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Improving Transplantation Education Requires a Multipronged Approach

By Melanie Padgett Powers

Although kidney diseases affect an estimated 37 million people in the United States, most people are unaware and may not be diagnosed until they reach kidney failure, or end stage kidney disease (ESKD). More than 786,000 people in the United States have kidney failure, with more than 61% receiving in-center dialysis (1).

Transplant is the gold standard for most of these patients, but getting to that stage can be a confusing, complex path with several barriers along the way. Multiple strategies are needed to improve kidney transplantation rates, experts say, including better patient education, engagement, and choice.

"One goal of ESKD treatment is to skip dialysis and aim for a preemptive transplantation, as this strategy provides the optimum benefit," said Vineeta Kumar, MD, professor of medicine and medical director of the Incompatible Kidney Transplant Program at The University of Alabama at Birmingham (UAB). "Every year you spend on dialysis, you are chipping away at that benefit of transplantation," Kumar said. "So preemptive transplantation is the way we want to go." However, in the United States, fewer than 10% of all kidney transplants are preemptive, she said, even after changes in the kidney allocation system to increase access to organs (2).

This is because "the care of the patient in the journey from kidney disease[s] to transplantation is very siloed," Kumar said. Patients may start with a primary care physician managing their early kidney diseases, then be referred to a nephrologist at a later stage, and ultimately reach a health care team at a dialysis center. If patients are connected to a transplant center, they will have a new transplant team and a transplant nephrologist. These multiple transitions of care oftentimes lead to missed opportunities, Kumar said. Plus, she added, they can exacerbate existing health care disparities among vulnerable populations.

Empowering patients with information

Although nephrologists should play a key role in patient education, oftentimes the education needs to start much

Continued on page 3

Glucose Absorption May Drive Cyst Formation in Polycystic Kidney Disease

By Tracy Hampton

Researchers have identified many of the genes that cause autosomal-dominant polycystic kidney disease (ADPKD) and other forms of PKD, which are characterized by fluid-filled cysts that arise from tubules in kidneys and other organs. They have developed human kidney organoids to model these conditions, but very little is known about the mechanisms underlying cyst formation in affected patients. By applying a microfluidic chip to the organoids, investigators recently uncovered new insights into how the flow of fluid within the kidney contributes to PKD. The work, which is published in *Nature Communications*, points to the importance of aberrant glucose absorption in cyst formation (1).

"The results…are significant because there is a whole class of molecules that block sugar uptake in the kidneys and are attractive therapeutics for a number of conditions," said co-senior author Benjamin Freedman, PhD, an assistant professor of medicine in the Division of Nephrology at the University of Washington School of Medicine in Seattle.

Combining kidney organoids with microfluidic chips allowed a mixture of water, sugar, amino acids, and other nutrients to flow over the organoids, which were derived from human pluripotent stem cells and contained podocyte, proximal tubule, and distal tubule segments in contiguous, nephron-like arrangements. In organoids that had been genetically edited to mimic PKD, the process of cyst swelling

Continued on page 4

Inside

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Improving Transplantation Education

Continued from cover

earlier, Kumar said. Patients, particularly those with diabetes or a family history of kidney diseases, should have their kidney function measured regularly and be taught what their numbers mean—their serum creatinine value, random urine albumin-to-creatinine ratio, and blood glucose number. This early detection could help prevent or slow progression of loss of kidney function. "It's empowering our patients with information as it applies to their condition so that they have the chance to be more active participants in the trajectory of their own care," Kumar said.

Kumar recognizes, however, that there are barriers to the ideal version of early, ongoing, effective education, especially for individuals who face negative social determinants of health, such as low income, lack of transportation, no health insurance, or interpersonal and structural racism. Racial and ethnic minorities in the United States are less likely than people who are White to receive kidney care before kidney failure, to receive a kidney transplant, and to go on home dialysis. Individuals who are Black in the United States, in particular, are less likely to be placed on the kidney transplant waitlist when compared with people who are White (3).

In addition, there are no standardized, evidence-based guidelines that tell health care providers how to educate a patient about transplant options, said Tanjala S. Purnell, PhD, assistant professor at the Johns Hopkins Bloomberg School of Public Health in Baltimore, MD, who researches ways to improve equity in access to kidney transplantation.

Medicare ESKD Form 2728 asks whether a patient has been informed of transplant options, but it does not go into details about that education. The form does not ask "exactly which components about transplant were they informed about or how long was the conversation, the timing of the conversation, none of that," Purnell said.

Furthermore, transplantation is an evolving field. Purnell wonders: "Are patients being told about innovative options beyond a living donor they know or beyond being placed on the deceased donor waiting list?" For example, studies have shown positive results in patients who have received kidneys from donors who have hepatitis C, now that more effective and tolerable, direct-acting antivirals are available to cure hepatitis C (4).

Another challenge is that physicians are often not taught in medical school and residency about how to engage a patient based on his or her individual learning style or culture. "Care isn't cookie cutter," said Quin Taylor, a 2015 kidney transplant recipient and patient advocate on ASN's Excellence in Patient Care Advisory Committee. "You can't approach every patient the same way and expect [him or her] to understand and be proactive in the same way, especially culturally. Patients have a care team for a reason, and I think each partner in that care team needs to take the time to find an effective way to help patients understand not only why transplantation is important but also to address their concerns."

As a child, Taylor watched her father go through years of dialysis before getting a transplant. But because of complications he went through, when Taylor was first told she needed a transplant, she wanted no part of it. She planned to stick with dialysis at first. "There were certain things that I had to learn for myself, and one of the biggest things was that transplantation isn't a cure…. Once I was able to understand that, it helped me on the journey."

Taylor switched from in-center dialysis to at-home dialysis and became very proactive in the transplantation process. She worked through barriers, such as needing to lose weight first. "I was very self-motivated, but not all patients are."

Like with Taylor, it can take time for patients to choose or accept the decision their health care team believes is the best one for them. Having these conversations early and often "gives patients the opportunity to figure out what this is [because] a lot of times patients crashed into dialysis because they didn't know they had kidney disease[s]," Taylor said.

Including patient goals in decision-making

Patient choice and decision-making need to be a part of the educational process, Taylor added. A 2022 *CJASN* study (5) showed that those on the kidney transplant waitlist would be willing to have a kidney with fewer years of quality if it meant they could get the transplant now, rather than spend 2 more years on the waitlist for a better kidney. Approximately 20% of deceased donor kidneys are discarded in the United States each year. Could some of those kidneys benefit patients?

In the *CJASN* study of 605 participants (5), the average respondent said he or she would accept a kidney today that had 6½ years of expected graft survival rather than waiting 2 more years for a kidney with 11 years of expected graft survival. Those less willing to accept increases in wait time for improvements in kidney quality were more likely to be older, Black, not have a college degree, and have a lower Karnofsky Performance Status score, which assesses a patient's ability to handle activities of daily living.

Health care providers "don't always include patients in on the decision-making," Taylor said. "Doctors sometimes write goals for patients, instead of including [patients] in their conversation—what are their goals? You might want them to get transplanted; they might just want to be able to travel." Taylor continued, "I always say, doctors are the experts in the science of diseases; the patients are the experts in the experience of those diseases. So, when it comes to connecting the dots, patients have an insight that doctors will never have, no matter how many times they treat a patient."

Purnell has been researching initiatives to increase the number of living donor transplants. Oftentimes, a person needing a transplant may not know how to ask or be comfortable with asking others for help, especially beyond his or her close family members and friends. Purnell has been partnering with church and community leaders in Baltimore to develop ways to increase awareness among healthy people about the need for donations and to create support systems. Such help could include providing transportation to dialysis or pairing someone up with a medical professional in his or her community who can attend doctors' appointments with him or her as an advocate.

"Many times there's this notion that certain communities just aren't stepping up, or certain communities just aren't interested," Purnell said. "But in reality…communities are willing to step up, and communities do care. It's just that that's not a topic often that many community members are introduced to until a loved one is faced with this decision."

Helping patients find healthy living donors

Health care professionals can also help patients think beyond their close circle for a potential live kidney donor. Chronic conditions such as diabetes and kidney diseases are often clustered in social networks, Purnell said, making it more important to widen the search for a healthy living donor.

One successful initiative has been the Live Donor Champion program, in which people on the transplant waitlist identify someone close to them to be their champion. The champion receives education and materials through the program to help spread awareness about live donation. Ultimately, the goal is for the champion to help find a donor for his or her friend or family member on the transplant waitlist. Such programs can help people learn how to get the word out and ask for help, which can be uncomfortable and difficult.

At UAB, Kumar and her team have instituted a living donor champion and navigator program that helps those on the waitlist identify and ask potential donors. The ability for those in the program to identify a potential living donor increased two- to threefold. The navigator then helps the donor through the entire evaluation process, from identification to final decision and donation.

In one of their studies of 56 program participants, UAB researchers found that program participation was the strongest predictor of having a living donor screened—an increase of more than ninefold compared with standard of care. African American participants were eightfold more likely to have a donor screened than African American non-participants and threefold more likely than Caucasian non-participants, according to the study published in January 2020 in *Transplantation* (6).

Doctors sometimes write goals for patients [but instead should ask] what are their goals? You might want them to get transplanted; they might just want to be able to travel.

Throughout a patient's journey through CKD and transplantation, education needs to be ongoing and interactive, Kumar said. "In the name of education, we sit them down for an hour and talk at them for that entire time," she said. "That's information sharing, which is important but not the same as education."

Education is providing information and then stopping to ask questions to see what they have retained, she said, ultimately ensuring that the knowledge they gained empowers them to care for themselves during vulnerable periods in their transplantation journey. It also includes space for patients or their loved ones and caregivers to ask questions and discuss the unknowns. "Education can be optimized by being early, by being bite-sized, by being progressive, and by [empowering] our patients so they can be true participants in their own care and partners with their medical care teams, as opposed to being present and led along." ■

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Glucose Absorption

Continued from cover

involved the absorption of fluid inward through cells from outside the cyst. This discovery was surprising, as the team expected cysts to form by pushing fluid outward through cells. Therefore, although the research did not rule out secretion as a causative mechanism in PKD cyst formation, it revealed that absorption also appears to play a critical role.

To observe the process of cyst formation in real time, the scientists collected time-lapse images of young PKD organoids undergoing cyst formation in culture. Cysts formed from the peripheral epithelium of the organoids that faced outward toward the media, rather than from internal regions.

Also, increasing the levels of glucose in dish cultures augmented cyst swelling, which was blocked in the presence of the sodium-glucose co-transporter inhibitors phloridzin or dapagliflozin. "Sugar uptake is something that kidneys do all the time," Freedman said. "We found that increasing the levels of sugar in the dish cultures caused cysts to swell. And when we employed drugs known to block sugar absorption in the kidneys, it blocked this swelling. But I think it relates less to blood sugar level and more to how kidney cells take in sugar—which in this process seemed to go rogue and give rise to cysts."

The cell experiments were supported by additional experiments conducted in a mouse model of PKD. When the scientists injected fluorescent glucose into mice with PKD, they found that the mouse cysts also took up glucose.

"Organoids are a powerful tool for disease modeling, but organoid culture systems are typically static. By combining a flow-based system with PKD organoids, the Freedman group has elegantly demonstrated that it is the transport of glucose which drives cystogenesis," said Edward Kelly, PhD, who is an associate professor in the Department of Pharmaceutics at the University of Washington School of Medicine and was not involved with this research.

Numerous glucose inhibitors are under investigation for the treatment of various kidney diseases. This work suggests that patients with PKD are also likely to benefit from such drugs.

Gopi Rangan, PhD, FRACP, MBBS, MBA, a professor of genetic kidney disease at The University of Sydney and the director of the Michael Stern Laboratory for Polycystic Kidney Disease at the Westmead Institute for Medical Research, stated that "it is a fascinating study which has provided novel insights into disease mechanisms, verifying the importance of fluid flow in mediating cyst growth and (converse to previous understanding) that cystic cells have an absorptive phenotype. In addition, the organoid model provides a superior high-throughput method for screening and selecting compounds for further preclinical evaluation."

But Rangan stressed that more work is needed to determine whether the findings will be translatable to human disease. "The organoids do not replicate [the] human microcyst environment. They are derived from proximal and distal tubular segments, and collecting ducts are not included; and PKD is induced by bi-allelic mutations, rather than heterozygous in human ADPKD. In humans, it is hypothesized that cysts are primarily derived from distal nephron segments, rather than proximal segments," he said. "It is also not clear if the concentrations of phloretin or dapagliflozin are relevant to humans. In this regard, only the highest concentration of phloretin reduced cyst growth, and the highest concentration of dapagliflozin reduced the live/dead ratio of cysts but not cyst growth."

The research may also help advance the study of organ systems by showing that simulating fluid flow with microfluidic chips can provide a more realistic environment for analyzing human organoids in the lab. "Coupling the structural and functional characteristics of organoids with the controlled, microfluidic microenvironments of organ-on-a-chip devices is a promising approach to in vitro disease modeling," Freedman and his co-authors wrote.

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FDA Approves Oral Agent for Anemia in Dialysis

Daprodustat Is First HIF-PHI to Hit Market

By Eric Seaborg

The US Food and Drug Administration (FDA) announced in February its approval of the first oral agent to treat anemia in patients on dialysis.

Daprodustat is the first in the class of hypoxia-inducible factor-prolyl hydroxylase inhibitors (HIF-PHIs) to receive approval after the FDA declined to approve two previous drugs in the class—roxadustat and vadadustat—over safety concerns.

In its announcement, the agency specified that daprodustat received approval for use in patients who have been on dialysis for at least 4 months but not "for patients with anemia due to chronic kidney disease who are not on dialysis because its safety has not been established in that population." The FDA's action conformed to the recommendations of the advisory committee that considered daprodustat's efficacy and safety data in the fall of 2022. "With an oral drug option in addition to the FDA-approved injection options, adults with chronic kidney disease on dialysis now have multiple ways to treat their anemia," Ann Farrell, MD, director of the FDA's Division of Non-Malignant Hematology, said in a press release (1).

Injections of erythropoietin-stimulating agents (ESAs) have been a mainstay in treatment of the anemia common in patients with chronic kidney disease for some 30 years and greatly reduced the need for blood transfusions. However, the kidney care community has been looking forward to an alternative agent because ESAs are associated with cardiovascular risks, and up to 10% of patients do not respond adequately to ESAs.

[T]he kidney care community has been looking forward to an alternative agent because ESAs are associated with cardiovascular risks.

Daprodustat's initial use will most likely be to treat these ESA hyporesponders, especially those who require high doses, according to Daniel W. Coyne, MD, professor of medicine in the Division of Nephrology at Washington University School of Medicine in St. Louis (MO). Coyne says that the drug's impact as an oral agent would have been much greater had the FDA allowed its use in patients before they reached the dialysis stage because giving injections to dialysis patients is not a barrier to the use of ESAs. In addition, the requirement that patients are established on dialysis means that most of them will have already been started on an ESA if they need treatment for anemia. There will be little reason to change the drug regimen for those who respond to an ESA, so daprodustat will not be a front-line treatment, Coyne explains.

Both ESAs and HIF-PHIs aim to increase the levels of erythropoietin, but the HIF-PHIs have a less direct mechanism of action. By stabilizing the HIF, the drugs inhibit the oxygen pathway to induce a "pseudo-hypoxic" state and work by mimicking the body's reaction to the lower oxygen levels encountered at high altitude to increase erythropoietin. The approach is designed to avoid the supraphysiological peaks in erythropoietin production seen with exogenous ESA use.

The hope that this different mechanism of action might lessen the risk of major adverse cardiovascular events associated with ESAs has not panned out, as shown by the experience with roxadustat and vadadustat. Coyne noted, however, that these two drugs have been approved for use in China, Japan, and many parts of the European Union based on the same safety data that the FDA cited in turning them down.

Coyne said that many nephrologists may regard daprodustat skeptically because of the safety record of the other drugs in its class. "I believe some nephrologists will want to wait and see what happens with this class of drugs because we need longer term safety data given that the drugs affect a large number of genes to a variable amount. Only time will tell whether daprodustat is safer, as safe, or inferior to the ESAs that we are using now," Coyne said.

Manufacturer GlaxoSmithKline will market daprodustat under the brand name Jesduvroq. "Jesduvroq has a boxed warning for an increased risk of thrombotic vascular (blood clotting) events including death, heart attack, stroke, and blood clots in the lungs, legs, or dialysis access site," the FDA noted in its press release (1). Daprodustat should not be used by patients with uncontrolled blood pressure, and the most common side effects include high blood pressure, thrombotic vascular events, abdominal pain, dizziness, and allergic reactions.

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Clinicopathologic Predictors of Prognosis in Anti-Glomerular Basement Membrane Disease—Can We Do Better?

By Nasim Wiegley and Ana Naidas

Anti-glomerular basement membrane (anti-GBM) disease is a rare autoimmune disease with an incidence of 0.5–1 per million population. The pathogenic autoantibodies target the non-collagenous domain of the α3 chain of type IV collagen found in the basement membrane of the glomeruli in the kidneys and alveolar capillary walls in the lungs, leading to significant organ injury with a high risk of morbidity and mortality. Patients commonly present with rapidly progressive glomerulonephritis, at times accompanied by alveolar capillaritis and pulmonary hemorrhage (1, 2). Over the past decades, aggressive treatments, such as plasma exchange for rapid removal of the pathogenic antibody and immunosuppression with glucocorticoids and cyclophosphamide, have played a crucial role in improving patient survival outcomes (3), with post-treatment 5-year patient survival reaching >90% (4). However, kidney survival remains suboptimal, with many patients progressing to end stage kidney disease (ESKD) (4, 5).

Considering the aggressive nature of this disease, improving our prognostication can aid in individualized care to enhance patient-related outcomes while reducing treatment-related adverse events. Oligoanuria and dialysis dependence at presentation have been previously associated with poor patient and kidney outcomes (6). Therefore, recent Kidney Disease: Improving Global Outcomes (KDIGO) glomerular disease guidelines recommend withholding aggressive immunosuppressive therapy in patients with a dialysis need at presentation, crescents in 100% of glomeruli sampled, or >50% glomerulosclerosis on kidney biopsy in the absence of pulmonary hemorrhage (7) to reduce unnecessary medication-related toxicity. To improve outcomes for these complex and vulnerable patients, there is a great need for better risk-stratification tools and an improved understanding of clinicopathologic predictors of outcome to aid informed decision-making and individualized treatment approaches.

The renal risk score (RRS) was initially developed as a prediction tool for anti-neutrophil cytoplasm antibody-associated vasculitis (8); however, to date, there have not been any dedicated risk-stratification tools for anti-GBM disease. A recent retrospective cohort study by Floyd et al. (9) aimed to further investigate various clinicopathologic factors that can aid in identifying patients who might benefit from immunosuppressive therapy, despite aggressive disease at presentation, and validate the use of RRS for anti-GBM disease. A total of 174 patients with biopsy-proven anti-GBM disease from seven European kidney-referral centers and registries were included in this study, a subset of whom required dialysis support on presentation. Interestingly, this study showed that the RRS is usable for risk stratification in anti-GBM disease as well (Harrell's C = 0.760; 95% confidence interval [CI], 0.69–0.83; p < 0.001). In multivariate analysis, the combination of the need for kidney replacement therapy (KRT) at diagnosis and the percentage of normal glomeruli in histopathology were independent predictors for ESKD. On further analysis, the presence of 10% normal glomeruli in the biopsy separated kidney outcomes and rate of recovery. Patients with 10% or more normal glomeruli on biopsy had a higher rate of kidney recovery, even if they were initially dialysis dependent on presentation. In comparison, dialysis-independent patients with little or no normal glomeruli (<10%) developed ESKD more often.

In line with this, a bivariable prediction model composed of these two factors (initial KRT need and percentage of normal glomeruli) yielded superior discrimination for long-term kidney survival compared with the RRS alone (C = 0.840; 95% CI, 0.79–0.89; p < 0.001). In this study, a sensitivity analysis of biopsies with at least 10 glomeruli (134/174) did not detect a significant difference in the performance of this tool (C = 0.820). However, since this prediction model is based on the number of normal glomeruli in kidney biopsy, caution is needed in analyzing biopsies with <10 glomeruli.

Future prospective validation of this prediction tool would be valuable, although the rarity of anti-GBM disease will make this task difficult. Overall, the added prognostic information provided by prediction tools can aid in identifying individuals with a good potential for kidney recovery and improve patient-related outcomes based on an individualized treatment approach. In addition, although the utility of kidney biopsy in oligoanuric patients with anti-GBM disease has been questioned in the past (6), the results of this study shed light on the additive value of histologic information in risk stratification, further highlighting the benefits of individualizing care.

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The authors report no conflicts of interest.

[I]mproving our prognostication can aid in individualized care . . . while reducing treatment-related adverse events.

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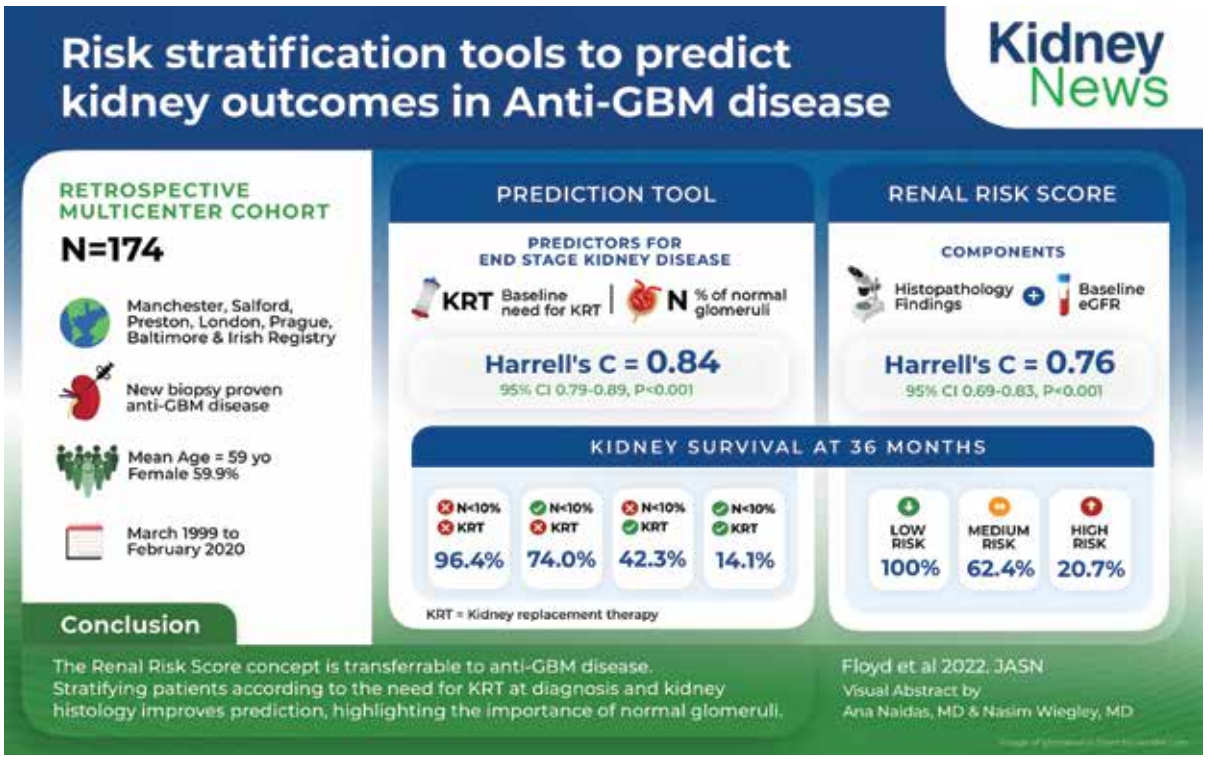

ASN President's Update

A World without Kidney Diseases

By Michelle A. Josephson

March is our month! Not only do we celebrate National Kidney Month in the United States, but we also make our brackets to compete in NephMadness and, together with our colleagues across the globe, observe World Kidney Day on Thursday, March 9, 2023.

While you, like me, may think every day is kidney day, World Kidney Day is an annual initiative to raise awareness about the importance of kidneys to our health and the public health challenges of kidney diseases. Started in 2006 as a joint effort by the International Society of Nephrology (ISN) and the International Federation of Kidney Foundations, World Kidney Day is observed on the second Thursday of March and has a different focus each year. The theme for 2023 is "Kidney Health for All: Preparing for the Unexpected, Supporting the Vulnerable!"

There are several important reasons for ASN to advocate for kidney health outside the United States, North America, and the Americas. Despite the society's name, ASN is an international organization. More than 35% of ASN members live outside the United States in 139 countries, approximately 45% of participants at Kidney Week are international, and an estimated 70% of manuscripts submitted to the *Journal of the American Society of Nephrology* (*JASN*) come from abroad. We are part of the global kidney community whose effectiveness is synergized, amplified, and heard when we all work collaboratively, rather than in silos. Finally, in its strategic plan, ASN's vision is to "Create a World without Kidney Diseases," so we have an obligation to consider our field globally (1).

With this goal in mind, ASN Past President Susan E. Quaggin, MD, FASN; President-Elect Deidra C. Crews, MD, ScM, FASN; Executive Vice President Tod Ibrahim; and I met with our counterparts from the European Renal Association (ERA) and ISN in January in Brussels, Belgium (Table 1). These leaders from ASN, ERA, and ISN discussed issues and initiatives of mutual interest that are important to the more than 850 million people living with kidney diseases worldwide.

In addition to reaching agreement several years ago on the number of people worldwide living with kidney diseases (2), the three organizations have worked together to advance several shared goals, including the World Health Organization's recognizing kidney diseases as one of the top noncommunicable diseases driving premature death worldwide, educating the kidney community about ethical challenges confronting nephrologists, and addressing the state of the global nephrology workforce (3).

Disaster relief—both from natural and human causes—was an area of shared interest for which all three societies have experience and expertise. This discussion ranged from earthquakes in Japan, hurricanes in the Caribbean, the COVID-19 pandemic, and multiple global conflicts. Last month's tragic earthquake in Turkey and Syria reinforced the importance of disaster preparedness worldwide as well as how the type of catastrophe varies by geographic location. If you would like to contribute to Direct Relief's efforts to help the people of Turkey and Syria, please visit https://www.asn-online.org/news/item.aspx?ID=341.

Also, February 24, 2023, marked the first anniversary of the war in Ukraine. Lessons learned from addressing the needs of dialysis and transplant patients in Ukraine and other war-ravaged countries were discussed. At last year's World Kidney Day commemoration, ASN, ERA, and ISN appealed "for kidney health for all war victims." Past President Quaggin stated, "People with kidney failure and kidney transplants urgently need to find alternatives, because wars are destroying dialysis facilities, interrupting energy and water supplies, causing medical staff shortages, and making travel to facilities unsafe."

ASN, ERA, and ISN also expressed concern for kidney patients and their caregivers who are in harm's way, thanked the companies and organizations that have already contributed aid, commended the countries that have opened their borders to receive people in need, and urged governments to do more. To date, ASN's partnership with Direct Relief has raised nearly $25,000 (4).

Table 1. ASN-ERA-ISN joint leadership meeting participants

American Society of Nephrology	European Renal Association	International Society of Nephrology
Michelle A. Josephson, MD, FASN (President)	**Christoph Wanner, MD** (President)	**Agnes B. Fogo, MD** (President)
Deidra C. Crews, MD, ScM, FASN (President-Elect)	**Ivan Rychlík, MD, PhD, FASN** (Secretary-Treasurer)	**Masaomi Nangaku, MD, PhD** (President-Elect)
Susan E. Quaggin, MD, FASN (Past President)	**Danilo Fliser, MD** (Renal Science Chair)	**Vivekanand Jha, MD** (Past President)
Tod Ibrahim (Executive Vice President)	**Monica Fontana** (Executive Director)	**Charu Malik, PhD** (Executive Director)

Last month, the leaders of ASN, ERA, and ISN also discussed the many ongoing efforts to support sustainability, or "green nephrology," throughout the world. Each society is committed to addressing this critical issue, but we recognize that to be most effective, we need to work locally, then coordinate and collaborate globally. To this end, the three societies plan to collaborate through a joint working group.

The intersection of the environment and nephrology is increasingly coming to public attention. Ed Kashi—a photojournalist who "uses photography, filmmaking and social media to explore geopolitical and social issues that define our times"—has focused his camera on individuals living with chronic kidney disease of undetermined etiology (or unknown cause [CKDu]), humanizing the problem and increasing awareness of this worldwide epidemic (5). In some of the most compelling photojournalism I have seen, he is bringing attention to this issue in short films and still photographs:

- His 2015 documentary, "Under Cane," depicts the devastation of kidney diseases in sugar cane workers in Nicaragua.
- "Hidden Under the Indian Sun," a 2017 documentary, follows individuals with kidney diseases who worked in the rice fields in Southeastern India.
- His 2018 documentary, "With Every Breath," shares the tragic story of a family and others with kidney diseases in Peru.
- A 2022 documentary, "Too Hot to Work," follows a group of laborers who traveled from Nepal to Qatar, some of whom became dialysis dependent after working for hours in the heat.

Some experts have attributed CKDu to environmental nephrotoxin exposure in agricultural areas (6). Others have argued that the basis for this disease is occupational heat stress (7). It has also been noted that CKDu is occurring in disadvantaged populations that are at risk for lower nephron mass for several reasons, starting as early as the time of fetal growth and development (8, 9).

Although the causes of CKDu or CKD of nontraditional origin (CKDnt) are unclear, what is clear is that an increasing number of people are experiencing kidney failure as a result, requiring dialysis or a kidney transplant. Affected people are often the breadwinners in their family and are left unable to work. Thus, the impact of their illness has dire consequences not only for the individuals with kidney diseases but also for their families.

Regardless of whether the changing environment is driving incidence of CKDu or CKDnt worldwide, there are signs that repeated exposure to higher temperatures has significant consequences for kidney health. *The Washington Post* (10) and *The New Yorker* (11) are among the major media outlets reporting on the connection between a warming planet and kidney health. A recent article in *The New Yorker*—"A Hotter Planet Takes Another Toll on Human Health"—by American environmentalist Bill McKibben, quoted research by ASN member David S. Goldfarb, MD, FASN, that considers whether the increasing incidence of nephrolithiasis in African Americans in the United States can be, in part, connected to historic discriminatory redlining practices that led to minoritized populations living in neighborhoods that are for all practical purposes "urban heat islands" in which the temperatures are hotter, a situation only being exacerbated by the warming planet (12).

The leaders of ASN, ERA, and ISN also discussed the final report of the National Kidney Foundation (NKF)–ASN Task Force on Reassessing the Inclusion of Race in Diagnos-

ing Kidney Diseases. Released in September 2021, the final report provides a new race-free approach to diagnose kidney diseases. NKF and ASN recommended the following: 1) "the adoption of the new eGFR [estimated glomerular filtration rate] 2021 CKD EPI [epidemiology collaboration] creatinine equation that estimates kidney function without a race variable"; 2) "increased use of cystatin C combined with serum (blood) creatinine, as a confirmatory assessment of GFR or kidney function"; and 3) more funding for "research on GFR estimation with new endogenous filtration markers and on interventions to eliminate race and ethnic disparities" (13).

As NKF and ASN work to implement these three recommendations in the United States, ERA and ISN leaders indicated that country-specific formulas may perform better in other parts of the world. The task force's first two recommendations, which work well for the US population, may not work as well for some other countries. Recognizing the limitations of currently available equations, unacceptable variance will continue to exist until an affordable, non-creatinine-based, universally applicable and available GFR measure exists.

Diversity, equity, and inclusion, along with health care justice, were important topics discussed by the leaders of the three societies. With attention brought to how these efforts are gaining traction in some countries, the discussion focused on how to implement them more broadly. The meeting illustrates the importance of working together to achieve shared goals worldwide.

If I have not convinced you yet that we need to think globally while acting locally, let us examine the US workforce. Nephrologists working in the United States come from all over the world. International Medical Graduates (IMGs) currently comprise 50.5% of the 11,407 practicing nephrologists in this country (14). That percentage is likely to rise as IMGs make up 66% of the current fellows training in US nephrology fellowship programs (15). While some of these professionals will return to their countries of origin or pursue other opportunities abroad, many will stay in the United States.

This migration causes a "brain drain" for the countries from which these nephrologists depart. At the same time, the lives of these nephrologists and their families often benefit, as does the specialty in the United States. Unfortunately, despite our benefiting from IMGs who work here, their ability to stay is challenging because of the onerous visa requirements. Currently, the Conrad 30 waiver program is the only federal mechanism for IMGs to apply for a waiver of the 2-year foreign residence requirement after completion of graduate medical education on a J-1 visa. The Conrad 30 has extremely limited capacity, however, with only 30 spots a year for each state across all physician specialties and subspecialties. We need to make the system less difficult for IMGs who wish to stay and work in the United States, but we must also consider how best to address problems caused by the brain drain throughout the world.

Former ASN President Anupam Agarwal, MD—who was recently named Dean of The University of Alabama at Birmingham Marnix E. Heersink School of Medicine—notes, "IMGs are critical members of the nephrology workforce in both academic and community practice settings in the United States. A significant number of nephrology fellowship trainees are also IMGs who provide important service to our patients in our hospitals and clinics. They often practice in underserved rural areas for years due to requirements to fulfil immigration obligations. As an IMG myself, I have greatly benefited from the training, mentorship, and amazing opportunities offered to me throughout my more than 30 years of being in this country. Given the significant shortages of physicians and the projected numbers in the coming years to be even worse, making pathways for IMGs to continue to work in the United States easier and less cumbersome is critically important."

As we enjoy March, celebrate National Kidney Month, play NephMadness, and mark World Kidney Day, I want to take a moment to applaud, highlight, and support all efforts to raise awareness and emphasize the importance of kidney diseases throughout the world. We may live in a world divided into 195 countries, but kidney diseases have no citizenship, know no borders, and are clearly a growing public health challenge across the globe. ■

Michelle A. Josephson, MD, FASN, is Professor of Medicine and Surgery, University of Chicago, IL, and is ASN President.

We are part of the global kidney community whose effectiveness is synergized, amplified, and heard when we all work collaboratively.

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Correction

The article "ASN President's Update: Priorities for 2023 Include Transplantation, Nephrology Training, and Environmental Sustainability" in the January *Kidney News* omitted a name in the sentence:

"I was able to recruit wonderful colleagues who have worked with me at different points, including James Chon, Amishi Desai, Pradeep Kadambi, Sambhavi Krishnamoorthy, Yousuf Kyeso, Basit Javaid, and Pratik Shah."

The sentence should read:

"I was able to recruit wonderful colleagues who have worked with me at different points, including James Chon, Patrick Cunningham, Amishi Desai, Pradeep Kadambi, Sambhavi Krishnamoorthy, Yousuf Kyeso, Basit Javaid, and Pratik Shah."

COVID-19 Vaccination and De Novo Glomerular Disease: Causation or Coincidence?

By Matthew Abramson and Kristin Meliambro

Given the increased risk of hospitalization and mortality from SARS-CoV-2 infection and COVID-19, vaccination against SARS-CoV-2 is strongly recommended for patients with pre-existing chronic kidney disease and glomerular disease (1, 2). However, a growing number of case reports have highlighted a possible link between de novo glomerular disease and COVID-19 vaccines, particularly mRNA vaccines (Pfizer-BioNTech and Moderna) (3–6). Whereas a potential association between vaccines and glomerular disease is not a novel phenomenon, with influenza vaccine-associated glomerulopathies being the most commonly cited (7), the overall risk appears minimal and drastically lower than the adverse health consequences of infection with the microbial targets of recommended vaccines.

In a recent issue of *Kidney360,* Waldman et al. (8) reported the results of the International Registry of COVID-19 Vaccination and Glomerulonephritis (IRocGN2), a National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health-launched registry to study COVID-19 vaccine-associated glomerular diseases (CVAGDs). Inclusion criteria required de novo biopsy-proven glomerular diseases and vaccine dose given within 3 months of biopsy. A total of 98 cases were entered in IRocGN2 over 11 months, encompassing 44 centers internationally. The majority of patients were from the United States, were White, and had received mRNA vaccines (Figure 1). Immunoglobulin A nephropathy (IgAN) and minimal change disease (MCD) were most commonly reported, followed by Pauci-immune crescentic glomerulonephritis and membranous nephropathy. Although most pathologies occurred after the second vaccine dose, MCD presented more frequently after the first dose.

The age distribution of CVAGDs reflected those of glomerular diseases in the general population. Patients who were Black/African Americans represented only a small percentage of cases but disproportionately had collapsing glomerulopathy; high-risk *APOL1* genotypes were found in two-thirds of patients. In 75% of cases, kidney-related symptoms were seen within 2 weeks of vaccine administration. At biopsy, the median proteinuria was 4 g/g (interquartile range [IQR], 2–9), creatinine was 1.7 mg/dL (IQR, 1.0–3.7), and the estimated glomerular filtration rate was 42 mL/min/1.73 m^2 (IQR, 15–81).

Renin-angiotensin inhibition was implemented in 30% of cases, and 60% of patients received immunosuppression. Over a median follow-up of 89 days (IQR, 27–177), complete or partial remission occurred in 60% of patients, with the highest remission rates seen in MCD and IgAN. Spontaneous recovery occurred in 11% of patients. Dialysis was required for 9% of patients, mainly due to anti-glomerular basement membrane disease or Pauci-immune crescentic glomerulonephritis.

The authors detailed the difficulties of assigning causality to vaccines, given the possible subtlety of kidney-related signs and symptoms, the lack of specificity for one particular COVID-19 vaccine (or COVID-19 vaccines in general), and the need for elucidation of potential mechanisms underlying CVAGDs. It must be noted that the cases identified in this registry could also represent background disease prevalence across the population, given that 60%–70% of all individuals in the world received the vaccination over a discreet time period. Conversely, the recurrence of glomerular disease following vaccine re-challenge in six patients strengthened the possibility of causality, although follow-up data were limited.

This study represents the largest published series to date of de novo glomerular disease cases temporally associated with COVID-19 vaccination. In the future, data from diverse patient populations with expanded serological testing over an extended follow-up period will help define the overall risk of CVAGDs, identify potential high-risk subgroups, and explore vaccine re-challenge. Although it is important to enhance our understanding of CVAGDs, the overall risk appears very low and should not alter current recommendations for COVID-19 vaccination in patients with kidney diseases, even those with known glomerular diseases. Moreover, the majority of cases identified in this registry as potentially being associated with vaccination achieved complete or partial remission. ■

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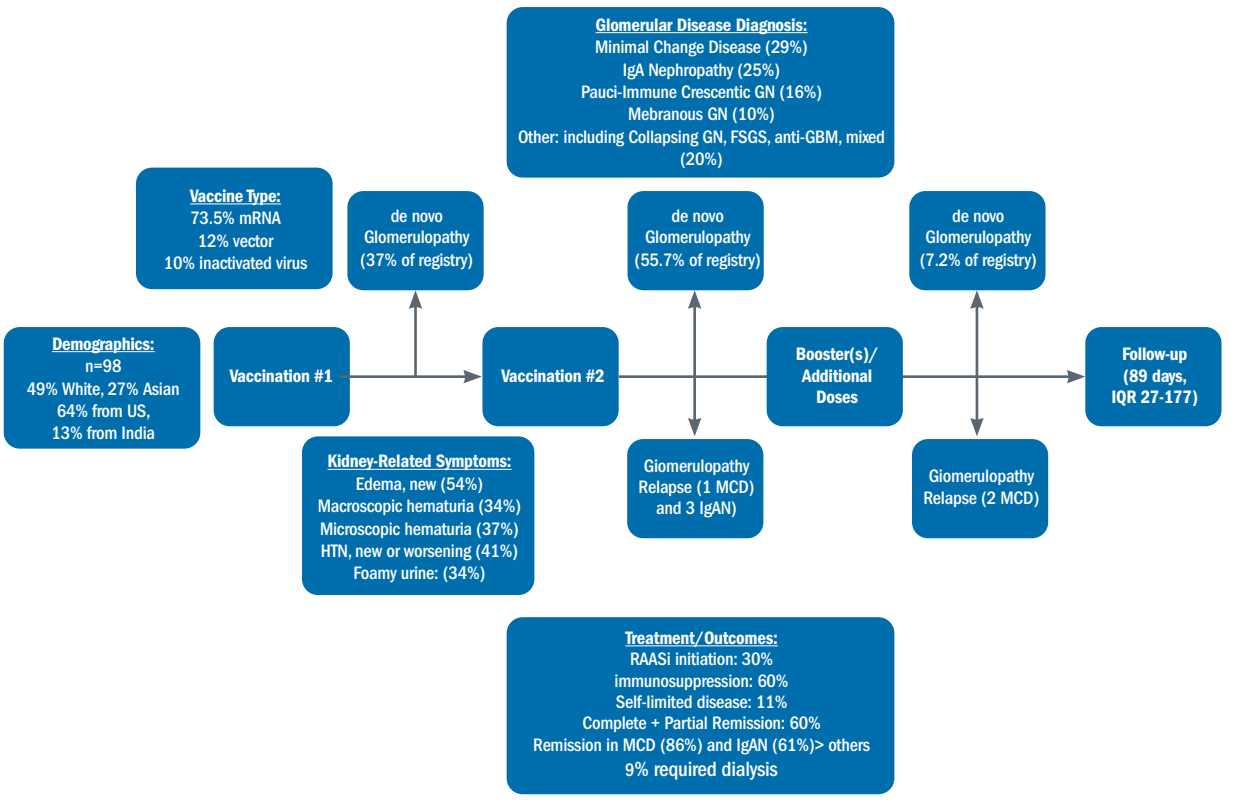
The authors report no conflicts of interest.

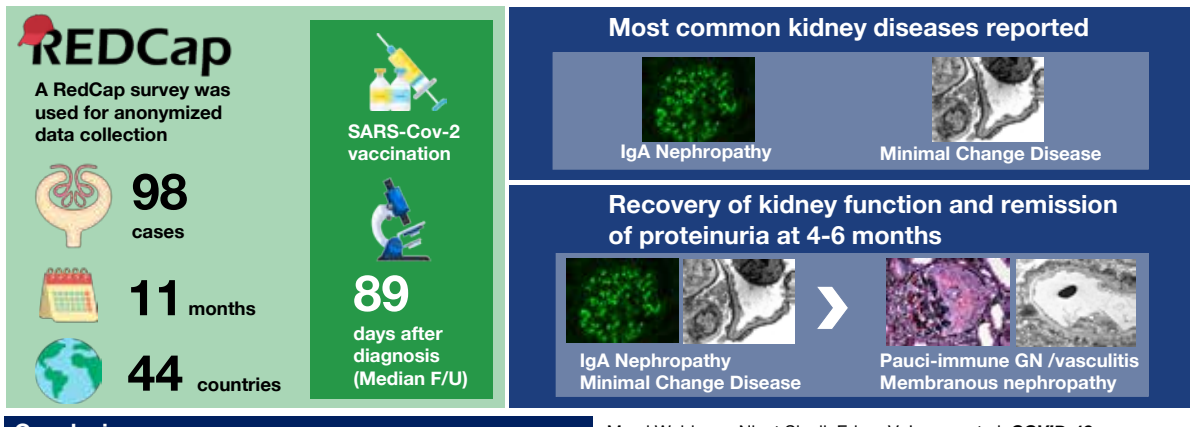
Figure 1. Timeline and summary from the IRocGN2



FSGS, focal segmental glomerulosclerosis; GBM, glomerular basement membrane; GN, glomerulonephritis; HTN, hypertension; RAASi, renin-angiotensin-aldosterone inhibition.

Characterization of *de novo* glomerular diseases and clinical course/outcomes after vaccination against SARS-CoV-2

Kidney360



Conclusions Development of *de novo* glomerular diseases after vaccination against SARS-CoV-2 may be a very rare adverse event. Temporal association is present for IgAN and MCD, but causality is not firmly established. Kidney outcomes for IgAN and MCD are favorable. No changes in vaccination risk-benefit assessment is recommended based on these findings.

Meryl Waldman, Ninet Sinaii, Edgar V. Lerma, et al. ***COVID-19 Vaccination and new onset glomerular disease: Results from the IRocGN2 International registry.*** Kidney 360.
Visual Abstract by Edgar Lerma, MD, FASN

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The European Association of Urology Guidelines on Urolithiasis: The Role of the Nephrologist

By María Ramos Cebrián

The prevalence of urolithiasis has increased worldwide over the past decades. Urolithiasis represents a longitudinal health problem requiring continuity of care that may extend beyond the treatment of stone episodes. It may seriously impair quality of life (1–3). Urolithiasis is additionally associated with increased morbidity and mortality, including an increased risk of chronic kidney disease and end stage kidney disease, mineral and bone disorders, bone fractures, and cardiovascular diseases (4–6).

The recently updated guidelines on urolithiasis from the European Association of Urology (EAU) (7) represent an advancement in the treatment of stone disease because they consider the associated risk of urolithiasis and the need for follow-up (Figure 1). There is a lack of clinical collaboration between the nephrologist and the urologist in the treatment of complex metabolic abnormalities in patients with urinary stones (7). The identification of patients with high clinical risk of recurrence is necessary and mandatory for improving the quality of life of patients and for collaborating for the sustainability of the health system. The factors that define a patient at high risk for stone recurrence are the presence of monogenic genetic diseases, anatomic and metabolic disorders, and diseases associated with stone formation.

Urologists have a chance to identify patients with conditions that need a multidisciplinary approach. Although the suspicion of secondary causes of urolithiasis and the metabolic alterations associated with stone disease were the main reasons for referral to nephrologists, unfortunately, the medical management of urolithiasis does not constitute a professional priority for nephrologists and is thus not emphasized during their training. On the other hand, lack of referral to nephrology by urology could be because many urologists are comfortable giving initial recommendations and only refer when impaired kidney function is identified. However, a close collaboration with the nephrologist is needed, not only during the acute phase of stone-related kidney injury but also during the clinically stable phase of the disease.

The new EAU guidelines emphasize patient follow-up after stone identification. Patients with low risk of recurrence should be monitored with an imaging test at 6 months, 12 months, and thereafter annually. Patients with a high risk should be followed up with an imaging test, a metabolic evaluation, and treatment monitoring at 8–12 weeks after starting pharmacological prevention of stone recurrence. This enables the drug dosage to be adjusted if urinary risk factors have not normalized, with further 24-hour urine measurements if necessary. Once urinary parameters have been normalized, it is sufficient to perform a 24-hour urine evaluation every 12 months.

The main limitations of the EAU guidelines are the lack of consideration of quality of life, patient preferences, and shared decision-making. Therefore, some concepts might be more appropriate in future releases to substitute the term "fluid" with "water" when referencing intake. It seems that a new time for collaboration has come between nephrologists and urologists.

María Ramos Cebrián, MD, is a consultant nephrologist with La Fe University and Polytechnic Hospital, Valencia, Spain.

The author reports no conflicts of interest.

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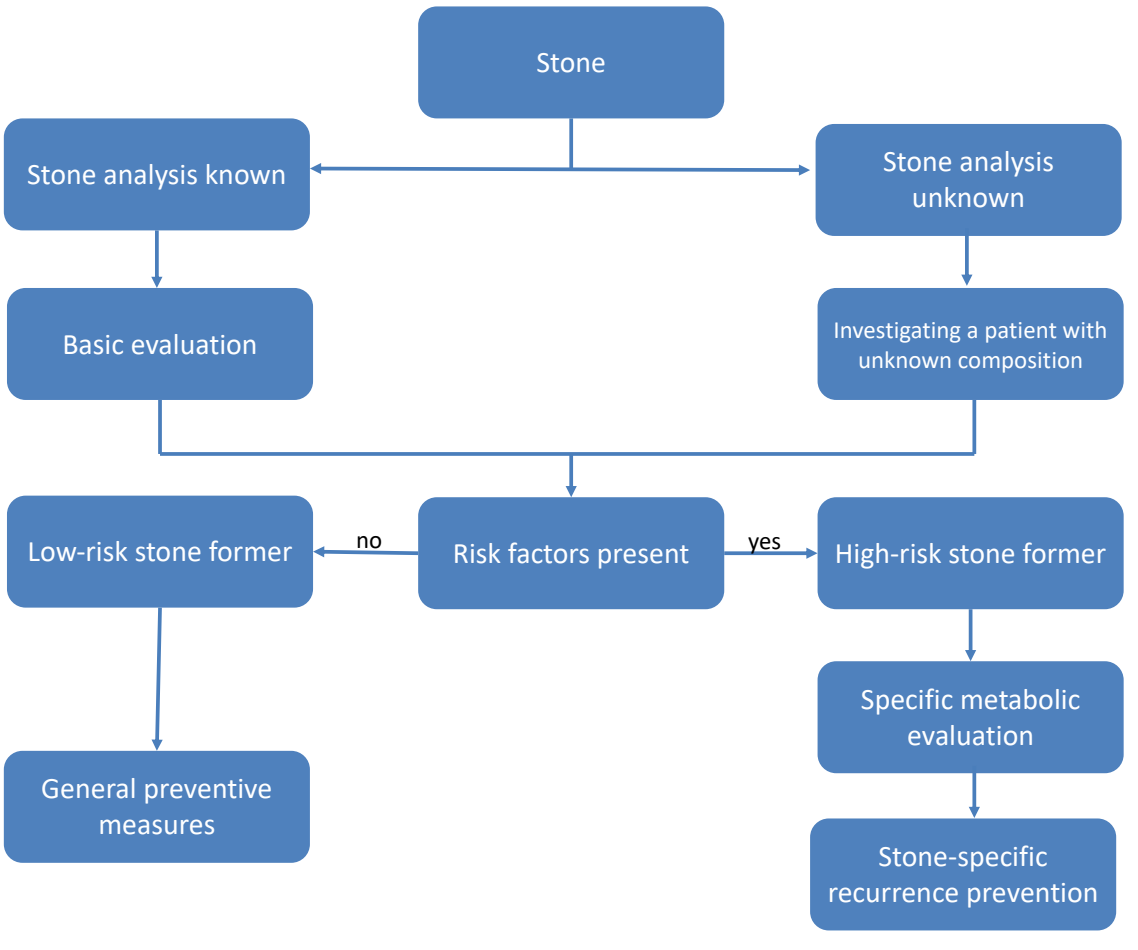
Figure 1. Assignment of patients to low- or high-risk groups for stone formation



Reprinted from the European Association of Urology (7).

Excess Mortality from Gout Linked to Kidney Diseases and Other Comorbidities

Comorbid conditions—including kidney and digestive disorders, among others—are associated with an increased risk of death among patients with gout, reports a study in *Arthritis Care & Research*.

Using electronic health records, the researchers identified 559,243 patients with gout in the Veterans Health Administration (VHA) system from 1999 to 2015. The patients were matched for birth year, sex, and year of VHA enrollment to 5.4 million gout-free controls. Associations of gout with all-cause and cause-specific mortality were assessed by multivariable Cox regression.

Nearly all patients in the VHA sample were men; the mean age was 67 years. The analysis included 246,291 deaths in gout patients over 4.25 million patient-years and 2 million deaths in non-gout controls over 40.44 million patient-years.

On initial analysis of matched groups, patients with gout were at higher risk of death from any cause: hazard ratio (HR), 1.09. However, the association became non-significant after adjustment for comorbidity.

On analysis of cause-specific mortality, genitourinary disease was the most commonly over-represented cause of death in the gout cohort: HR, 1.50. Specific associations were noted for nephritis (HR, 1.91), chronic kidney disease (HR, 1.71), and acute renal failure (HR, 1.54). An association with urinary calculi fell short of significance.

Gout patients were also at increased risk of death from digestive diseases, especially gastritis and liver disease. Associations were also noted for mortality from blood disorders, musculoskeletal disease, skin disease, infections, and cardiovascular disease (CVD). Some causes of death were less frequent in the gout cohort, including nervous system disease, mental health disorders, respiratory disease, malignancy, external causes, and metabolic disease.

Gout is a common disorder, especially in the VHA population. Patients with gout are at elevated risk of a variety of other chronic health conditions. The increase in all-cause mortality associated with gout is typically ascribed to CVD.

In the new analysis, excess mortality among veterans with gout is related to comorbid conditions. While CVD contributes to this increased risk of death, the strongest associations are noted for genitourinary and digestive diseases. The authors highlight the need to clarify the interplay between gout and related comorbidities [Helget LN, et al. Cause-specific mortality in patients with gout in the US Veterans Health Administration: A matched cohort study. *Arthritis Care Res (Hoboken)*, published online ahead of print March 16, 2022. doi: 10.1002/acr.24881; https://onlinelibrary.wiley.com/doi/10.1002/acr.24881]. ■

Dapagliflozin Reduces Hospitalizations in Patients with CKD

For patients with chronic kidney disease (CKD)—with or without type 2 diabetes—treatment with the sodium-glucose co-transporter-2 (SGLT2) dapagliflozin reduces the hospitalization rate overall and for certain categories of disease, according to a study in the *Annals of Internal Medicine*.

The analysis included data on 4304 patients from the Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease (DAPA-CKD) trial. All patients had an estimated glomerular filtration rate of 25–75 mL/min/1.73 m^2 and a urinary albumin-creatinine ratio of 200–5000 mg/g. Approximately two-thirds of patients had type 2 diabetes. Patients were randomly assigned to receive dapagliflozin (10 mg once daily) or placebo. Rates of first and subsequent hospitalizations were assessed, along with cause-specific admission risks.

Over a median follow-up of 2.4 years, 28.4% of patients were hospitalized one or more times for any cause. On intention-to-treat analysis, patients assigned to dapagliflozin were at lower risk of initial hospitalization (hazard ratio [HR], 0.84) and of any hospitalization or death (HR, 0.79).

Dapagliflozin-associated reductions in hospitalization rate were unrelated to the presence of type 2 diabetes at baseline. The dapagliflozin group also had lower rates of hospitalization for cardiac disorders, renal and urinary disorders, metabolic and nutritional diseases, and neoplasms. Other causes showed no significant differences, including infections, nervous system disorders, and gastrointestinal disorders. Patients on dapagliflozin also had an increased number of days alive and out of the hospital.

Patients with CKD are at high risk for hospitalizations, associated with increased costs and decreased quality of life. While previous studies have explored the effects of SGLT2 inhibitor therapy on kidney and cardiovascular outcomes, this post hoc analysis adds new evidence on all-cause hospital admissions.

Dapagliflozin reduces hospitalization risk in patients with CKD, with or without type 2 diabetes, the new results suggest. The researchers conclude, "These findings highlight additional benefits of dapagliflozin...[that] should be considered when evaluating the totality of evidence favoring provision of dapagliflozin to patients with CKD" [Schechter M, et al. Effects of dapagliflozin on hospitalizations in patients with chronic kidney disease: A post hoc analysis of DAPA-CKD. *Ann Intern Med* 2023; 176:59–66. doi: 10.7326/M22-2115].

Do We Need to Test for CHD before Kidney Transplant?

Preoperative testing for coronary heart disease (CHD) does not reduce the risk of myocardial infarction (MI) or death in the early weeks after kidney transplantation, reports a study in *JAMA Internal Medicine*.

Using the US Renal Data System, the researchers identified 79,334 adults undergoing first-time kidney transplantation from 2000 through 2014. All were enrolled in Medicare for at least 1 year before and 1 year after transplant. The mean age was 56 years; 62% of patients were men, and 61% were White.

The researchers performed an instrumental variable (IV) analysis, with program-level rates of preoperative CHD testing in the year of transplantation as the IV. Non-urgent CHD testing, invasive or non-invasive, was analyzed for an association with a primary composite outcome of death or MI during the first 30 days after transplantation.

A primary composite outcome event occurred in 5.3% of patients: acute MI in 2.9% of patients and death in 2.6%. From 2012 to 2014, program-level rates of preoperative CHD testing ranged from 56% in the top quintile to 24% in the bottom quintile.

In the main IV analysis, the CHD testing rate was unrelated to the 30-day risk of MI or death: the rate difference of 1.9% was not statistically significant. The findings were consistent across most study periods. The exception was from 2000 to 2003 when CHD testing was associated with higher risk of primary outcome events: rate difference, 6.8%.

Screening for CHD before kidney transplantation is widely recommended and performed—despite a lack of evidence that it affects transplant outcomes. One study has suggested that patients selected for screening are a group at higher risk of MI. Until the results of an ongoing randomized trial are available, IV analysis provides a means of drawing causal inferences from observational data.

Testing for CHD before kidney transplant does not reduce the risk of adverse outcomes during the early posttransplant period, the quasi-experimental study concludes. The results, added to ongoing interventional studies, "may pave the way to deescalating CHD testing before kidney transplantation," the researchers conclude [Cheng XS, et al. Association of pretransplant coronary heart disease testing with early kidney transplant outcomes. *JAMA Intern Med* 2023; 183:134–141. doi: 10.1001/jamainternmed.2022.6069]. ■

Traditional Risk Factors Explain Higher CKD Risk in Black Americans

The higher incidence of chronic kidney disease (CKD) among Black compared with White US adults is largely explained by traditional CKD risk factors, concludes a study in the *American Journal of Kidney Diseases*.

The analysis included 4198 Black and 7799 White participants from the "Reasons for Geographic and Racial Differences in Stroke" (REGARDS) study. All were at least 45 years old at enrollment in 2003–2007, with a baseline estimated glomerular filtration rate (eGFR) greater than 60 mL/min/1.73 m^2. CKD incidence and risk factors were compared between Black and White participants. The study definition of CKD was eGFR of less than 60 mL/min/1.73 m^2 with a decline of at least 40% from baseline or kidney failure. At 9.4 years' follow-up, CKD incidence was 9%, ranging from 4% for adults aged 45 to 54 years to 18% in those aged 75 or older. Black race was associated with higher risk of eGFR change during follow-up, after adjustment for age, sex, and race.

However, the racial association was no longer significant in a fully adjusted model accounting for all risk factors. Independent risk factors for CKD included age, low income, residence in the Southeastern "Stroke Belt" states, systolic blood pressure, body mass index, diabetes, hyperlipidemia, and albuminuria.

Risk factors were similar on analysis of CKD incidence. For both eGFR change and CKD, albuminuria was a stronger risk factor in Black compared with White adults and for participants living in the Stroke Belt.

There are known racial disparities in the prevalence and associated costs of CKD in the US population. There are few data on the incidence of and risk factors for CKD in a contemporary US population, including possible differences by race, sex, or region.

Modifiable risk factors, such as diabetes, hypertension, and obesity, account for most of the increased incidence of CKD among Black Americans, the new results suggest. Further study is needed to clarify the importance of albuminuria and Stroke Belt residence as risk factors for incident CKD and eGFR decline [Cheung KL, et al. Risk factors for incident CKD in Black and White Americans: The REGARDS study. *Am J Kidney Dis*, published online ahead of print January 5, 2023. doi: 10.1053/j.ajkd.2022.11.015; https://www.ajkd.org/article/S0272-6386(23)00005-7/fulltext]. ■

NephMadness 2023: It's Back

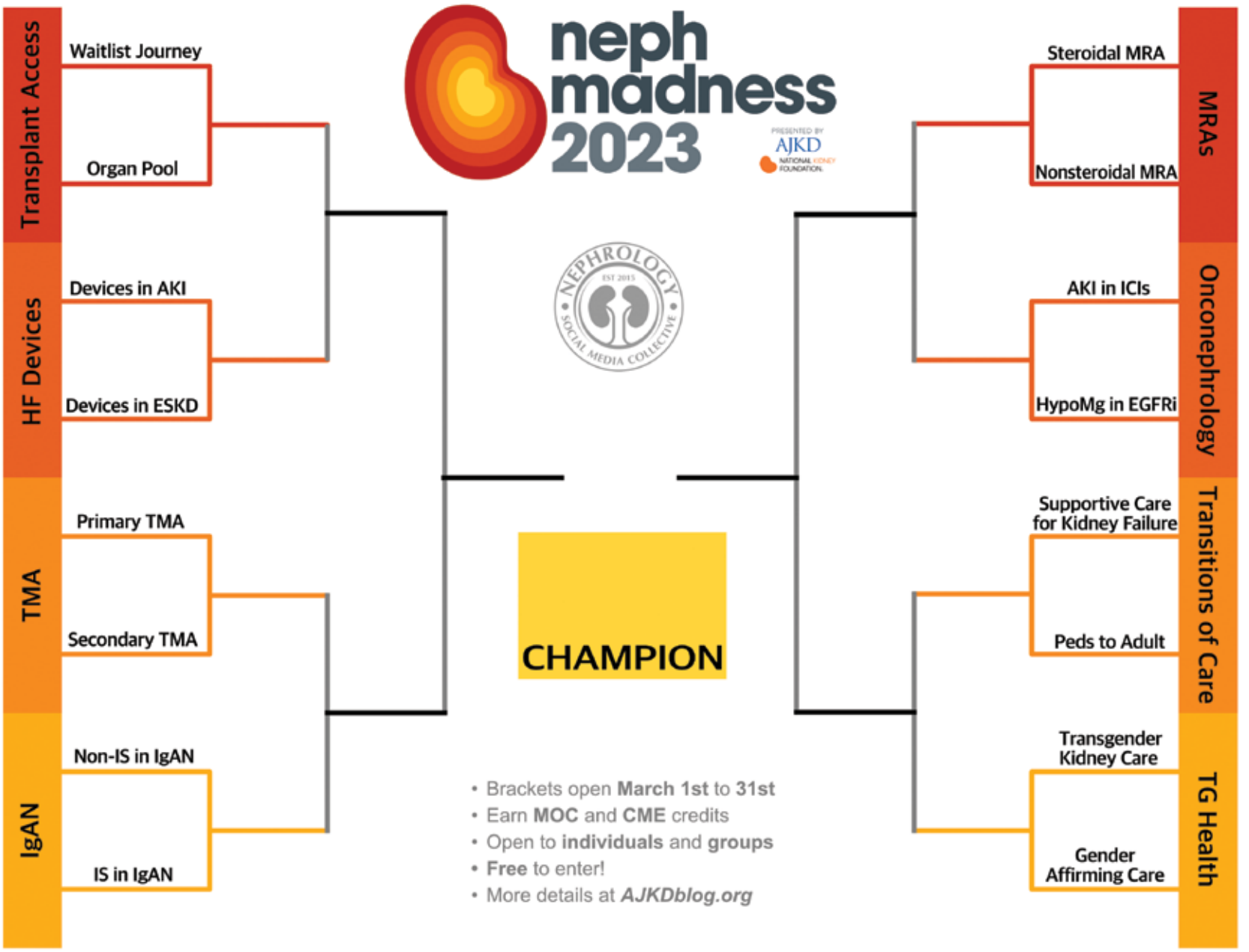
NephMadness signals the beginning of spring—a time to get together to celebrate, and debate, the many advances in our field. NephMadness is a great way for your practice, division, department, residency, or fellowship program to showcase your knowledge of kidney health.

NephMadness, now in its 11th year, is a single-elimination tournament consisting of 16 nephrology concepts (decreased from the 32 teams last year), divided into 8 distinct regions. NephMadness serves as a vehicle to discuss and debate each topic during the month of March. We made it easy for your group to throw a NephMadness party by making a PowerPoint presentation describing each of the concepts. Go on social media using the hashtag #NephMadness to engage with the online nephrology community. NephMadness will also feature eight podcasts covering each of the regions in what is called a PodCrawl, featuring podcasts by The Nephron Segment, Freely Filtered, Core IM, The Curbsiders, The Cribsiders, Cardionerds, The Fellow on Call, and the International Society of Nephrology (ISN) Global Kidney Care Podcast.

Fill out your brackets (individually or as a team), and see if your picks match the nine-member Blue Ribbon Panel consisting of a diverse group of fellows, nephrologists, and kidney patients. Winners of each match-up will be determined by this group. The four rounds of voting will finish in the crowning of the NephMadness champion. You can even get Continuing Medical Education (CME) and Maintenance of Certification (MOC) credit! NephMadness bracket submissions are open from March 1 through March 31, 2023.

This year's regions are Transplant Access, Heart Failure (HF) Devices, Thrombotic Microangiopathy (TMA), IgA Nephropathy (IgAN), Mineralocorticoid Antagonists (MRAs), Onconephrology, Transitions of Care, and Transgender (TG) Health. (Figure 1).

Figure 1. 2023 NephMadness Tournament



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C3G, complement 3 glomerulopathy; IgA, immunoglobulin A.

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Detective Nephron

Detective Nephron, world-renowned for his expert analytic skills, trains budding physician-detectives in the diagnosis and treatment of kidney diseases. Mackenzie Ula Densa, a budding nephrologist, plans to present a new case to the master consultant.

Mac runs into the office of Dr. Nephron, moving everything in his path, asking excitedly for Detective Nephron.

Nephron (*enjoying his cup of steaming coffee*) Calm down! Why are you in such a hurry?

Mac A 28-year-old man on hemodialysis is in the emergency room.

Nephron (*abruptly interrupted, rolling his eyes*) Hemodialysis? I know the answer already…volume overload or insufficient dialysis.

Mac Not at all! This case is extraordinary, with all its letters!

Nephron Really? Your enthusiasm deserves my attention. On previous occasions, when I see you like this, you always surprise me. What do you have for me this time, my apprentice (*as he slowly resumes sipping his cup of coffee*)?

Mac The patient was sent from his hemodialysis unit because during his session, he developed bluish discoloration of his skin and oxygen desaturation of 46% with a headache, which did not improve despite supplemental oxygen of up to 6 liters of nasal cannula.

Nephron (*surprised look*) Easy…pulmonary thromboembolism…an expected event given the great thrombogenicity generated by the hemodialysis circuit. It is not as extraordinary as you think, my dear apprentice. However, the cyanosis has me perplexed.

Mac We thought the same when he arrived at the emergency department, but how do you explain that all seven dialysis session partners simultaneously experienced the same symptoms and signs? The medical director of the unit decided to suspend the session and sent everyone for evaluation at emergency services of different hospitals.

Nephron (*after 3 seconds of silence*) This is getting interesting; give me more information please.

Mac In the report, they write, and I quote: "The blood in the circuit turned chocolate-colored; the patients presented with cyanosis, dizziness, and slight dyspnea, and all of them had low oxygen saturation when measured with two different pulse oximeters." Upon arrival at the emergency room, our patient presented with a blood pressure of 126/86 mm Hg, heart rate of 96 beats per minute, respiratory rate of 22 breaths per minute, temperature of 36.2°C, and pulse oxygenation of 882% on room air; the lungs were clear; and the lung POCUS evaluation did not reveal too many B-lines. His exam was not noted for any cardiac murmurs or edema. The hemoglobin level was 9.5 g/dL; the last value 1 month ago was 11.8 g/dL.

Nephron Cyanosis with relatively decent peripheral oxygen saturation (SpO_2)? How interesting. Cyanosis is caused by high levels of deoxygenated hemoglobin circulating within the superficial dermal capillaries and subpapillary venous plexus. Central cyanosis is generally of great concern, as it requires reduced arterial oxygen saturation or abnormal hemoglobin derivatives to be present. This problem can be approached in two ways. The first focus is on pulmonary and cardiac abnormalities, which do not seem to be the etiologies of this case. The second group focuses on abnormalities related to hemoglobin.

Mac The chest X-ray and EKG were both unremarkable. An arterial blood sample was done on room air and showed chocolate-colored blood with a pH of 7.54, $PaCO_2$ of 31 mm Hg, PaO_2 of 108 mm Hg, and HCO_3 of 29 mEq/L. When 4 liters of nasal cannula was added, there was a slight increase in oxygen saturation (97%).

We need to focus on something that all the patients would have been exposed to since they all had the same signs and symptoms.

Nephron (*shocked*) I completely agree with you. The hemodialysis session was the point of convergence. But what did all of them share? The unit's air conditioning and the dialysis fluid! Call the hemodialysis unit and ask if this has happened before and if any events in the last few hours have been conspicuous.

A few minutes later, Mac returns.

Mac They tell me that this has never happened before. The only new, relevant finding is that last night, the unit received the monthly maintenance cleaning process of the water system.

Nephron That matters a lot! Remember that municipal water is impure and presents a risk for contamination. The water must be treated thoroughly before it can be used as a dialysate. There are standards that regulate this purification process. Please request a measurement of chlorine derivatives in the water, and verify the patency of the carbon filters and the reverse osmosis (RO) processes.

Mac The dialysis unit told us that the carbon filters were changed just 4 months ago (the average durability is 6 months) and that its RO machine works perfectly. The dialysis unit already requested an independent evaluation of chemical derivatives in the water.

Nephron Let's get back to the patient. Remember that pulse oximetry relies on the red and infrared light absorption characteristics of oxy- and deoxygenated blood (hemoglobin); therefore, its accuracy is affected in those patients with peripheral cyanosis (falsely low PaO_2). This can be circumvented with an arterial blood gas sample, as co-oximetry uses at least four wavelengths of light to measure not only oxy- and deoxy-hemoglobin but also other forms of hemoglobin (e.g., carboxyhemoglobin and methemoglobin). Please, my apprentice, take an arterial blood gas with co-oximetry.

Minutes later, Mac returns with the arterial blood co-oximetry in his hand and a huge smile on his face. Nephron turns to stare at him and after 2 seconds of silence…

Mac The methemoglobin value is high at 7.9%; normal is <1.0%. This could explain the clinical presentation!

Nephron Indeed, methemoglobinemia has this clinical presentation. In these patients, it is important to distinguish between congenital and acquired causes. In this case, it is obviously acquired. Dear apprentice, chloramines derived from chlorine and ammonium are usually added to municipal water as disinfectants and may contaminate dialysis fluid and enter the blood of dialysis patients leading to hemolytic anemia or in some cases, methemoglobinemia. In most dialysis centers, activated carbon filters are used to remove chlorine and chloramine, which are not usually removed by RO. Correct functioning of the carbon filter in the dialysis unit water-treatment room is essential for this process. One important aspect of the proper functioning of carbon beds within the carbon filter is the contact time of the water with the carbon. At least 10 minutes are required for thorough removal of both chlorine and chloramine. This may require adjustment of the pH of the feed water and assurance that no other substances are preventing the chloramine to reach the carbon surface (such as corrosion inhibitors).

Mac How does this lead to anemia?

Nephron The chloramines are a group of compounds that contain chlorine and nitrogen. There are three different forms: monochloramine (NH_2Cl), dichloramine ($NHCl_2$), and trichloramine (NCl_3). They are easily converted from one to another. Chloramines are yellow to colorless liquids with a strong ammonia odor. Chloramines, especially monochloramine, have been used as water disinfectants. Monochloramine is a weaker disinfectant than chlorine but is more stable. Because of this, monochloramine provides better protection against bacterial regrowth in systems with large storage tanks and dead-end water mains. Chloraminated water that meets local standards is safe to use for drinking, bathing, cleaning laundry, and other household activities but at certain levels, can lead to toxicity.

In toxic amounts, the chloramines can liberate hypochloric acid, hypochlorite, and free oxygen radicals. In addition, chloride and chlorates are oxidants that reduce glutathione, further enhancing the oxidative effect of free radicals, and can produce organic halogenation by chlorinating the amino acids of structural proteins (spectrin, a large cytoskeletal protein, and hemoglobin), changing the shape of erythrocytes and causing the formation of micronuclei, followed by complete hemolysis, resulting in Heinz bodies. The oxidation of hemoglobin by chlorates and chlorides leads to formation of methemoglobin, which is an altered form of hemoglobin. The iron molecule in this remains in an oxidized state (ferric /Fe^{3+}), which alters its ability to transport oxygen to tissues leading to oxygen desaturation, cyanosis, and ultimately hemolytic anemia.

Mac Hemolytic anemia? That explains the drop in hemoglobin compared with the previous month. I will request that the hematology service review the case.

Nephron Let's not waste more time while the hematologists search for hemolysis. Let's treat the methemoglobinemia, administer intravenous methylene blue, and check methemoglobin levels 1 hour after application. Methylene blue reacts with red blood cells to form leukomethylene blue, which is a reducing agent of oxidized hemoglobin converting the ferric ion back to its oxygen-carrying ferrous state.

Mac returns 2 hours later.

Mac The new post-methylene blue methemoglobin values decreased and are now at normal levels, 0.7%, like magic! The hematologist found Heinz bodies in his peripheral blood smear. After a transient decrease during methylene blue administration, SpO_2 gradually improved to 100% over the next 20 minutes.

The next day, Mac walks into Nephron's office with a sheet.

Nephron Does that sheet have important information?

Mac Yes. It is the quantitative report of the chloramine values in the water of the hemodialysis unit, which are elevated to 0.78 mg/L (when what is allowed is <0.5 mg/L). With this, we can conclude that it was a case of methemoglobinemia acquired by chloramine poisoning. I think the carbon filters were defective. Something did not go as planned.

Nephron What an interesting and unexpected case. Hemodialysis is not a procedure that is free of risks and complications. The blood of patients is exposed to a large amount of municipal water, 100–200 liters per session, and the only barrier between the blood of the patient and the dialysate is a small, permeable filter. Given these complications, the quality of the water used for hemodialysis should be monitored, ensuring limited exposure to potentially harmful contaminants. The most effective way to remove chlorine and chloramine from municipal water is the activated carbon filter. Older methods of activated charcoal, sodium bisulfite, and/or ascorbic acid are rarely used now. We have a lot of processes of cleaning the water: RO, deionization, and the carbon filter. All are essential in their functioning to provide safe water to the patient.

Mac (*with excitement*) Well put!

A few hours later…

Mac The carbon filter was defective. It is being rectified at this moment.

Nephron (*laughing*) There you go again! Fascinating diagnosis and quick thinking, my apprentice. Do no harm first, my friend, do no harm! Let's have some NY-style coffee today. ■

Detective Nephron was developed by Kenar D. Jhaveri, MD, professor of medicine at the Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, Hempstead, NY. Special thanks goes to Dr. Jonathan Samuel Chávez Iñiguez, professor at the University of Guadalajara, University Center for Health Science, Guadalajara, Jalisco, México, for submitting this case discussion. Thanks also go to Dr. Rimda Wanchoo, professor of medicine at the Donald and Barbara Zucker School of Medicine at Hofstra/Northwell for her editorial assistance. Please send correspondence regarding this section to: kjhaveri@northwell.edu or kdj200@gmail.com.

ASN Encourages USPSTF to Adopt CKD Screening

By Lauren Ahearn

Following nearly a decade of advocacy by ASN and other members of the kidney care community for federal support of routine screening to identify kidney diseases and intervene earlier to stop or slow progression, ASN was pleased to comment on the U.S. Preventive Services Task Force's (USPSTF's) Draft Research Plan: Chronic Kidney Disease: Screening (1) on February 15, 2023.

Focused on improving health across the nation, USPSTF offers evidence-based recommendations about clinical preventive services. The release of this draft research plan follows USPSTF's addition of chronic kidney disease (CKD) screening to its list of preventive services under active consideration in 2022. This is not the first time USPSTF has considered the development of screening guidelines for CKD. In 2012, USPSTF released a similar proposed research plan for CKD screening but ultimately recommended against the formation of official guidelines.

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's comments addressed both the individual elements and questions of the research plan. The comments can be grouped into nine areas of top concerns for ASN:

1. **Scope of evidence review -** The most robust evidence for CKD screening comes from targeting those with CKD risk factors such as hypertension and diabetes. Despite this fact, the current USPSTF proposed research plan excludes studies in which patients were selected due to these preexisting conditions. ASN expressed very strong concern regarding this exclusion and firmly recommended that the research plan be amended to review the existing evidence based around CKD screening in at-risk populations. CKDs are associated with extreme comorbidity across a wide range of conditions. The exclusion of studies that focus on these at-risk populations would lead to an incomplete and misleading assessment of CKD, ASN maintained.
2. **Tests used for screening -** The proposed research plan lacked clarity regarding which tests would be used to assess CKD. ASN reminded USPSTF that CKD is not merely a number, and ASN strongly recommended that USPSTF evaluate and consider CKD screening using both glomerular filtration rate estimation and proteinuria/albuminuria measurement.
3. **CKD stages -** ASN recommended that USPSTF add CKD stage 4 to its draft plan since the current plan only included evaluation of CKD stages 1–3. ASN acknowledged that there often is less precision and reliability in diagnosing the earlier stages of CKD and stressed the importance of considering patient preferences when screening for early indication of CKD.
4. **Harm and disparities -** USPSTF outlined a plan to examine the benefits and harms of CKD screening, specifically in socially disadvantaged and marginalized communities, yet ASN believes there was a lack of clarity regarding the definition of the terms "harm" and "disparities." ASN drew attention to this issue and encouraged USPSTF to use well-defined terminology during this evaluation. ASN contended that any harms associated with screening are important to consider, but those harms must be properly assessed against the serious and potentially fatal consequences of not detecting and delaying progression of CKD.
5. **Education and pharmacological and non-pharmacological interventions -** ASN highlighted the fact that the proposed study failed to address patient education and pharmacological and non-pharmacological interventions. Simply identifying a disease is futile, ASN observed, unless it is linked to actions that improve clinical outcomes. Since the last time USPSTF considered CKD screening, kidney care has witnessed a revolution in novel therapeutics for CKD to slow disease progression, including 1) sodium-glucose co-transporter 2 inhibitors, 2) nonsteroidal mineralocorticoid antagonists, and 3) glucagon-like peptide-1 receptor agonists. ASN strongly urged the evidence review to address both pharmacological and non-pharmacological interventions.
6. **Access to care -** Individuals of at-risk populations often face challenges when it comes to accessing and affording early preventive care. ASN believes that USPSTF and the broader kidney care community need to explore this intersection of screening with access to care.
7. **Social determinants of health (SDOHs) -** Health systems are increasingly recognizing the importance of screening individuals for adverse SDOHs. ASN recommended that USPSTF's research explore SDOHs and their resulting impact on individuals and the progression of CKD to kidney failure to ensure a more comprehensive approach to its recommendation.
8. **COVID-19 -** Individuals with kidney diseases and other chronic illnesses are at higher risk of more serious illness and complications from COVID-19. ASN recommended that USPSTF incorporate a review of the potential health benefits for preventing severe COVID-19 illness (along with other serious infections) into its research plan.
9. **Study time frame -** USPSTF did not define a timeline for the proposed research plan. ASN stressed the importance of an extended timeline to effectively evaluate the potential harms and benefits of CKD screening.

ASN joined 16 members of the Coalition for Kidney Health, including the American Heart Association, the National Kidney Foundation, and the Renal Physicians Association, in a coalition comment letter to USPSTF at the same time (2). The comments and recommendations of both letters were closely aligned.

Kidney care is at an inflection point because of the many advancements made since the USPSTF last considered CKD screening in 2012. ASN advocated that now, more than ever, it is imperative to address kidney diseases through prevention, detection, and management. ASN wholeheartedly commended USPSTF for undertaking this important initiative and stands ready to provide assistance in any way possible. To read ASN's full comments on USPSTF's Draft Research Plan: Chronic Kidney Disease: Screening, please visit the ASN Advocacy and Public Policy home page at https://www.asn-online.org/policy/webdocs/02.15.23.USPSTF.Letter.pdf.

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INFECTIOUS DISEASES AND THE KIDNEY

By Mayuri Trivedi and Itunu Owoyemi

Infectious diseases have been known to be the cause and effect of kidney diseases for a long time. Kidney damage occurs through direct invasion or via immune-mediated injury. Patients with underlying kidney diseases, including kidney transplant recipients, are known to have a greater chance of serious and atypical infections. Interestingly, the spectrum of infections and kidney diseases varies widely across the world. Kidney diseases depend on local epidemiological, environmental, and socioeconomic factors. Immune diseases caused by infections are still rampant in many parts of the world with very little data directing their treatment protocols.

The development of highly effective therapies for treating infections has also led to increased utilization of organs from donors with infections such as hepatitis B and C.

In this special issue of *Kidney News*, we highlight the interesting spectrum of infections and kidney diseases around the world. ■

Mayuri Trivedi, MD, MBBS, DNB, DM, is with the Lokmanya Tilak Municipal General Hospital, Mumbai, India. Itunu Owoyemi, MBBS, is a transplant nephrologist at The University of Kansas Medical Center, Kansas City, KS.

The authors report no conflicts of interest.

***Plasmodium Vivax* and the Kidney:** The Not-So-Benign Parasite

By Sayali B. Thakare

Despite consistent public health efforts for over half a century for mitigation of its spread, malaria—caused by five species of plasmodium—remains a widely prevalent disease affecting 84 countries as of today (1). Newer challenges continue to plague malaria control programs, with a recent example being disruption of services due to the COVID-19 pandemic. An undeniable rise in the incidence, morbidity, and mortality attributable to *Plasmodium vivax* in the last decade has led to a renewed interest in its pathogenicity and an acute need of realistic estimates of its global disease burden (2, 3).

P. vivax is the most geographically spread of malarial parasites. Although the World Health Organization (WHO) captures a decline in case proportions of *P. vivax* (1), an increasing body of evidence emphasizes the not-so-benign nature of vivax malaria. *P. vivax* has broken the evolutionary barrier and is increasingly reported from Duffy blood group-negative sub-Saharan Africa (4, 5). The WHO's global technical strategy for malaria operates under a highly ambitious target of eliminating malaria from 35 countries by 2030 and reducing incidence and mortality rates worldwide by 90%. *P. vivax* has been recognized as a major epidemiological challenge to achieving these targets, chiefly due to key differences in parasite and vector biology (3) (Table 1).

Likewise, host factors contribute to enhanced pathogenicity in vivax malaria. Pronounced inflammatory response despite low parasitemia (6); higher cytokine production (interferon-γ/interleukin-10 ratio and C-reactive protein) (7); endothelial stimulation (8); capillary sequestration (8); and persistent hepatic, splenic, and bone marrow reservoir formation lead to severe disease with multi-organ dysfunction not unlike that with *Plasmodium falciparum*. *P. vivax* disproportionately affects other high-risk groups, such as pregnant women and children, in areas of high transmission (3, 9–11).

Cytoadherence leading to formation of rosettes and clumps is implicated in impaired microcirculation and organ damage in vivax malaria. Coupled with hypovolemia and shock, this contributes to acute kidney injury (AKI) (Figure 1). Malarial kidney biopsies show acute tubular necrosis, acute cortical necrosis, thrombotic microangiopathy, glomerulonephritis, or tubulo-interstitial nephritis (12–17). Postinfectious glomerulonephritis (18) and crescentic glomerulonephritis (19) have also been reported. Recent studies have demonstrated the presence of *P. vivax* DNA in kidney biopsies (14). Sequestrated parasites in donor organs can lead to symptomatic disease in transplant recipients (20–23). Curiously, one of the early reports describes synchronous, high-grade fever in two kidney transplant recipients attributed to *P. vivax* acquired from the same deceased donor (24).

Multiple large case series of malarial AKI from the Indian subcontinent report the proportion of *P. vivax* as 15.2% (25), 20.4% (26), 41.79% (27), and 54.4% (28). Renal replacement therapy was required in 33.3%–76.6% of these cases. Mortality was observed to be 15%–20%. Predictive factors for mortality var-

Continued on page 20 >

Plasmodium Vivax and the Kidney

Continued from page 19

ied across studies; however, most pointed toward advanced multi-organ dysfunction reflecting severe malaria. Prognosis of vivax malaria-associated kidney injury is favorable. Approximately two-thirds of cases show complete recovery within 2–3 weeks. Appropriate anti-malarial drugs, anti-hypnozoite therapy (Primaquine), non-dialytic supportive care and timely initiation of renal replacement therapy for AKI (most effectively, hemodialysis), and treating multi-organ dysfunction are the cornerstones of management.

The conventional perspective of human malaria needs to evolve to accommodate the obscure disease burden and changing epidemiology of vivax malaria. *P. vivax* has proven to be a tenacious parasite. Newer research directed towards detection, accurate estimation of morbidity and mortality, preventive, and curative therapy is imperative for further progress.

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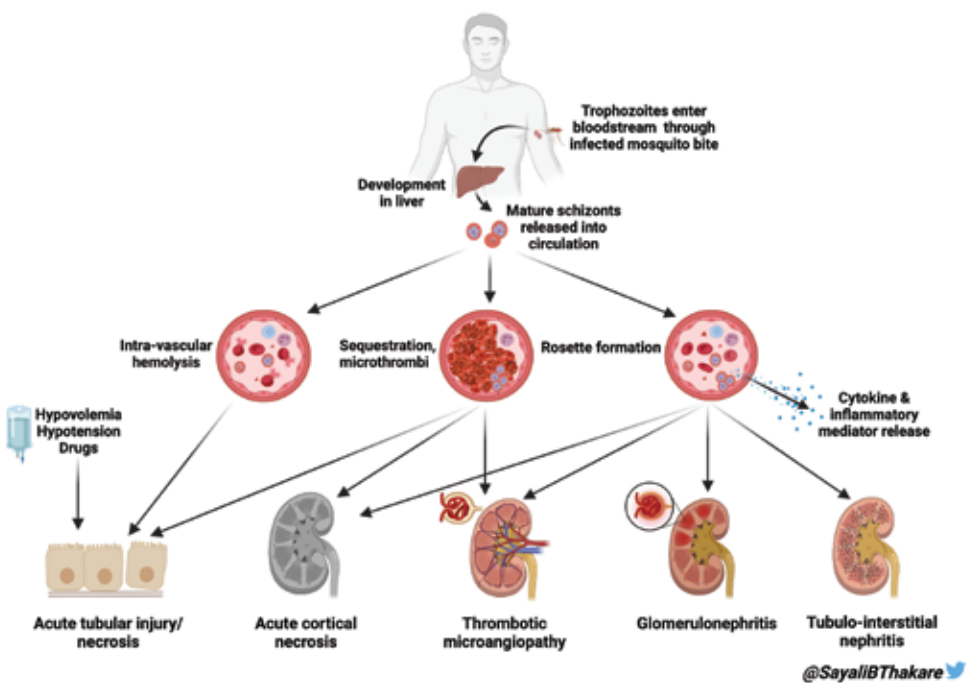
Table 1. Challenges to public health measures for control of vivax malaria

Vector biology	
1.	Diverse anopheline vectors with wide geographical range (challenge to vector control)
2.	Exophilic day-time biters (ineffectiveness of control measures directed toward *P. falciparum*, such as insecticide-treated bed nets or indoor residual spraying)
3.	More efficient transfer of gametocytes to vectors at lower blood densities
4.	Rapid development in mosquito midgut across a wide range of temperatures (spread to relatively colder subtropical and temperate climates, e.g., Korea, Mexico, south Brazil, and China)
Parasite biology	
1.	Acquisition of early-life immunity due to recurrent infections (subclinical disease causing imprecise estimates of disease burden)
2.	Concurrent sexual and asexual parasitemia (potential to disseminate infection prior to detection)
3.	Ability to migrate beyond venous sinuses during active disease (lower parasitemia, suppressed clinical disease, and reservoir formation in spleen and bone marrow with potential for recrudescence and transmission)
4.	Dormant liver stage (transmission during recurrence)
5.	Reduced sensitivity of rapid diagnostic tests (lower detection and false estimates)

Figure 1. Pathophysiology of renal involvement in vivax malaria



A Randomized Controlled Trial on Corticosteroid Efficacy in IRGN—A Commentary

By Natarajan Gopalakrishnan and Tanuj Moses Lamech

Infection-related glomerulonephritis (IRGN) is typically considered an immune-complex glomerulonephritis. Previously known only as "post-streptococcal" glomerulonephritis, it is now recognized that any infection can trigger immunologically mediated glomerular injury, which can even occur concurrently with the infection that precipitated it.

Observational data suggest that a significant number of patients with IRGN experience incomplete or even non-recovery of kidney function (1–3). Consequently, the possibility that the natural history of the disease might be amenable to manipulation with broad immunosuppression using corticosteroids was entertained by many authors (4–7). In fact, steroid administration became standard clinical practice in many clinical settings, despite the absence of clear evidence of its benefit (8, 9).

The trial

The single-center, open-label, parallel-arm, 1:1 randomized controlled trial, reported in *Kidney International Reports* (10), included adults with IRGN and a serum creatinine of >1.5 mg/dL. Patients who met trial inclusion and exclusion criteria were randomly assigned to receive either corticosteroids plus supportive care (intervention arm) or supportive care alone (control arm). Steroids were administered in the form of intravenous methylprednisolone, 1 g daily for 3 days, followed by oral prednisolone, 1 mg/kg/day for 1 month, and then a slow taper of 5 mg per week.

The disruptions to routine clinical care that ensued during the COVID-19 pandemic necessitated the premature termination of the trial in May 2020, at which time, 52 patients had undergone randomization. At 6 months post-randomization, the primary end point of complete renal recovery (defined as an estimated glomerular filtration rate >60 mL/min/1.73 m^2) was achieved in 65.4% of patients in the intervention arm and in 53.8% of patients in the control arm—a difference that did not reach statistical significance. Adverse events, however, were significantly higher in the steroid arm, with infectious complications being the most frequent, followed by other signs of steroid toxicity.

Discussion

Although the trial's primary outcome was not met, it should be kept in mind that the study was underpowered, as it did not reach its target sample size. A potential benefit of steroids in specific patient subsets, such as those with crescentic IRGN and dialysis-requiring IRGN, cannot therefore be ruled out. The significant adverse effects of steroids, particularly infection risks, should give us pause, particularly when treating patients with long-standing diabetes. Furthermore, the steroid doses used in the trial are, by today's standards, exceptionally high, although they were in keeping with standard practice at the time of the trial design.

Our interpretation of the data is that the efficacy of steroids remains unclear, whereas the potential harms are evident. Nevertheless, because of the otherwise poor prognosis in certain specific subgroups of patients, such as those with crescentic IRGN or rapidly progressive glomerulonephritis, we suggest that, in the absence of better data, a short, closely supervised trial of steroids could still be attempted at the discretion of the treating clinician. However, we suggest that the doses used be much lower than those used in the previous trial.

Potential avenues for further research

The lack of a specific diagnostic biomarker and the heterogeneity of the histopathology in patients with IRGN necessitate continued reliance on the Nasr et al. diagnostic criteria (9). This results in a non-homogeneous study population that complicates the interpretation of trial data. Recent literature suggests that anti-factor B antibodies may help to specifically identify cases of acute post-streptococcal glomerulonephritis (11). Identification of a similar biomarker for other forms of IRGN would simplify enrollment in future clinical trials.

Given the increasing recognition of the primary role of the complement system in driving the pathogenesis of at least some forms of IRGN, it follows that perhaps therapies specifically targeting the complement cascade may be more appropriate than broad immunosuppression with corticosteroids. However, this currently remains within the realm of speculation.

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The authors report no conflicts of interest.

. . . [A]ny infection can trigger immunologically mediated glomerular injury, which can even occur concurrently with the infection that precipitated it.

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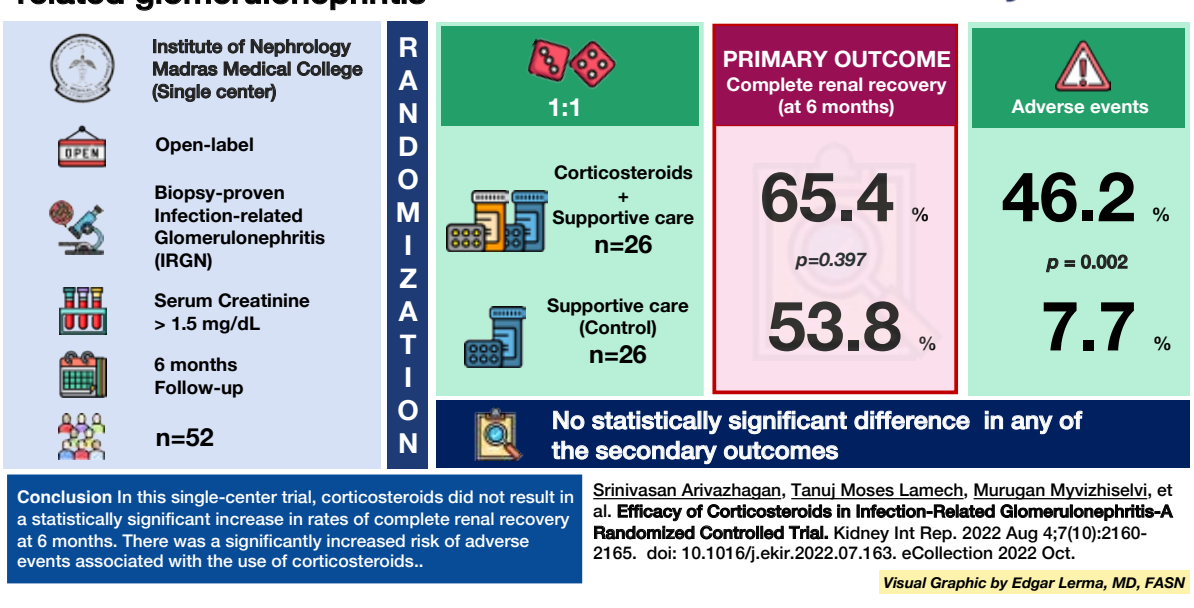

Adenovirus Nephritis in Kidney Allograft Recipients: An Important Differential Diagnosis

By Krishna Kumar Agrawaal and Priti Meena

Viral infections are an important cause of morbidity and mortality in kidney transplant recipients. Adenovirus, a double-stranded DNA virus, is a rare cause of infection in this group of patients. The prevalence of asymptomatic adenovirus viremia in kidney transplant recipients is estimated to be approximately 6.0%–6.5% (1). Research on adenovirus as the source of nephritis has been limited, making it an understudied cause. Nevertheless, a recent study by Jagannathan et al. (2) has provided an in-depth look at the issue.

This study was a retrospective, multicenter analysis of 11 kidney transplant recipients with adenovirus nephritis from 2010 to 2021. The authors compared the pathologic and transcriptomic characteristics of adenovirus nephritis cases with that of BK virus nephropathy. Because these were all "for cause" kidney biopsies, the entire cohort had elevations in serum creatinine. A majority of the individuals also exhibited fever and hematuria. The adenovirus DNA levels were all high. The median adenovirus DNA levels were 28,250 (interquartile ranges [IQRs]: 3525-75,550) copies/mL in the plasma and 1,900,000 (IQRs: 468,000-15,000,000) copies/mL in the urine. Histopathology findings revealed tubulointerstitial inflammation composed of a mixture of mononuclear leukocytes, neutrophils, and eosinophils involving cortex and medulla. All adenovirus nephritis cases showed scattered, smudgy nuclear viral inclusions. Immunohistochemistry for adenovirus in the tubular epithelial cells was positive.

The distinguishing characteristics of adenovirus nephritis compared with BK virus nephritis were more granulomas and less tubulointerstitial scarring in adenovirus nephritis; furthermore, adenovirus nephritis cases showed more rapid clearance of viral DNA from plasma (Table 1). Although adenovirus nephritis showed a more aggressive inflammatory response compared with BK virus nephropathy, it rarely resulted in allograft failure. Adenovirus infection mainly occurs in the first year of transplant when the doses of immunosuppression are high, although it can present after 1 year also, as demonstrated in another study (3). Hemorrhagic cystitis is the most common presentation of adenovirus nephritis, but it can also present as mass lesion, obstructive uropathy (4). Currently, Kidney Disease: Improving Global Outcomes (KDIGO) does not recommend routine screening in kidney transplant recipients, but based on this study, in kidney allograft recipients who present with fever and hematuria, adenovirus nephritis is an important differential diagnosis. Treatment of adenovirus nephritis in this case series included reduction in immunosuppression, intravenous immunoglobulin, and less commonly antiviral agents, like cidofovir or valganciclovir. Thus, this study showed that there is improved allograft survival in kidney transplant recipients with adenovirus nephritis despite aggressive neutrophil-rich infiltrates. ■

Table 1. Differences in characteristics of adenovirus nephritis and BK virus nephropathy

Characteristics	Adenovirus nephritis (n = 11)	BK virus nephropathy (n = 33)	p value
Microhematuria	10 (91%)	4 of 21 (19%)	<0.001
Granulomas	9 (82%)	0	<0.001
Pure tubulointerstitial nephritis	1 (9%)	32 (97%)	<0.001

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The authors report no conflicts of interest.

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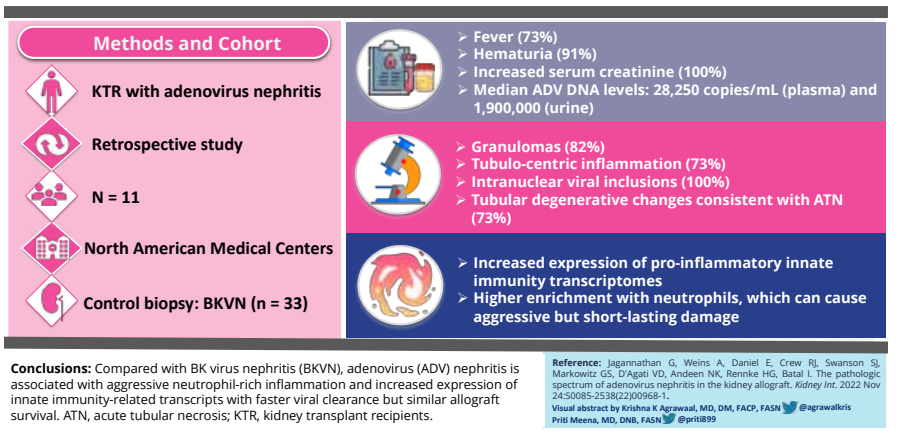

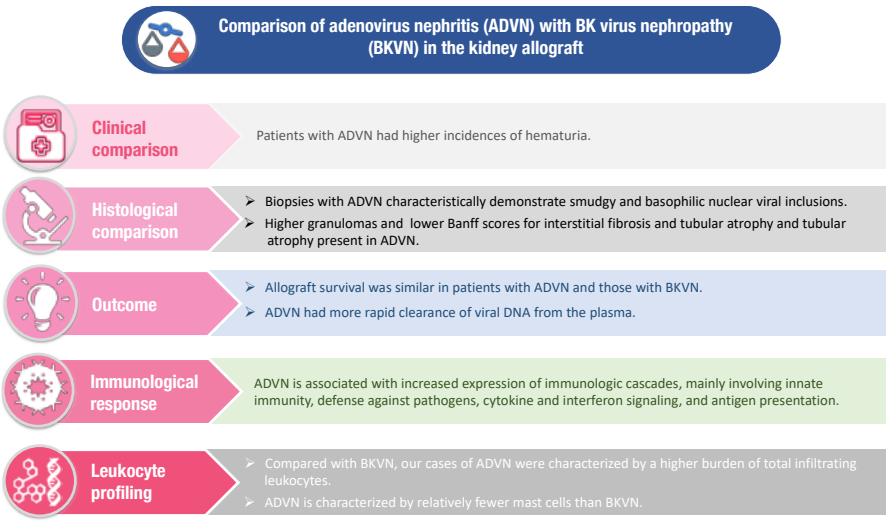

Tuberculosis Post-Transplantation: A Real-World Issue in Developing Countries

By Sandhya Suresh and Sowrabha Rajanna

Although the first descriptions of tuberculosis (TB) date back to ancient times, diagnostic and therapeutic challenges persist in the management of this infection. Transplant recipients, with their net state of immunosuppression, are at risk of reactivation of latent TB, may not have a typical clinical presentation, and have higher risk of complications due to TB as well as to treatment for TB (1, 2). The number of transplants is on a rising trend in most regions around the world including in developing countries, many of which are endemic for TB (3, 4). TB is likely to remain a significant challenge in these countries.

Defining the extent of the problem

Among recipients of solid organ transplants (SOTs), the incidence of TB after transplant is estimated to be 20–74 times more frequent than that in the general population. Incidence varies depending on the local endemicity of TB, with low endemic regions reporting rates of 0.5%–6.4% compared with rates as high as 15.2% in areas of high endemicity (1). Among kidney transplant recipients, the prevalence of TB ranges from 4.4% (1.3%–14.7%) in Asia and 2.4% (1.7%–4.5%) in Latin America to 0.5% (0.4%–1.6%) in Western Europe and 0.4% (0.3%–0.4%) in North America (2). Underreporting as well as underdiagnoses are significant problems in developing countries, and the actual burden of posttransplant TB may be higher than estimated (4, 5). For example, in the Indian subcontinent, nearly half of the adult population is thought to have been infected with *Mycobacterium tuberculosis*. With over 4000 kidney transplants occurring in this population every year and with as many as one in every seven recipients likely to be affected by TB after transplant, the absolute number of patients with posttransplant TB is presumed to be significant (6).

What are the risk factors for posttransplant TB?

In addition to the epidemiological risk factors, several other patient- and transplant-related factors contribute to the risk. Diabetes mellitus, chronic liver disease, malnutrition, past history of untreated TB, hepatitis C infection, and other co-existing infections are associated with higher risk of posttransplant TB in SOT recipients (6, 7). The organ transplanted is also a contributing factor, with lung transplant recipients at 5.6 times higher risk of posttransplant TB in comparison with other SOT recipients (1). Ethnicity may be an important determinant of risk, as studies in South Asians have shown an association between certain human leukocyte antigen (HLA) phenotypes and development of TB after transplant (8).

In most developing countries where reactivation of latent infection is the primary mode of acquiring posttransplant TB, the net state of immunosuppression plays a major role. Use of T cell-depleting antibodies and anti-rejection treatment is associated with higher risk of developing this infection (7).

The type and intensity of recipient screening for TB also determine the degree of posttransplant risk (1). Considering the high endemicity in developing countries, there is a need for better screening for TB among both transplant candidates and donors.

Why is posttransplant TB significant?

• *Challenges in screening for latent TB*

There is a paucity of evidence-based guidelines for screening recipients for latent TB in regions of high endemicity (7). Most international guidelines recommend one of the following tests, both of which are based on the demonstration of cellular immune response against *Mycobacterium tuberculosis* antigens, and provide indirect evidence of infection: tuberculin skin test (TST) or interferon-gamma release assay (IGRA). Although they have shown good predictive value in countries of low endemicity, there are several limitations to their routine use for screening in developing countries (1).

1. Both tests do not require the presence of viable bacilli, which are sources for future infection in transplant candidates (9).
2. In populations with widespread Bacillus Calmette–Guérin vaccination, childhood exposure to tubercle bacilli, and significant anergy to TST among end stage kidney disease patients, the utility of these tests to predict posttransplant TB is limited by low likelihood ratios (10, 11).
3. Although IGRAs may be preferred, they are limited by high cost in resource-limited settings.

• *Chemoprophylaxis for latent TB—risks vs benefits*

Studies from the Indian subcontinent have demonstrated the benefit of chemoprophylaxis in reducing the risk of posttransplant TB (10, 12). However, this must be balanced against the risk of emergence of isoniazid (INH) resistance in highly endemic countries, which has been noted to be as high as 25% in India. The hepatotoxicity of anti-tuberculous medications should also be considered (7). Neither universal screening for latent TB in recipients nor chemoprophylaxis is recommended in a recent publication of a South Asian expert group opinion (7). In highly endemic regions, transplant candidates should undergo thorough evaluation for the presence of active TB, and anti-tuberculous treatment should be reserved for this group.

• *Diagnostic challenge*

The clinical presentation of posttransplant TB is often varied and atypical. It may present with non-specific symptoms of unknown origin, such as pyrexia, or only with allograft dysfunction. Extrapulmonary involvement and disseminated TB are not uncommon (13). Therefore, TB was not among the initial suspicions in nearly one-third of the patients with posttransplant TB, and up to 5% may be detected only after a recipient's death (1). Immunodiagnostic tests are not useful in diagnosis in most tropical endemic regions, and the diagnosis requires histopathological or microbiological confirmation. Several infections in the transplant population can also mimic TB, making the diagnosis difficult. Furthermore, in the tropics, infections do not follow the dictum of "Occam's razor" with the possibility of another infection co-existing with TB (10).

• *Therapeutic challenge*

Use of rifampicin in the anti-tuberculous regimen is limited by its drug interactions. As an inducer of cytochrome P450 (CYP) enzymes, it results in significant reduction in levels of calcineurin inhibitors, steroids, and mammalian target of rapamycin (mTOR) inhibitors. Extended therapy with non-rifampicin-containing regimens including rifabutin or fluoroquinolones may be used. The toxicity of each drug is also a consideration, with INH-associated hepatotoxicity being a significant problem in liver transplant recipients, occurring in as many as 41% of patients (7).

• *Effect on patient and graft survival*

TB in the transplant population has 10 times higher risk of mortality compared with that in the general population, with mortality rates of 19%–40%. Much of this fatality is usually attributable to TB occurring due to delayed diagnosis and a higher proportion of disseminated disease. Drug interactions causing a reduction in levels of immunosuppression may be associated with risk of rejection, with graft loss occurring in approximately one-third of patients with posttransplant TB (1).

Conclusion

In the posttransplant period, a high index of suspicion in this at-risk population would enable early diagnosis and appropriate treatment for TB. Further research is required to determine methods to predict the development of TB after transplant in prospective recipients and establish differential preventative strategies specific for these highly endemic regions. ■

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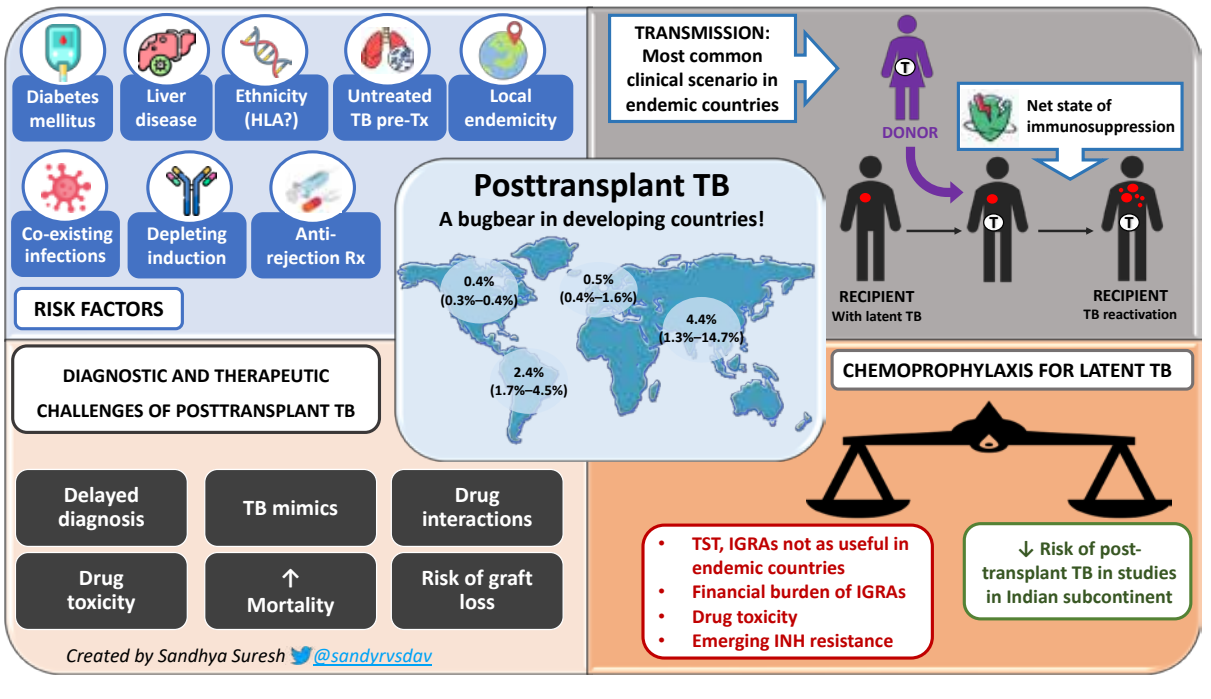

Tuberculosis Post-Transplantation

Continued from page 23

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The authors report no conflicts of interest.

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Norovirus Infections in Kidney Transplant Recipients

By Sanjeev Nair

Diarrhea post-kidney transplantation is a common complication. It is often attributed to immunosuppressive regimens. Norovirus (NoV) infections are the most common causes of acute gastroenteritis worldwide (1). In the transplant population, NoV infections can result in chronic diarrhea, which has long-standing after-effects on nutrition, quality of life, elevated tacrolimus levels, and resultant toxicity and graft dysfunction. Even though the first cases were reported in 2009 (2), awareness about this infection and approaches to its management leave space for improvement.

The knowledge gap is accentuated because the illness is not uniformly defined. It has been suggested that in the absence of an agreed-upon definition, nephrologists use the World Health Organization definition to diagnose patients with diarrhea, i.e., three or more loose or liquid stools per day. Acute diarrhea would last fewer than 14 days, whereas patients with symptoms lasting more than 14 days or for 1 month would be classified as having persistent or chronic diarrhea, respectively (3). As recently as 2020, an observational study published in India researched posttransplant diarrhea and identified 51.5% of participants as having infectious causes of diarrhea but concluded that 75% of these infectious diarrheas could not have an identified causative organism (4).

Published in December 2021, a study by Gäckler et al. (5) sought to address the gaps in our understanding about the clinical characteristics of NoV infections post-kidney transplantation. The study enrolled 60 patients with kidney transplants diagnosed with NoV infection by a positive stool polymerase chain reaction (PCR) test and aimed to identify the characteristics of chronic NoV infections in kidney transplant recipients and their effect on allograft function. The study also evaluated the safety and efficacy of using intravenous immunoglobulin (IVIg) as a therapeutic measure in patients with chronic diarrhea. NoV gastroenteritis occurred a median of 52 months after transplant and resulted in a cumulative median hospital length of stay of 8 days for patients admitted with acute gastroenteritis. Thirty-one of the 60 patients were found to have chronic infection. Patients with chronic infections compared with those with acute infection stayed longer in the hospital (10 vs. 7 days) and were hospitalized more frequently for their illness (17 patients vs. 1 patient). Multivariate analysis showed that both diabetes mellitus and the administration of lymphocyte-depleting induction therapy were independent prognostic factors for the development of chronic NoV infection among kidney transplant recipients (diabetes mellitus: $p = 0.042$; hazard ratio [HR], 4.9; 95% confidence interval [CI], 1.1–22.9 and lymphocyte-depleting induction therapy: $p = 0.035$; HR, 13.6; 95% CI, 1.2–153.2).

Of the total patients, 45% developed acute kidney injury at the time of initial admission, which normalized in those patients with acute NoV infection. However, long-term allograft outcome was affected among patients for whom chronic NoV infection developed. These patients continued to exhibit impaired kidney function 6 and 12 months after initial admission ($p = 0.001$). In addition, 18 kidney transplant recipients with chronic NoV infection were treated with IVIg based on severity perceived by treating clinicians. Thirteen of these patients had no further clinical signs of NoV infection and did not require further hospitalizations. However, 10 of the 13 patients demonstrated NoV in stool samples even following therapy (see visual abstract for details).

This study goes a long way in demonstrating the clinical significance of chronic NoV infection with regard to allograft function. With the availability of multiplex PCR panels to aid in the accurate identification of pathogens in community-acquired gastroenteritis (6), including NoV infections, kidney transplant recipients with acute or chronic diarrhea should ideally benefit from targeted pharmacologic therapy to treat infective causes. Currently, therapy is restricted to decreasing immunosuppression.

Nitazoxanide, a thiazolide antimicrobial agent that exerts its effect against parasitic worms, protozoa, bacteria, and viruses, has been used in patients with NoV infections. But unpublished data from a placebo-controlled randomized controlled trial showed that nitazoxanide, although safe for use, did not show any difference in symptomatic resolution or time to clinical resolution (7). Although immunoglobulins have been shown to play a central role in the clearance of NoV infections in animal studies (8), oral immunoglobulins have not proven to be consistently beneficial (9). The study by Gäckler et al. (5) provides evidence that patients improve symptomatically with IVIg even though this was not simultaneously associated with a clearance of the virus. Further clinical trials that stratify patients by pre- and post-treatment immunoglobulin levels along with severity of clinical symptoms may provide clearer insight into the benefits of IVIg as a therapeutic strategy in NoV infections.

Other strategies that have been tried include ribavirin and a vaccine against NoV, which require trials in the pretransplant population to demonstrate effectiveness in controlling the disease. It is also relevant to this discussion to note that sapovirus, another virus in the *Caliciviridae* family, can also present with similar symptoms and has been reported to cause infections in the posttransplant setting (10, 11) and in one reported instance following a treated case of NoV infection with persistent symptomatic infection, ultimately resulting in graft loss and a return to dialysis (12). ■

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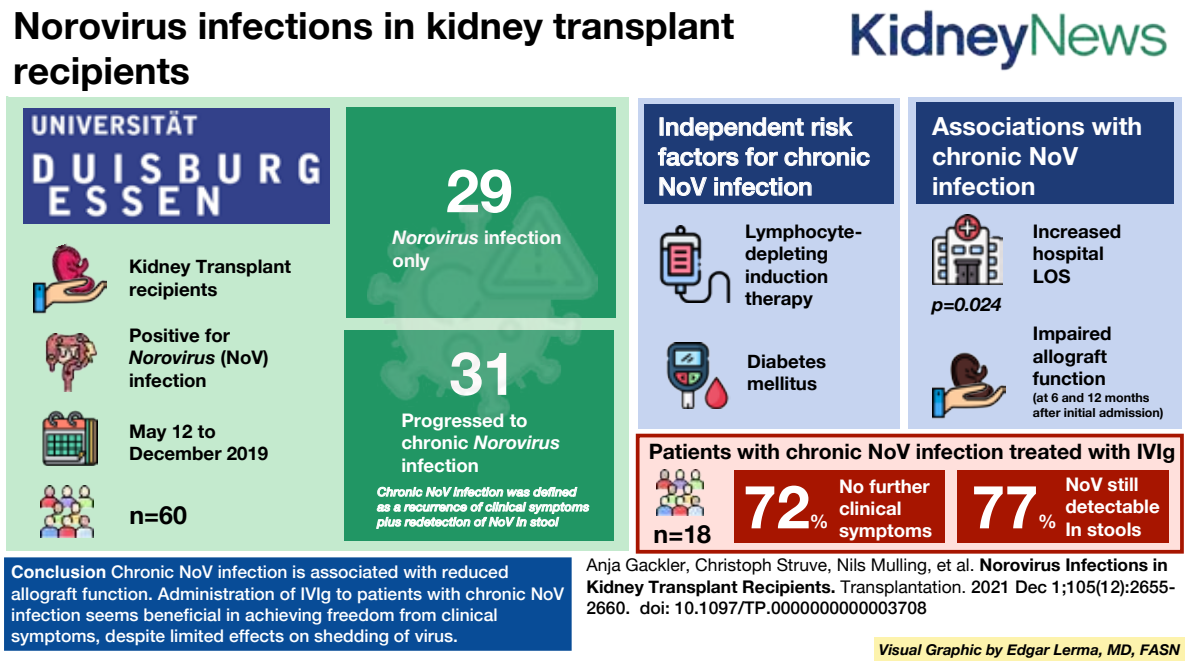

Kidney Transplantation from Deceased Donors with Hepatitis B and Hepatitis C—Facts Our Patients Want to Know

By Navya Eleti and Shikha Mehta

Nearly 100,000 patients with end stage kidney disease are waiting for a kidney transplant. Of these patients, 13 patients die every day, 3800 patients are removed from the list every year for being too sick, and only 25% of patients receive a deceased donor kidney transplant within 5 years (1). As nephrologists and transplant physicians, we strive for a system that maximizes equitable access to transplantation for every patient in need and reduces organ discards, which are magnified among donors with documented viral infections.

In the last decade, we have seen an increase in donor deaths from drug overdoses, with a subsequent increase in donors infected with hepatitis C virus (HCV) and hepatitis B virus (HBV). Historically, a majority of organs from these donors were discarded, but with the availability of highly effective direct-acting antiviral (DAA) agents and experience using them, there has been more willingness to accept kidneys from HCV-viremic donors, with an overall increase in recipients willing to accept HCV-viremic kidneys, from about 4% in 2009 to 43.8% in 2020 (1).

The risk of transmission always exists with an HCV-viremic kidney. However, landmark studies, including THINKER (2) and EXPANDER (3), showed promising results with transplanting HCV-viremic kidneys into HCV-negative recipients, with cure rates of >95% with DAAs and very few serious adverse effects. A larger retrospective study (4) showed no significant difference in 5-year graft survival with DAAs in recipients of kidneys from 2551 HCV-viremic donors compared with recipients of HCV-negative kidneys. Additionally, recipients of HCV-viremic donor kidneys were shown to have received better quality kidneys from younger donors. Long-term studies are currently underway to bridge our knowledge gaps regarding these drugs, risks of co-infections, and longevity of these allografts.

HBV infection is a vaccine-preventable infection. The largest series (5) describing transplantation of HBV-viremic kidneys into 56 HBV-negative recipients treated with entecavir showed no difference in patient survival and graft survival at 1 year compared with recipients of HBV-negative kidneys; additionally, these recipients had decreased waitlist times and dialysis duration. Studies have shown that patients who received the HBV vaccine before transplantation were more likely to remain immune following transplantation (6); therefore, early vaccination in patients with chronic kidney disease is strongly encouraged. Utilization of grafts from HBV-viremic donors could represent an opportunity to facilitate timely transplantation in patients with adequate immunity; however, more studies are needed to elucidate optimal protective strategies.

It is noteworthy that DAAs have provided access to a source of good-quality organs for patients on the waiting list and improved quality of life for these patients. The drugs used for both HCV and HBV treatment minimally interact with the standard posttransplant immunosuppressive medications used at most centers.

Today, these infections are treatable, and transplant centers have rigorous protocols to minimize risk of transmission, monitor for infection, and treat it. Given long wait times for deceased donor organs, it is of paramount importance to remember that the benefit of accepting a HCV-viremic or HBV-viremic donor kidney far outweighs the risk of longer duration both on the transplant waitlist and on dialysis. ■

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Dr. Eleti reports no conflicts of interest. Dr. Mehta is a principal investigator with the study A Trial of Transplanting Hepatitis C Kidneys into Hepatitis C-Negative Kidney Recipients (THINKER-NEXT).

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Direct-Acting Antiviral Therapies for Patients with Kidney Diseases and Hepatitis C Virus Infection

By James E. Dinulos and Meghan E. Sise

In a systematic review performed to support the recent Kidney Disease: Improving Global Outcomes (KDIGO) guidelines for the treatment of hepatitis C virus (HCV) in patients with kidney diseases (1), Balk and colleagues have summarized the safety and efficacy of direct-acting antivirals (DAAs) used to treat HCV in patients with chronic kidney disease (CKD). The authors analyzed all available studies in patients with pre-dialysis CKD (stage 4/5), patients with kidney failure receiving dialysis, and kidney transplant recipients (KTRs), focusing on a sustained virologic response at 12 weeks (SVR12) and clinically significant adverse events (those leading to hospitalization or treatment discontinuation) (1).

Overwhelmingly, DAAs were highly effective and had low adverse event rates across all three patient groups (Table 1). The authors found no direct evidence of clinically meaningful differences between DAA regimens; they also noted that current first-line treatment recommendations favored using pan-genotypic DAA regimens, including sofosbuvir and velpatasvir (Epclusa™) or glecaprevir and pibrentasvir (Mavyret™). Importantly, knowledge of drug-drug interactions between DAAs and immunosuppressive agents is important for treating KTRs. Both sofosbuvir/velpatasvir and glecaprevir/pibrentasvir can be co-administered with tacrolimus, but levels need to be closely monitored, as both DAAs and improvements in liver function induced by DAAs can impact tacrolimus levels. Patients taking glecaprevir/pibrentasvir should not take >100 mg of cyclosporin per day due to drug-drug interactions. Patients taking sirolimus should have drug levels monitored if taking glecaprevir/pibrentasvir due to a drug-drug interactions; there is no interaction between sofosbuvir/velpatasvir and sirolimus. Finally, although no major safety concerns emerged in the kidney failure population, very few patients receiving peritoneal dialysis were studied (35 of the 3817 with kidney failure).

The comparable safety of sofosbuvir-based therapies and their expanded approval in kidney failure increase the opportunity for DAA treatment in many lower- and middle-income countries, where sofosbuvir-based therapies may be the only accessible therapy (2), and in patients with advanced cirrhosis who cannot tolerate protease inhibitor-based therapy (glecaprevir).

HCV infection is associated with more rapid progression of CKD (3), and nephrologists should be aware that DAAs produce high cure rates and are well tolerated. Currently approved pan-genotypic regimens are approved for all levels of kidney function. This systematic review compellingly indicates that DAA treatment for patients with CKD, kidney failure, and KTRs is safe and effective. Referring patients with HCV for DAA therapy is an important part of optimizing their health and survival. ■

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Mr. Dinulos reports no conflicts of interest. Dr. Sise received research funding from Gilead, AbbVie, and Merck and worked on the KDIGO 2022 Clinical Practice Guideline for the Prevention, Diagnosis, Evaluation, and Treatment of Hepatitis C in Chronic Kidney Disease.

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Table 1. Summary of efficacy and safety of DAA usage by kidney disease group

CKD stage	SVR12	Serious adverse events attributed to DAAs or events leading to treatment discontinuation	Special considerations in each population
CKD 4/5 non-dialysis	~97%; no direct evidence of differences among regimens	Rare but limited evidence exists; no evidence of differences among regimens.	Inconsistency in estimates of SVR12 across studies, imprecise estimates, and sparseness of studies and minimal available data on the impact of DAAs on progression to kidney failure or death
Kidney failure on dialysis	≥94%; no direct evidence of differences among regimens	Rare; no evidence of differences among regimens	Only 35 of the 3817 studied were receiving peritoneal dialysis.
Kidney transplant recipients	Most studies, 100%; no evidence of differences among regimens	Rare; no evidence of differences among regimens	Possible drug-drug interactions between certain DAAs and calcineurin inhibitors and MTOR inhibitors; allograft loss rate is low (≤1%); reporting bias may be inflating estimates of allograft loss.

MTOR, mammalian target of rapamycin.

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