, nucleic acid test.

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Decoding IgG4-Related Kidney Disease: Unlocking Clinical Insights and Prognostic Clues

By Jacob Nysather and Prakash Gudsoorkar

Immunoglobulin G4 (IgG4)-related disease is a systemic, fibro-inflammatory disorder with pseudotumoral lesions, IgG4-positive lymphoplasmacytic infiltrates, and tissue fibrosis that can be seen within any organ (1). Serum IgG and IgG4 levels are typically elevated, but normal levels do not rule out the diagnosis. Kidney involvement occurs in 30% of cases, presenting as tubulointerstitial nephritis, glomerular lesions (e.g., membranous nephropathy), and macroscopic kidney abnormalities (bilateral kidney hypertrophy, pseudotumors, and hypermetabolic kidney lesions on 18-F-fluorodeoxyglucose-positron emission tomography-computed tomography [18-FDG-PET-CT]).

A retrospective, observational cohort study by Anis Chaba et al. (2) analyzed 101 adult patients from 35 European sites with IgG4-related kidney disease from January 1997 through December 2019. Patients were categorized into two groups: 1) kidney involvement without an alternative diagnosis and 2) established IgG4-related disease with kidney failure, proteinuria, and/or kidney lesions on imaging. Exclusions were retroperitoneal fibrosis and incomplete follow-up. Data on clinical, biological, imaging, and histopathological features; treatment; and outcomes were collected.

Kidney involvement was seen in 60% of patients, and 86% had systemic involvement at diagnosis. Extrarenal features included lymphadenopathies (57%), autoimmune pancreatitis (42%), sialadenitis (36%), lung involvement (28%), and cholangitis (25%). Laboratory findings revealed hypergammaglobulinemia, elevated IgG4 levels (94%), and decreased complement (C) levels (45%).

Among the patients, 51% had acute kidney injury (AKI), 23% had AKI-on-chronic kidney disease (CKD), and 14% had isolated CKD. Median serum creatinine (sCr) was 2.4 mg/dL (interquartile range [IQR], 1.6–3.6) with a corresponding estimated glomerular filtration rate (eGFR) of 25 mL/min/1.73 m² (IQR, 17–43). Primary urinalysis findings were often without active sediment; however, hematuria and leukocyturia were noted in 27% and 16%, respectively. The median urinary protein-to-creatinine ratio was 600 mg/g (IQR, 200–1100), with >1000 mg/g in 31% of cases, primarily indicating glomerular involvement. CT scan abnormalities were found in 61%, including bilateral kidney hypertrophy, pseudotumor, and low-density areas. An 18-FDG-PET CT scan was performed in 63% of patients, revealing hypermetabolic kidney lesions in 38% and extrarenal lesions in 74%.

Kidney biopsies were conducted in 82% of patients, showing tubulointerstitial involvement in all cases and additional glomerular lesions, most commonly membranous nephropathy, in 16% of cases. Tubulointerstitial lymphoplasmacytic infiltrates and predominant IgG4(+) plasma cells were observed. Dense fibrosis (>50% kidney tissue) was described in 42% of cases, whereas the storiform pattern was rare.

Corticosteroid (CS) therapy was administered to 90% of patients (mean dose, 0.8 ± 0.3 mg/kg/day), and 18 patients (18%) received rituximab as initial therapy (77% received 1 g at days 1 and 15, around two cycles). No specifications were made on which patients received chosen therapies. After a median follow-up of 24 months, 35% of patients experienced relapse, with a median relapse time of 12 months. Multivariable analysis showed that muti-organ involvement and low C3/C4 levels were associated with a higher relapse risk, whereas rituximab was associated with a lower risk. This effect persisted after weighting and propensity score analysis.

Patients who received rituximab first had lower relapse rates (22% vs. 37%) and similar kidney outcomes with lower rates of complications such as death (6% vs. 15%) and infections (17% vs. 25%). At the last follow-up, 71% of patients had CKD, with a median eGFR of 45 mL/min/1.73 m², and 32% had an eGFR ≤30 mL/min/1.73 m². Progression to end stage kidney disease occurred in 12% of patients, and 13% died. Factors associated with severe CKD were age, peak sCr, prolonged CS duration (>12 months), and cholangitis. Logistic regression analysis identified age, peak sCr, and serum IgG4 levels ≥5 g/L as independent predictors of severe CKD. Serum IgG4 levels at diagnosis and the state of interstitial fibrosis and tubular atrophy on kidney biopsy were related to eGFR at the last follow-up.

This retrospective analysis highlights IgG4-related kidney disease primarily affecting middle-aged males and presenting as tubulointerstitial nephritis with glomerular involvement in approximately 25% of cases. CSs are commonly used but carry a relapse risk, especially in patients with CKD. Rituximab shows promise as a first-line treatment to reduce relapse rates. Close monitoring is essential for individuals with organ involvement and elevated IgG4 levels, as these conditions are associated with poorer outcomes. Given the 23 years examined within this retrospective study, it is difficult to compare cases, particularly with advancements in biomarkers and therapeutics. Further controlled trials are needed to confirm these findings. ■

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The authors report no conflicts of interest.

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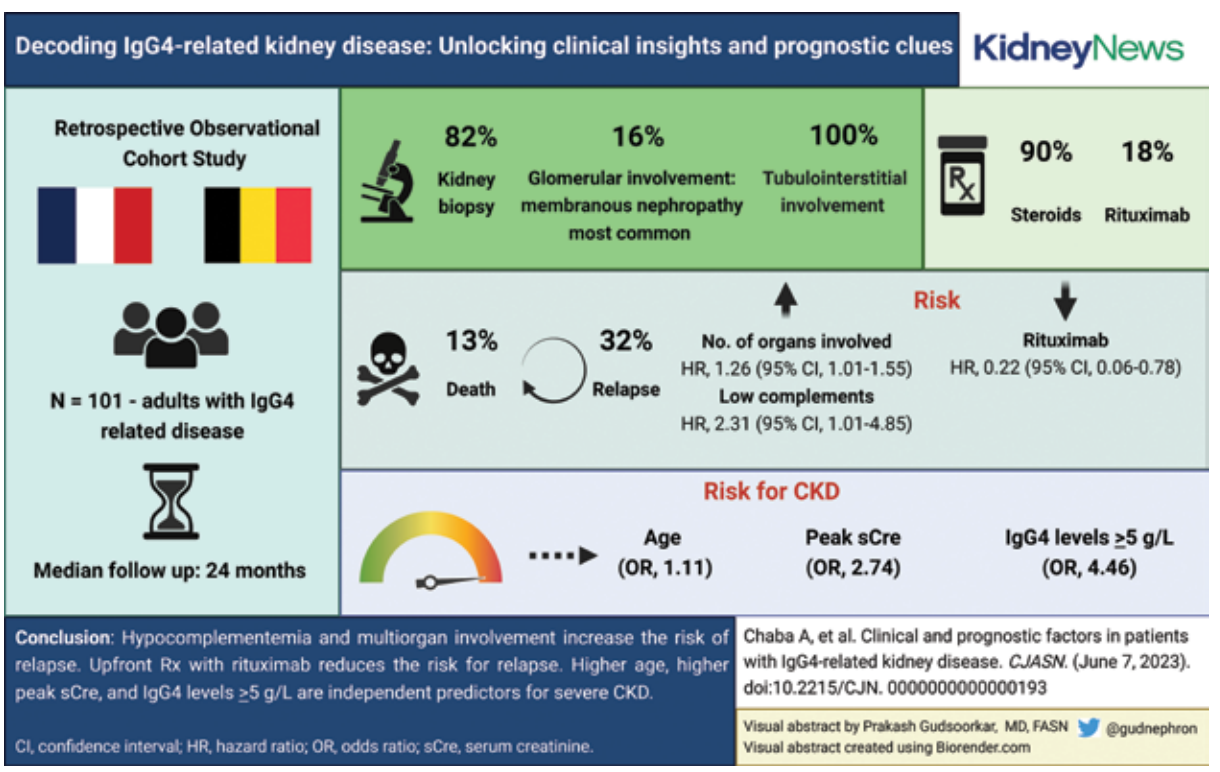

High Tides: Innovations in Obesity Treatment Bring Change to the Future of Nephrology

By Evan M. Zeitler and Koyal Jain

Obesity contributes (directly or indirectly) to a significant portion of chronic kidney disease (CKD), increasing the risk of adverse cardiometabolic outcomes in people with CKD. Fortunately, obesity therapy has advanced rapidly in the last decade with the advent of incretin-based therapies, which not only help patients to lose weight but also to reduce the risk of cardiovascular disease.

Two recent phase 2 studies published in *The New England Journal of Medicine* (*NEJM*) shed light on the potential to change the landscape of nephrology care with incretin-based treatments (1, 2). Both studies included adults with obesity or overweight and with a weight-related condition but not with diabetes mellitus. The first study tested multiple dosages of an oral glucagon-like peptide 1 receptor agonist (GLP1ra), orforglipron (1). The highest dose of orforglipron caused a mean 12.6% body weight decrease at 26 weeks (primary outcome) and a 15% decrease at 36 weeks (secondary outcome), significantly greater than the weight loss observed at currently approved dosages of the only other oral GLP1ra, semaglutide. However, the higher-dose semaglutide has recently been shown to produce a similar 15% weight loss (3). Mean systolic blood pressure (SBP) improved by 10.5 mm Hg in the high-dose orforglipron group compared with 1.8 mm Hg in the control group. The second study examined retatrutide, an injectable glucose-dependent insulinotropic polypeptide/GLP1/glucagon receptor triple agonist given weekly (2). The highest-dose group exhibited weight loss of 18% at 24 weeks and 24% at 48 weeks. Of the participants, 41% discontinued at least one blood pressure medication, with a significant decrease in SBP of 11 mm Hg compared with the control group's 3.4 mm Hg decrease. It should be noted that no patients with advanced CKD (estimated glomerular filtration rate <30 mL/min/m^2) were included in these studies.

Although incretin-based therapies have proven cardiovascular benefits, no study has conclusively demonstrated reduction in adverse kidney events as a primary outcome. The FLOW study of semaglutide in patients with type 2 diabetes and CKD should change that, however, and will help to elucidate a reduction in adverse kidney events, as the primary outcome is a composite of kidney outcomes (4).

...Two recent studies shed light on the potential to change the landscape of nephrology care with incretin-based treatments.

Despite limitations, the implications for nephrologists are clear. Cardiovascular disease remains the leading cause of death for patients with CKD, and comprehensive cardiometabolic care for our patients in the future is almost certain to include effective lifestyle and pharmacologic management of obesity. Treating obesity will benefit patients with CKD by helping control hypertension and diabetes, reducing the risk of heart attacks and strokes, and helping patients previously excluded from waitlists become eligible for kidney transplant. However, patients will see these benefits only if clinicians are prepared to implement the array of novel, effective tools at our disposal. The studies published in *NEJM* offer a glimpse into the future of obesity management, with safe and effective oral options and medical therapy with efficacy rivaling that of bariatric surgery (Figure 1) (1, 2). With the advent of new therapies, the future for nephrology patients and the field has never been brighter. ■

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Dr. Zeitler reports that his spouse receives research funding from vTv Therapeutics, Novo Nordisk, Rhythm Pharmaceuticals, and Dexcom. Dr. Jain reports serving as the principal site investigator for the FSGSALLAGE (NCT04065438) and FSGS pediatric (NCT02235857) clinical trials.

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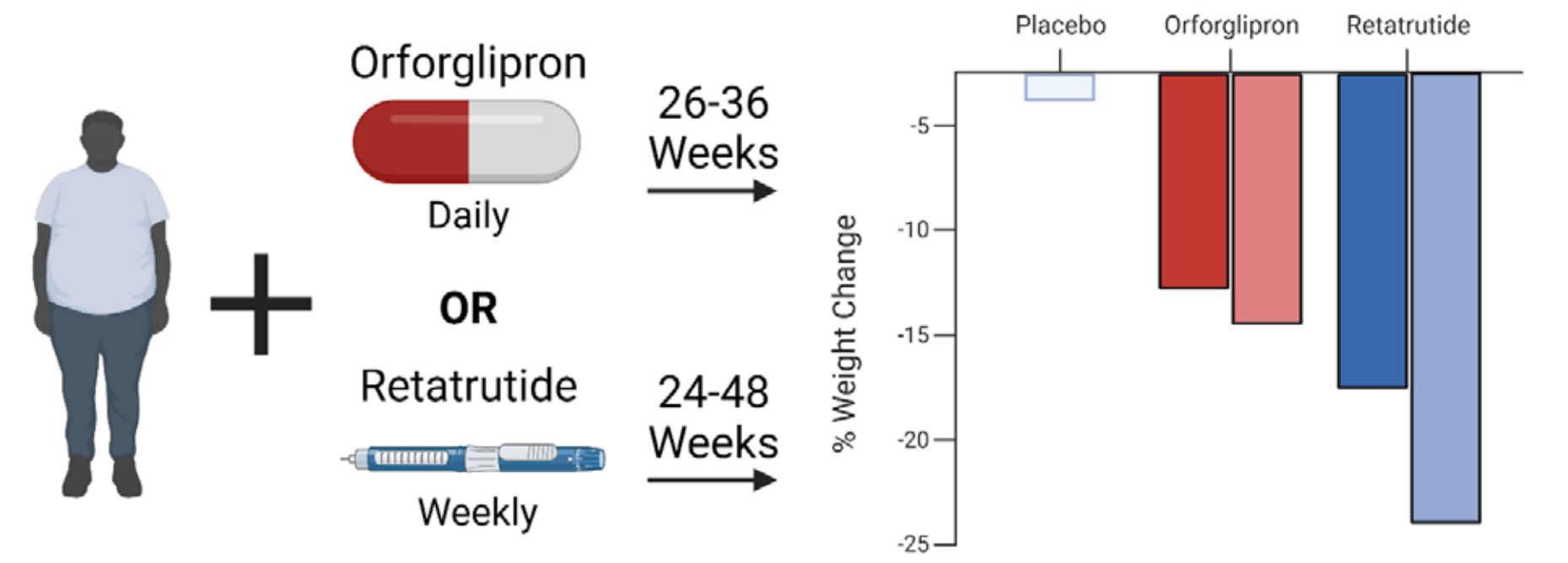
Figure 1. GLP1ra orforglipron and injectable triple agonist retatrutide



Daily oral GLP1ra orforglipron and weekly injectable triple agonist retatrutide are both efficacious and safe in phase 2 trials published in *NEJM*. The highest doses in each trial resulted in a mean weight loss of >10% and for retatrutide, over 20%. Dark bars, primary endpoint; light bars, secondary endpoints. Figure created with BioRender. Data adapted from Wharton et al. (1) and Jastreboff et al. (2).

The Challenge of GFR Assessment in Kidney Transplant Recipients

By Lesley A. Inker, Ashtar Chami, Krishna A. Agarwal, and Andrew S. Levey

In a recent issue of the *British Medical Journal*, Raynaud et al. (1) reported on the development and validation of a creatinine-based estimated glomerular filtration rate (eGFRcr) equation for use in kidney transplant recipients. There is good reason to think that eGFRcr equations developed for use in the general population, such as the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations, would have large errors in some kidney transplant patients. Following transplantation, kidney transplant recipients may have low muscle mass, reduced activity, or decreased protein intake or use medications that affect muscle mass (such as glucocorticosteroids) or that inhibit renal tubular secretion of creatinine (such as trimethoprim), all of which can lead to changes in serum creatinine independent of GFR (2, 3). GFR is used for many critical clinical decisions in kidney transplant recipients, such as detection of rejection and consideration of biopsy, or decisions regarding selection and dosage of prophylactic antimicrobials or use of contrast imaging to detect transplant complications (4, 5). As such, a comprehensive approach for assessment of GFR for patients with kidney transplants is necessary and has been missing.

The authors' equation was developed in 3622 patients from 3 French transplant centers and validated in 11,867 patients—from 8 centers in Europe, 1 center in Australia, 1 clinical center and 1 trial in the United States, and 1 international trial—who received kidney transplants between 2000 and 2021. Across the 12 validation cohorts, accuracy of the newly developed equation was variable, with percentage of estimates within 30% of measured GFR (mGFR; P_{30}) that ranged from 73% to 91%. ($1 - P_{30}$ is a measure of large errors.) It is generally established that P_{30} >75% is acceptable for many clinical decisions and that P_{30} >90% is optimal. The variation may have been due to a differing prevalence of clinical factors mentioned above but may also have been due to methodological differences in measurement of GFR or in creatinine. In particular, the creatinine assays were variably standardized within, as well as across, cohorts—a requirement for a validated equation (6, 7). Among these cohorts, the differential accuracy compared with CKD-EPI equations was also variable, with the difference in P_{30} between the two equations ranging from 0.1% to 16% (median difference of 3.8%). The variation in the relative accuracy between the equations likely reflects methodological differences in measurement of GFR or in creatinine, as well as differences in population characteristics, rather than having a kidney transplant. Indeed, the similar performance across the equations confirms prior studies demonstrating that the CKD-EPI equations are as accurate in kidney transplant recipients as in patients with other causes of CKD and who do not have a transplant (8, 9).

Thus, in our view, these results do not change the current recommendations for a single equation to report GFR by clinical laboratories for all adults or in using that eGFR value for routine care for most kidney transplant patients. However, the question of a comprehensive approach for assessment of GFR remains open. eGFRcr is recommended as the initial test, followed by eGFR from the combination of creatinine and cystatin C (eGFRcr-cys) or mGFR as supportive tests, depending on the clinical setting (2, 7) (Figure 1). Cystatin C has not been evaluated sufficiently in kidney transplant recipients, and careful investigations are required given the possible effect of medications on level of cystatin C independent of mGFR (10, 11).

This article reminds us of the challenge of assessment of GFR in transplant patients, and we encourage continued rigorous investigation. We recommend further studies to evaluate the accuracy of eGFRcr and eGFRcr-cys equations in kidney transplant recipients with specific consideration of the clinical settings, such as medication use and health status, which can inform a holistic approach to GFR assessment. ■

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The authors report no conflicts of interest.

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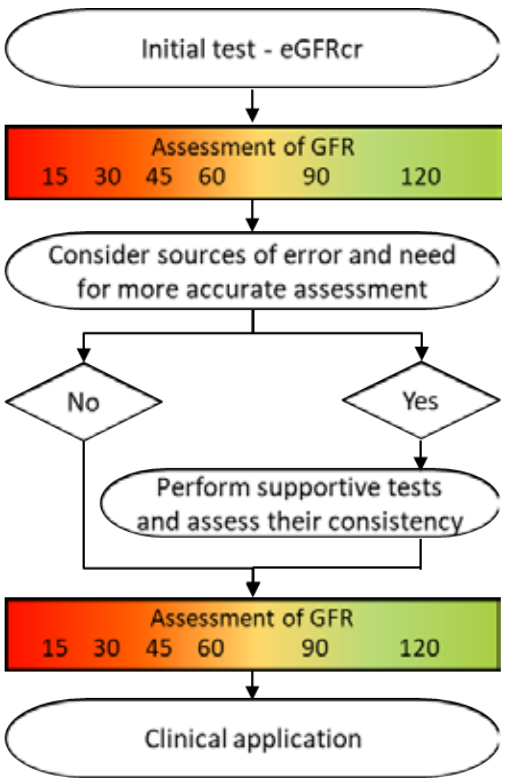
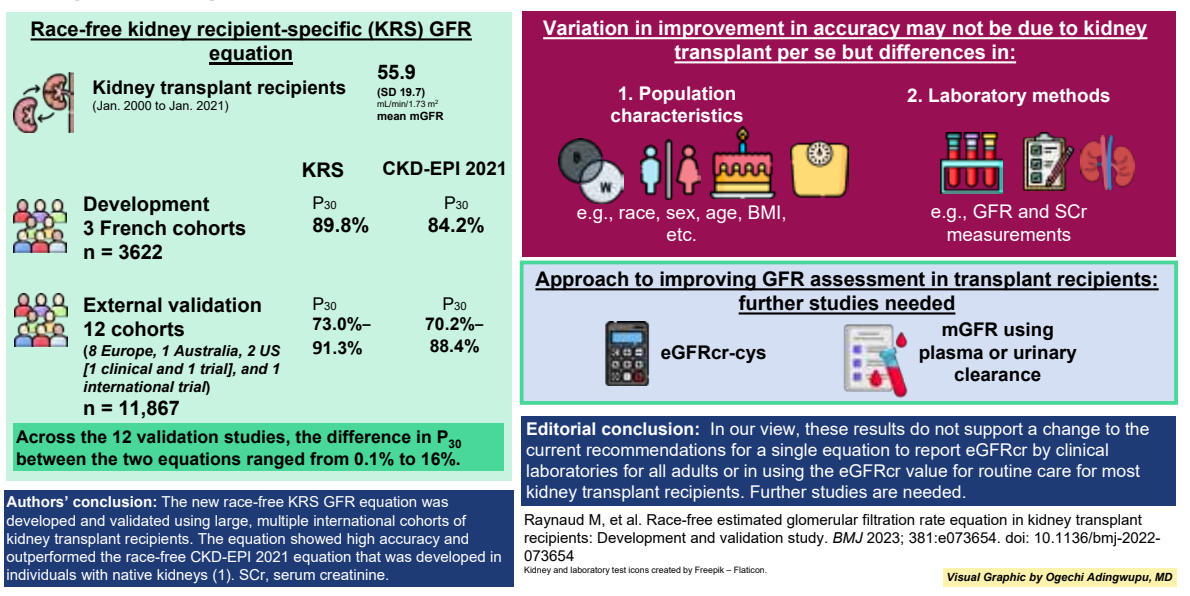
Figure 1. Approach for GFR assessment



Our holistic approach to assessment of GFR is to use initial and supportive testing to develop a final assessment and apply it in individual decision-making. eGFRcr is the appropriate initial test. If eGFRcr is expected to be inaccurate or if a more accurate assessment is needed, then supportive tests should be measured. In the non-kidney transplant population, there is evidence that eGFRcr-cys is more accurate than eGFRcr and eGFRcys and is recommended as the second test following eGFRcr. If eGFRcr-cys is expected to be inaccurate or if an even more accurate assessment is needed, then GFR should be measured using plasma or urinary clearance of exogenous filtration markers, if available. For kidney transplant recipients, we suggest more frequent measurements of GFR for clinical decisions that rely on the level of GFR given current uncertainty about the accuracy of eGFRcr-cys (2). Adapted from Inker and Levey (12).

The challenge of GFR assessment in kidney transplant recipients



Does Bariatric Surgery Affect Kidney Transplant Risks?

Available data suggest that patients with previous bariatric surgery are not at increased risk of complications or adverse outcomes after kidney transplantation, reports a meta-analysis in *Transplantation.*

A literature review identified 18 studies reporting on the outcomes of kidney transplantation in 315 patients with previous bariatric surgery. Approximately two-thirds of patients underwent sleeve gastrectomy, and most of the others underwent Roux-en-Y gastric bypass. Quality was rated good in all but one study. Data were pooled for meta-analysis of kidney transplant outcomes.

Reported percentage of excess weight loss was 46.3%–94.8%, with a mean of 62.8%. Delayed graft function and acute rejection each occurred in 16% of patients, based on reported data from 14 and 11 studies, respectively. Wound complications occurred in 5% of patients (from 12 studies), urinary complications in 19% (from 9 studies), and vascular complications in 2% (from 11 studies).

Eleven studies reported kidney transplant outcomes at follow-up times from 15 months to over 5 years. Based on data from 14 studies, the average rate of graft loss was 3%. In four studies reporting a comparison group of patients with obesity who underwent kidney transplantation without previous bariatric surgery, transplant outcomes and complications were similar between groups.

Obesity-related diseases are a major contributor to end stage kidney disease, and weight loss can improve access to kidney transplantation in patients with obesity. Although bariatric surgery has been suggested as a bridge to kidney transplant, its impact on transplant outcomes is unclear.

The new meta-analysis suggests that the outcomes of kidney transplantation after bariatric surgery are similar to those in other transplant recipients. The researchers emphasize the "urgent need" for larger, well-designed studies to clarify whether there are beneficial effects of bariatric surgery on kidney transplant outcomes [Pencovich N, et al. Outcomes of kidney transplantation in patients that underwent bariatric surgery: A systematic review and meta-analysis. *Transplantation*, published online ahead of print June 5, 2023. doi: 10.1097/TP.0000000000004680; https://journals.lww.com/transplantjournal/Abstract/9900/Outcomes_of_Kidney_Transplantation_in_Patients.434.aspx].

Hemodiafiltration May Improve Survival Compared with Hemodialysis

Trials comparing hemodiafiltration and hemodialysis have yielded inconclusive results but have had significant limitations. In *The New England Journal of Medicine* study, a recent meta-analysis of patient-level data suggested a survival benefit of hemodiafiltration when a convection volume was delivered at a high dose. This trial assessed survival in patients with kidney failure receiving high-dose hemodiafiltration versus conventional, high-flux hemodialysis.

The pragmatic, randomized trial included 1360 patients with kidney failure and at least 3 months on high-flux hemodialysis, enrolled at 61 European centers. All were considered candidates for a convection volume of at least 23 L per session in post-dilution mode. Patients were assigned to open-label treatment with high-dose hemodiafiltration or continued conventional, high-flux hemodialysis. All-cause mortality was assessed at a median follow-up of 30 months, along with secondary outcomes.

In the hemodiafiltration group, the mean convection volume was 25.3 L per session. All-cause mortality was 17.3% in patients assigned to hemodiafiltration versus 21.9% in the hemodialysis group. The survival benefit of hemodiafiltration was greater for patients without a baseline history of cardiovascular disease or diabetes: hazard ratios, 0.58 and 0.65, respectively. Risks of death from cardiovascular causes and a

composite of fatal or nonfatal cardiovascular outcomes were similar between groups.

This clinical trial finds a survival benefit of high-dose hemodiafiltration compared with conventional, high-flux hemodialysis in patients with kidney failure. The effects on survival may vary according to comorbidity and other patient characteristics [Blankestijn PJ, et al. Effect of hemodiafiltration or hemodialysis on mortality in kidney failure. *N Engl J Med*, published online ahead of print June 16, 2023. doi: 10.1056/NEJMoa2304820; https://www.nejm.org/doi/10.1056/NEJMoa2304820]. ■

Does Normothermic Machine Perfusion Improve Kidney Transplant Outcomes?

A period of normothermic machine perfusion (NMP) is feasible and safe before deceased-donor kidney transplantation but does not reduce the rate of delayed graft function (DGF) compared with standard static cold storage (SCS), reports a trial in *Nature Medicine*.

The randomized trial included 338 patients at four U.K. centers who were undergoing kidney transplantation from donation after circulatory death (DCD) donors. All kidneys underwent SCS, with a total cold ischemic time of approximately 800 minutes. After SCS, kidneys in the intervention group underwent a 1-hour period of NMP.

Intention-to-treat analysis included 147 kidneys assigned to SCS only and 143 to SCS plus NMP. DGF, defined as the requirement for dialysis within 7 days after transplantation, was the main outcome of interest.

The rate of DGF was almost identical between groups: 58.5% with SCS alone and 60.7% with SCS plus NMP. Patient and graft survival, acute rejection, and 12-month kidney function were similar as well. There were no significant differences

Continued on page 26 >

in adverse events, including transplant thrombosis or infectious complications.

Kidneys from DCD donors are an important source of organs for transplantation but are susceptible to cold ischemic injury, which may lead to DGF. In the emerging NMP technique, donor kidneys are perfused with a warmed, oxygenated, red cell-based solution, producing a near-physiologic state that enables functional testing. To date, the new report is the first randomized, multicenter trial comparing NMP with conventional SCS in DCD kidney transplantation.

The results show no reduction in DGF with a period of NMP before transplantation of DCD kidneys. The researchers write, "Nonetheless, we have demonstrated that this new technology for kidney preservation is feasible, safe and suitable for clinical application" [Hosgood SA, et al. Normothermic machine perfusion versus static cold storage in donation after circulatory death kidney transplantation: A randomized controlled trial. *Nat Med* 2023; 29:1511–1519. doi: 10.1038/s41591-023-02376-7]. ■

Model Predicts Kidney Failure Risk After Nephrectomy

A validated, six-item equation performs well in predicting the 5-year risk of kidney failure in patients undergoing surgery for localized kidney cancer, according to a study in the *American Journal of Kidney Diseases*.

The model was developed in a population-based cohort of 1026 adults in Manitoba, Canada, who underwent partial or radical nephrectomy for non-metastatic kidney cancer from 2004 through 2016. All patients underwent at least one measurement of estimated glomerular filtration rate (eGFR) both before and after surgery. Models were created to identify factors associated with the 5-year risk of incident kidney failure, defined as dialysis, transplantation, or eGFR less than 15 mL/min/1.73 m^2.

The resulting Kidney Cancer Risk Equation (KCRE) comprised six readily accessible variables: age, sex, eGFR, type of nephrectomy, diabetes, and urine albumin-to-creatinine ratio. In the development cohort, the equation showed good predictive performance, with an area under the curve (AUC) of 0.85. The KRCE performed similarly well in a validation cohort of 12,043 patients undergoing kidney cancer surgery in Ontario, Canada, between 2008 and 2018: AUC, 0.86. The findings were consistent in sensitivity analyses, and the model showed excellent calibration after adjustment of the baseline hazard.

Nephrectomy is an effective treatment for kidney cancers but carries a risk of later decreased kidney function or kidney failure. The KCRE was developed to meet the need for pre-operative tools to predict the long-term risk of kidney failure after surgery for localized kidney cancer.

The new study describes the KCRE as a simple, validated model to predict the risk of developing kidney failure after nephrectomy for kidney cancer. "The KCRE is an easy-to-use tool for urologists and nephrologists to apply in the pre-operative period for risk stratification and patient-centric counselling to identify those at risk of developing post-operative kidney failure in the next 5 years," the researchers write. They call for further validation in diverse patient samples [Harasemiw O, et al. A predictive model for kidney failure after nephrectomy for localized kidney cancer: The Kidney Cancer Risk Equation. *Am J Kidney Dis*, published online ahead of print June 30, 2023. doi: 10.1053/j.ajkd.2023.06.002; https://www.ajkd.org/article/S0272-6386(23)00695-9/fulltext]. ■

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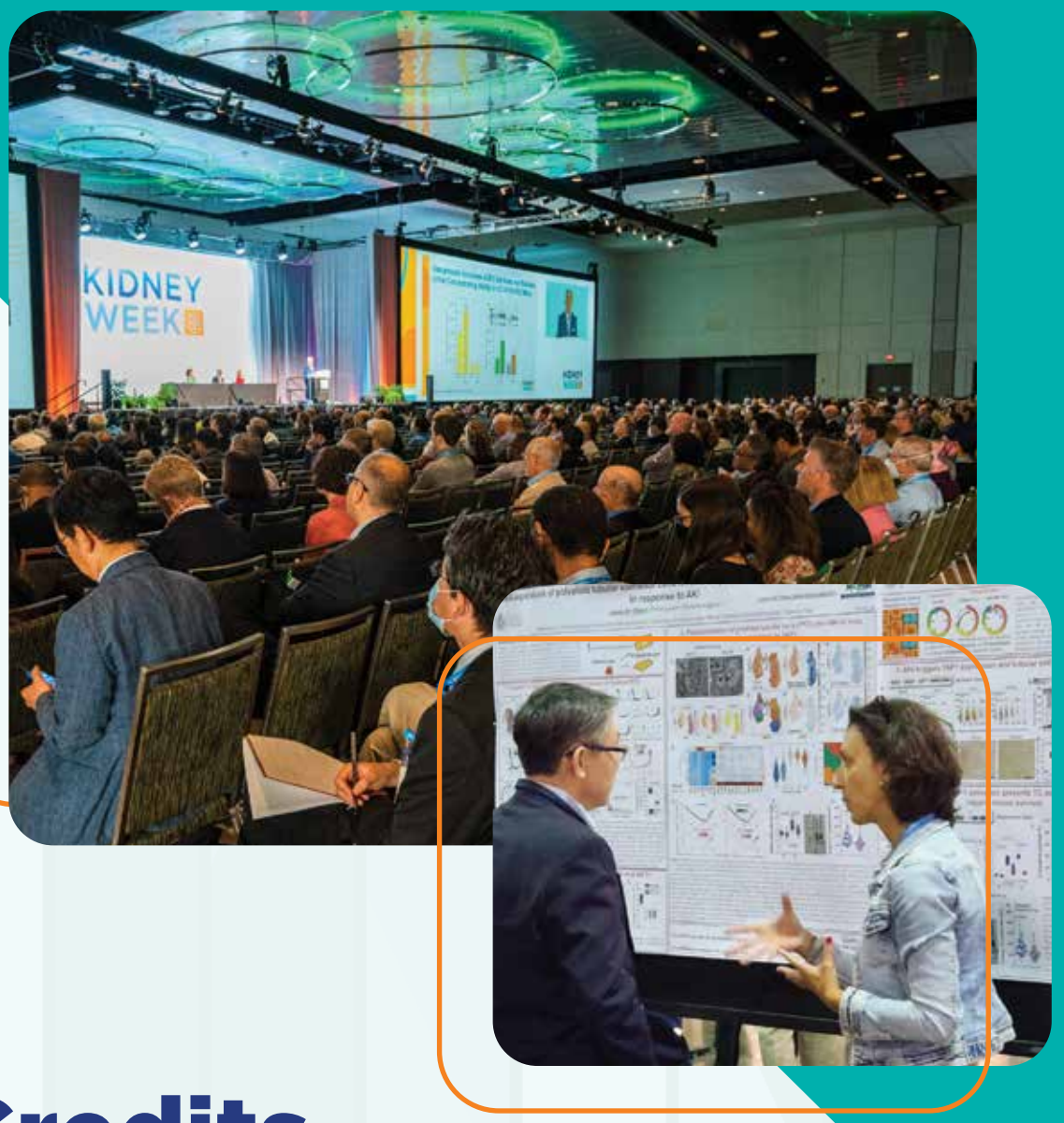

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C3G, complement 3 glomerulopathy; IgA, immunoglobulin A.

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