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Successful Pig-to-Human Xenotransplant Paves the Way for Clinical Studies

By Bridget M. Kuehn

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In late February, Towana Looney, 53, returned home to Alabama with normal kidney function 3 months after receiving a pig kidney xenotransplant at New York University (NYU) Langone Health in New York City. "I feel blessed," said Looney in a statement released by NYU Langone Health, where she received the transplant (1). "I'm so grateful to be alive and thankful to have received this incredible gift. It couldn't have happened without God and the amazing team of doctors, nurses, and researchers who have been by my side."

Looney had donated a kidney to her mother in 1999 but later developed kidney failure as a result of preeclampsia during pregnancy. She began dialysis in 2016 and joined the waiting list for a transplant in 2017 but had been unable to find a match due to a high level of sensitization. She was also developing heart and vascular complications from long-term dialysis. Looney was able to receive the xenotransplant under an expanded access application from the US Food and Drug Administration (FDA), filed by Jayme Locke, MD, MPH, who at the time was treating Looney as a transplant surgeon at The University of Alabama at Birmingham (UAB). Locke, who is now a clinical faculty member at NYU, partnered with Robert Montgomery, MD, DPhil, the H. Leon Pachter, MD, Professor of Surgery; chair of the NYU Grossman School of Medicine; chair of the Department of Surgery; and director of the NYU Langone Transplant Institute, to complete the transplant at NYU.

After her xenotransplant, Looney was hospitalized for 11 days and then closely monitored for 3 more months on an outpatient basis. Her clinicians successfully reversed an early episode of rejection. She will receive ongoing monitoring from physicians at UAB and monthly checkups at NYU. "She has done very well," Montgomery said. "It is really exciting—the success story that we really needed."

Montgomery said the success of Looney's transplant helped pave the way for FDA to approve the first human clinical studies of pig-to-human transplantation. A three-patient pilot study is underway at Massachusetts General Hospital in Boston using genetically engineered pig kidneys developed by eGenesis (2). The first patient received a

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Kidney Scorecard Provides New Information on Kidney Genetics

By Bridget M. Kuehn

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Using genetic data shared by more than 2.2 million people, Katalin Susztak, MD, PhD, professor of medicine at the Perelman School of Medicine, University of Pennsylvania, and director of the Children's Hospital of Philadelphia Kidney Innovation, and her colleagues have built a kidney genetic scorecard that will help scientists investigate the role of common genetic variants in kidney diseases and develop new targeted treatment approaches (1).

The risk of developing kidney diseases runs in families. Some forms of kidney diseases are linked to a single rare mutation and have a clear pattern of inheritance. However, for many people who develop kidney diseases, a collection of common genetic variations likely predisposes them and their family members to less favorable kidney health. It can be challenging for scientists to identify these more common variations that combine to increase the risk of kidney diseases.

Susztak and her colleagues overcame this challenge by working with colleagues to assemble genomic and kidney health data from the largest cohort of volunteers, to their knowledge, ever analyzed. To do this, they used data shared by investigators from nine major biobanks or large studies. Hongbo Liu, PhD, assistant professor at the University of Rochester Medical Center in New York, led the considerable effort to ensure the quality of the data and analyze them.

Continued on page 6

Inside

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INDICATION

XPHOZAH (tenapanor) 30 mg BID is indicated to reduce serum phosphorus in adults with chronic kidney disease (CKD) on dialysis as add-on therapy in patients who have an inadequate response to phosphate binders or who are intolerant of any dose of phosphate binder therapy.

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

XPHOZAH is contraindicated in:

- Pediatric patients under 6 years of age
- Patients with known or suspected mechanical gastrointestinal obstruction

WARNINGS AND PRECAUTIONS

Diarrhea

Patients may experience severe diarrhea. Treatment with XPHOZAH should be discontinued in patients who develop severe diarrhea.

MOST COMMON ADVERSE REACTIONS

Diarrhea, which occurred in 43-53% of patients, was the only adverse reaction reported in at least 5% of XPHOZAH-treated patients with CKD on dialysis across trials. The majority of diarrhea events in XPHOZAH-treated patients were reported to be mild-to-moderate in severity and resolved over time, or with dose reduction. Diarrhea was typically reported soon after initiation but could occur at any time during treatment with XPHOZAH. Severe diarrhea was reported in 5% of XPHOZAH-treated patients in these trials.

Please see Brief Summary of full Prescribing Information on the following page.

Reference: XPHOZAH® (tenapanor) full Prescribing Information. Waltham, MA: Ardelyx, Inc.; 2023.

ardelyx®

XPHOZAH (tenapanor) tablets, for oral use
Brief Summary of Prescribing Information

1 INDICATIONS AND USAGE

XPHOZAH is indicated to reduce serum phosphorus in adults with chronic kidney disease (CKD) on dialysis as add-on therapy in patients who have an inadequate response to phosphate binders or who are intolerant of any dose of phosphate binder therapy.

4 CONTRAINDICATIONS

XPHOZAH is contraindicated in patients under 6 years of age because of the risk of diarrhea and serious dehydration *[see Warnings and Precautions (5.1), Use in Specific Populations (8.5)]*.

XPHOZAH is contraindicated in patients with known or suspected mechanical gastrointestinal obstruction.

5 WARNINGS AND PRECAUTIONS

5.1 Diarrhea

Diarrhea was the most common adverse reaction in XPHOZAH-treated patients with CKD on dialysis *[see Dosage and Administration (2) in the full Prescribing Information, Contraindications (4) and Adverse Reactions (6.1)]*. In clinical trials, diarrhea was reported in up to 53% of patients, reported as severe in 5%, and associated with dehydration and hyponatremia in less than 1% of patients. Treatment with XPHOZAH should be discontinued in patients who develop severe diarrhea.

6 ADVERSE REACTIONS

6.1 Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety data described below reflect data from 754 adults with CKD on dialysis taking XPHOZAH in clinical trials as monotherapy and in combination with phosphate binders. Among the 754 patients, 258 patients were exposed to tenapanor for at least 26 weeks and 75 were exposed to tenapanor for at least one year. *[see Clinical Studies (14) in the full Prescribing Information]*.

Most Common Adverse Reaction

Diarrhea, which occurred in 43-53% of patients, was the only adverse reaction reported in at least 5% of XPHOZAH-treated patients with CKD on dialysis across trials. The majority of diarrhea events in the XPHOZAH-treated patients were reported to be mild-to-moderate in severity and resolved over time, or with dose reduction. Diarrhea was typically reported soon after initiation but could occur at any time during treatment with XPHOZAH. Severe diarrhea was reported in 5% of XPHOZAH-treated patients in these trials *[see Warnings and Precautions (5.1)]*.

7 DRUG INTERACTIONS

7.1 OATP2B1 Substrates

Tenapanor is an inhibitor of intestinal uptake transporter, OATP2B1 *[see Clinical Pharmacology (12.3) in the full Prescribing Information]*. Drugs which are substrates of OATP2B1 may have reduced exposures when concomitantly taken with XPHOZAH. Monitor for signs related to loss of efficacy and adjust the dose of concomitantly administered drug as needed.

Enalapril is a substrate of OATP2B1. When enalapril was coadministered with XPHOZAH (30 mg twice daily for five days), the peak exposure (Cmax) of enalapril and its active metabolite, enalaprilat, decreased by approximately 70% and total systemic exposures (AUC) decreased by 50 to 65% compared to when enalapril was administered alone *[see Clinical Pharmacology (12.3) in the full Prescribing Information]*. However, the decrease in enalaprilat's exposure with XPHOZAH may be offset by the inherently higher exposures observed in patients with CKD on dialysis due to its reduced renal clearance. Therefore, a lower starting dose of enalapril, which is otherwise recommended in patients with CKD on dialysis is not required when enalapril is coadministered with XPHOZAH.

7.2 Sodium Polystyrene Sulfonate

Separate administration XPHOZAH and sodium polystyrene sulfonate (SPS) by at least 3 hours. SPS binds to many commonly prescribed oral medicines.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Tenapanor is essentially non-absorbed systemically, with plasma concentrations below the limit of quantification (less than 0.5 ng/mL) following oral administration *[see Clinical Pharmacology (12.3) in the full Prescribing Information]*. Therefore, maternal use is not expected to result in fetal exposure to the drug.

The available data on XPHOZAH exposure from a small number of pregnant women have not identified any drug associated risk for major birth defects, miscarriage, or adverse maternal or fetal outcomes. In reproduction studies with tenapanor in pregnant rats and rabbits, no adverse fetal effects were observed in rats at 0.2 times the maximum recommended human dose and in rabbits at doses up to 15 times the maximum recommended human dose (based on body surface area) *[see Nonclinical Toxicology (13.1) in the full Prescribing Information]*.

The estimated background risk of major birth defects and miscarriage for women with CKD on dialysis with hyperphosphatemia is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the United States general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Animal Data

In an embryofetal development study in rats, tenapanor was administered orally to pregnant rats during the period of organogenesis at dose levels of 1, 10 and 30 mg/kg/day. Tenapanor doses of 10 and 30 mg/kg/day were not tolerated by the pregnant rats and was associated with mortality and moribundity with body weight loss. The 10 and 30 mg/kg dose group animals were sacrificed early, and the fetuses were not examined for intrauterine parameters and fetal morphology. No adverse fetal effects were observed in rats at 1 mg/kg/day (approximately 0.2 times the maximum recommended human dose) and in rabbits at doses up to 45 mg/kg/day (approximately 15 times the maximum recommended human dose, based on body surface area). In a pre- and post-natal developmental study in mice, tenapanor at doses up to 200 mg/kg/day (approximately 16.5 times the maximum recommended human dose, based on body surface area) had no effect on pre- and post-natal development.

8.2 Lactation

Risk Summary

There are no data available on the presence of tenapanor in either human or animal milk, its effects on milk production or its effects on the breastfed infant. Tenapanor is essentially non-absorbed systemically, with plasma concentrations below the limit of quantification (less than 0.5 ng/mL) following oral administration *[see Clinical Pharmacology (12.3) in the full Prescribing Information]*. The minimal systemic absorption of tenapanor will not result in a clinically relevant exposure to breastfed infants. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for XPHOZAH and any potential adverse effects on the breastfed infant from XPHOZAH or from the underlying maternal condition.

8.4 Pediatric Use

Risk Summary

XPHOZAH is contraindicated in patients less than 6 years of age. In nonclinical studies, deaths occurred in young juvenile rats (less than 1-week old rats; approximate human age-equivalent of less than 2 years of age) and in older juvenile rats (approximate human age-equivalent of 2 years of age) following oral administration of tenapanor, as described below in Juvenile Animal Toxicity Data.

The safety and effectiveness of XPHOZAH in pediatric patients have not been established.

Juvenile Animal Toxicity Data

In a 21-day oral dose range finding toxicity study in juvenile rats, tenapanor was administered to neonatal rats (post-natal day (PND) 5) at doses of 5 and 10 mg/kg/day. Tenapanor was not tolerated in male and female pups and the study was terminated on PND 16 due to mortalities and decreased body weight (24% to 29% reduction in females at the respective dose groups and 33% reduction in males in the 10 mg/kg/day group, compared to control).

In a second dose range finding study, tenapanor doses of 0.1, 0.5, 2.5, or 5 mg/kg/day were administered to neonatal rats from PND 5 through PND 24. Treatment-related mortalities were observed at 0.5, 2.5, and 5 mg/kg/day doses. These premature deaths were observed as early as PND 8, with majority of deaths occurring between PND 15 and 25. In the 5 mg/kg/day group, mean body weights were 47% lower for males on PND 23 and 35% lower for females on PND 22 when compared to the controls. Slightly lower mean tibial lengths (5% to 11%) were noted in males and females in the 0.5, 2.5, and 5 mg/kg/day dose groups on PND 25 and correlated with the decrements in body weight noted in these groups. Lower spleen, thymus, and/or ovarian weights were noted at the 0.5, 2.5, and 5 mg/kg/day doses. Tenapanor-related gastrointestinal distension and microscopic bone findings of increased osteoclasts, eroded bone, and/or decreased bone in sternum and/or femorotibial joint were noted in males and females in the 0.5, 2.5, and 5 mg/kg/day dose groups.

In juvenile rats administered tenapanor at 0.03, 0.1, or 0.3 mg/kg/day on PND 5 through PND 61, treatment-related mortalities were observed at 0.3 mg/kg/day. Lower mean body weight gains were noted in the 0.3 mg/kg/day group males and females compared to the control group primarily during PND 12–24 but continuing sporadically during the remainder of the dosing period; corresponding lower mean food consumption was noted in this group during PND 21–33. As a result, mean body weights were up to 15.8% and 16.8% lower in males and females, respectively, compared to the control group; the greatest difference was on PND 24 for males and PND 21 for females. Mean body weight in the 0.3 mg/kg/day group males was only 3.9% lower than the control group on PND 61. There were no tenapanor-related effects on mean body weights, body weight gains, or food consumption in the 0.03 and 0.1 mg/kg/day group males and females. A dosage level of 0.1 mg/kg/day was considered to be the no-observed-adverse-effect level (NOAEL) for juvenile toxicity of tenapanor *[see Contraindications (4), Warnings and Precautions (5.1)]*.

In a 21-day oral dose range finding study in older (weaned) juvenile rats administered tenapanor at 0.1, 1, or 5 mg/kg/day on PND 21 through PND 41 (approximate human age-equivalent of 2 to 12 years of age), treatment-related mortalities or moribundities were observed during the first two days of the study in the 1 mg/kg/day males and the 5 mg/kg/day males and females. Watery feces, decreased food consumption, and lower mean body weight were also observed in the 1 and 5 mg/kg/day groups.

In weaned juvenile rats administered tenapanor at 0.1, 0.3, and 0.7 (males) or 1 (females) mg/kg/day on PND 21 through PND 80, no mortalities were observed. Significant decreases in mean body weights were observed in the 0.3 and 0.7 mg/kg/day males throughout the dosing period (up to 20.3% lower than control) and in the 1 mg/kg/day females between PND 23 to 35 (up to 16.7% lower than control), with food consumption notably decreased on PND 21 to 29. There were also reductions in tibia length between PND 76 and 80 in the 0.3 and 0.7 mg/kg/day males, and between PND 36 and 64 in the 0.7 mg/kg/day males, which were not observed during the 14-day recovery period. The NOAEL was considered to be 0.1 mg/kg/day for juvenile toxicity of tenapanor.

8.5 Geriatric Use

Of 1010 adult patients with CKD on dialysis randomized and treated in two randomized, double-blind, placebo-controlled randomized withdrawal clinical trials for XPHOZAH (TEN-02-201 and TEN-02-301) as well as a third randomized, double-blind, placebo-controlled trial (TEN-02-202) for XPHOZAH in combination with phosphate binders, 282 (28%) were 65 years of age and older. Clinical studies of XPHOZAH did not include sufficient numbers of patients aged 65 and older to determine whether they respond differently than younger patients.

10 OVERDOSAGE

No data are available regarding overdosage of XPHOZAH in patients. Based on nonclinical data, overdose of XPHOZAH may result in gastrointestinal adverse effects such as diarrhea, as a result of exaggerated pharmacology with a risk for dehydration if diarrhea is severe or prolonged *[see Warnings and Precautions (5.1)]*.

17 PATIENT COUNSELING INFORMATION

Advise Patients:

Diarrhea

Instruct patients to contact their healthcare provider if they experience severe diarrhea *[see Warnings and Precautions (5.1)]*.

- Instruct patients not to use stool softeners or laxatives with XPHOZAH.

Administration and Handling Instructions

Instruct Patients:

- To take XPHOZAH just prior to the first and last meals of the day *[see Dosage and Administration (2.2) in the full Prescribing Information]*.
- Patients should be counseled not to take XPHOZAH right before a hemodialysis session, and to take XPHOZAH right before the next meal, as some patients may experience diarrhea after taking XPHOZAH.
- If a dose is missed, take the dose just before the next meal. Do not take 2 doses at the same time *[see Dosage and Administration (2.2) in the full Prescribing Information]*.
- To keep XPHOZAH in a dry place. Protect from moisture. Keep in the original bottle. Do not remove desiccant from the bottle. Keep bottles tightly closed *[see How Supplied/Storage and Handling (16) in the full Prescribing Information]*.

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Successful Pig-to-Human Xenotransplant Paves the Way for Clinical Studies

Continued from cover

transplant in February. United Therapeutics has also received FDA clearance to launch a six-patient phase 1–2 safety clinical trial using the company's genetically engineered pig kidney (3). If the results in the first 6 patients are promising, the company has clearance to expand the trial to up to 50 patients.

From progress to pilot

The studies mark a major leap forward for kidney xenotransplantation after three decades of research in animal models. In recent years, developments in genetic engineering and immunosuppression have enabled primate animal models to survive for up to 2 years with a transplanted pig kidney and are continuing to help refine the procedure (4). Those successes led Locke and Montgomery to develop and test the genetically engineered pig kidney transplants in decedent human models, providing preliminary proof of concept (5, 6).

A series of genetically engineered pig-to-human heart and kidney transplants conducted under compassionate use exemptions for patients with few options has helped clinicians and scientists further refine their methods. Before Looney, Richard Slayman received a genetically engineered pig kidney at Massachusetts General in March 2024, which lasted for 2 months without signs of rejection before he died of heart complications.

"We were able to learn that the pig kidney can maintain all the important balances required by the kidney, including water balance and mineral balance in a manner very similar to a human kidney," Leonardo V. Riella, MD, PhD, medical director for kidney transplantation at Massachusetts General Hospital, said. The transplant also found no evidence of transmission of pig viruses, a key concern with xenotransplant.

The eGenesis pilot study will allow Riella and his colleagues to see how well the genetically engineered pig allografts perform in patients with a greater chance of long-term success because they have fewer comorbidities and less time on dialysis than previous recipients.

In late January, Tim Andrews, 66, became the first of three patients to receive a genetically engineered pig kidney created by eGenesis as part of the pilot study. Andrews had been on dialysis for more than 2 years and was struggling with fatigue and severe dialysis complications that included a heart attack in 2023. As a patient with a rare O blood type, Andrews faced a long and uncertain wait for a human allograft. His low chance of receiving a human allograft and his dialysis-related complications made him a candidate for the study. "As soon as I woke up after the surgery, the cloud of dialysis disappeared," Andrews said in a statement from eGenesis released after the procedure (7). "I felt re-energized and revitalized. It was a miracle."

The eGenesis kidneys have been genetically edited to remove three pig antigens that would otherwise trigger hyperacute rejection. They also have seven human genes to reduce the human immune response, reduce inflammation, and reduce clotting caused by incompatibility, according to the company. Numerous endogenous pig retroviruses have also been removed from the pig's genome to reduce the risk of infection with a pig virus.

Andrews and other patients in the pilot study will also receive an immunosuppression regimen that includes tegoprubart, an investigational monoclonal antibody targeting the CD40L pathway, to help increase safety and reduce immune suppression side effects.

"[Tegoprubart] is important because it blocks antibody production and so prevents antibody mediator rejection, but it also is capable of controlling the innate immune system, which is our more primitive part of the immune system that we believe is also important and potentially could cause or contribute to rejection in the case of xenotransplantation," Riella said.

When *Kidney News* spoke to Riella, Andrews had been off of dialysis for 41 days and had seen his energy skyrocket, allowing him to go to the gym and take his dog for long walks. He also reports being able to think more clearly, Riella said.

Riella and his colleagues are in the process of recruiting the next two patients. They are hoping that the data that they collect from these first three patients over 6 months will provide sufficient data to support their application to launch a larger trial this year.

New era

The United Therapeutics clinical trial is designed to seamlessly progress through phases 1, 2, and 3. The first transplant is expected by mid-2025. Two groups of patients will be eligible for participation in the trial: those who have been turned down for the human allograft waitlist and those on the waitlist who have a higher likelihood of dying or being de-listed before undergoing transplant.

The trial will use United Therapeutics' xenokidney called UKidney, which has 10 gene edits. Montgomery noted that many of the edits are similar to those in the eGenesis kidneys. One difference, he said, is that United Therapeutics' kidneys come from larger pigs and have edits to growth hormone genes to prevent the organ from growing too large.

According to Montgomery, six patients at two centers will receive transplants and be monitored for zoonosis transmission, allograft longevity and function, and signs of rejection during the first two phases. To help minimize the chance of rejection, the team will use an immunosuppression regimen that includes a complement inhibitor and the costimulatory inhibitor belatacept in addition to more traditional immunosuppressive drugs. Montgomery said the regimen is similar to that currently used in highly sensitized transplant recipients.

If a good proportion of the allografts are still functioning well after 6 months, and there are no major safety signals, the company will engage with FDA before progressing into the phase 3 trial with more patients and more centers participating.

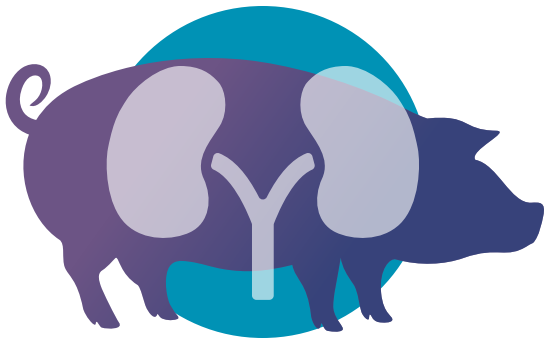
Riella said the two clinical studies testing slightly different approaches should provide valuable information about which gene edits or immunosuppressive approaches provide the best results. "We are eager to learn from each other and keep pushing the field forward," he said.

If the clinical studies are successful, it could herald a new era in kidney transplantation. "It's going to be transformative," Montgomery said. "It could end the waitlist. It could end death on the waitlist."

Both teams cited collaboration among academic centers, industry, and FDA with rapidly advancing the field and helping to overcome what once felt like insurmountable hurdles. Riella highlighted frequent data sharing with FDA to increase the agency's confidence in the trial and create opportunities for agency leaders to provide feedback in real-time. "It's a true partnership," he said. "We've been very transparent in sharing everything that we've been learning on a weekly basis with [FDA]."

Patients have also played a pivotal role in advancing xenotransplant into trials. Riella and Montgomery have seen a high level of enthusiasm from patients and received inquiries about participation in the studies. Riella said he and his colleagues were unsure what the response would be to an experimental therapy with no guarantees about how long the allografts would last, but patients have been overwhelmingly supportive. He said it reflects the impact of dialysis on patients' lives and how eager patients are for better options.

"They are the ones advocating for us to keep pushing and [to] move forward so [that] this can be an alternative option to dialysis," Riella explained. "The support and all the messages [that] we received definitely told us that they're looking for alternatives, and they want it soon." ■



The studies mark a major leap forward for kidney xenotransplantation after three decades of research in animal models.

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In Memoriam

Honoring the Life of William Couser, Pioneer in Glomerular Disease Research

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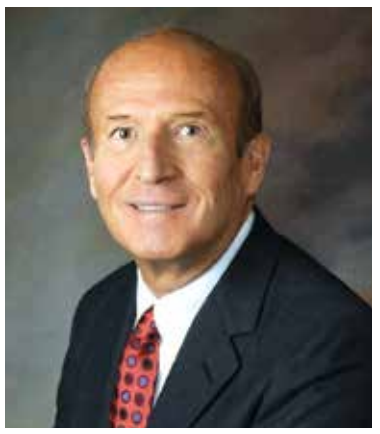

Born on July 11, 1939, in Lebanon, NH, William "Bill" G. Couser, MD, FASN, passed away on February 24, 2025, at the age of 85 (1). Deemed "one of the great academic nephrologists of the modern era" (2), Couser made significant contributions to the study of glomerular diseases. He was among the first to explore the pathogenesis of membranous nephropathy and the role of the complement system in immune-mediated glomerular diseases. His work, including the discovery that immune complexes could form in situ in the glomerulus, has been foundational in the understanding of membranous nephropathy.

Couser earned his undergraduate degree from Harvard College, going on to obtain a Bachelor of Medical Sciences from Dartmouth Medical School in 1963 and a Doctor of Medicine (cum laude) from Harvard Medical School in 1965. He completed his residency and nephrology training at top institutions, including the University of California, San Francisco, and The University of Chicago. From 1965 through 1967, Couser was a captain in the Medical Corps of the US Army, serving in Vietnam.

He was recruited to the University of Washington in 1982, where he was the Belding Scribner Professor of Medicine and led the Division of Nephrology for two decades. Under his leadership, the division became internationally recognized for research and training in glomerular diseases. Couser coauthored over 150 research publications and was instrumental in securing National Institutes of Health training grants and establishing a transplant fellowship program. Beyond his decades of seminal academic work, he was dedicated to training the next generation of nephrologists.

In addition to serving as president of ASN from 1995 to 1996, Couser served as editor-in-chief of *JASN* and was the president of the International Society of Nephrology from 2005 to 2007. Among numerous recognitions and awards, he received the John P. Peters Lifetime Achievement Award from ASN in 2018 for his contributions to nephrology.

Described by those who knew him as a "true role model for physician-scientists" (3), Couser leaves a remarkable legacy and lasting contributions to the field. ■

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Kidney Scorecard Provides New Information

Continued from cover

"We mapped the entire genome—6 million nucleotides associated with kidney function—of each individual systematically," Susztak said. "Most of the variations that explain kidney function heritability are identified by our study."

The massive effort paid off by allowing the study to reach the so-called saturation point, of which Susztak and colleagues believe they have identified nearly all genetic variations contributing to kidney diseases. The team identified 1026 genetic variations linked to kidney function, including 97 new ones. Then, through a series of additional experiments in smaller cohorts, they explored how these mutations contribute to gene regulation, such as open chromatin, and their patterns of expression in individual cell types. Thereafter, they assembled these data into a kidney scorecard tool that other scientists can use.

"The magnitude of what [the team] accomplished was impressive," said Matthew Sampson, MD, MSCE, the Warren E. Grupe Chair of Pediatric Nephrology at Boston Children's Hospital, associate professor of pediatrics at Harvard Medical School, and associate member of the Broad Institute. "There are a lot of smart people in nephrology—physician-scientists and investigators—around the world who, given access to high-quality data such as [these], could make great inferences and really advance their discoveries. But it's a limited number of folks in the world who [like Susztak and her team] can generate this high-quality data."

Solving genetic mysteries

While assembling the genomic data of 2.2 million people was a key part of the study, it represented just a fraction of the overall work. In addition to identifying individual genetic mutations that contribute to kidney diseases, Susztak and her team also wanted to understand the role of gene regulation in contributing to kidney disease risk. She explained that 2% of the genes encode proteins, which she likens to the words in a language. The other 98% of the genome plays a role in regulating those proteins and providing a set of rules that control how they function, similar to how grammar creates a structure for words. "Most of the variations we find are not within the words but in how the words are regulated, how the words are put together," she explained.

To better understand the role of interactions between coding and noncoding genetic variants in kidney diseases, the team used kidney tissue samples from approximately 1000 volunteers to connect disease-linked noncoding variants with the coding variants that they control. Then, they used single-cell genetic sequencing to trace the effects of these variants on individual kidney cell types and began teasing out the potential mechanisms explaining how the variations may contribute to kidney diseases. "This was an enormous amount of work from many, many people," Susztak said.

The result is a three-dimensional kidney map that outlines which genes contribute to kidney diseases, where they operate, and how they cause diseases. Susztak said the work was similar to the detective game Clue, in which players try to decipher where, how, and which suspect committed a murder. "In the Clue game, geneticist version, we are looking for the same things," she said. "Who is the murderer? What is the gene? Where did the murder happen? What is the cell type? And what was the weapon? So how did the murder take place?"

Data trove

The team condensed all of the information into a kidney disease genetic scorecard to make this massive trove of data more helpful to investigators. The scorecard is searchable by gene, cell type, and chromosome. The resource is available online on Susztak's laboratory website (2). "It's a starting point," Susztak said. "Many additional data sets could be added, or [the data] could be improved. We hope to work with the [nephrology] community [to build this resource]."

Sampson anticipates that he and other researchers will use the tool to validate the results of their own human studies and to see how a gene of interest relates to open chromatin, for example. He said researchers studying kidney diseases in animal models may also use it to identify whether disease-causing gene candidates are relevant in humans.

It may also help foster drug development or repurposing of existing drugs for kidney diseases. Sampson noted that having a clear genetic mechanism is often a prerequisite for a drug company to begin developing a drug and to help it gain US Food and Drug Administration approval. "Ultimately, we're all looking to treat or cure individuals with kidney [diseases] or even prevent [them] from happening," he said. "Drugs that have a genetic justification or genetic mechanism for their action have significantly increased odds of ultimately being approved."

Susztak said she is hopeful that the scorecard will also one day help to match patients with the right therapies based on their genetic variations or to identify patients based on genetic biomarkers. She also thinks it may help identify existing drugs that could be repurposed to treat kidney diseases. She noted that there are existing drugs targeting 160 of the genes they identified. However, getting funding for the necessary studies to verify the clinical benefits of repurposed drugs can be challenging. "There are lots of new, interesting targets," she said. "I'm very, very excited about the potential repurposing of drugs, anything that could help patients. First and foremost, this is a very important first blueprint to move forward."

Susztak thanks all of her collaborators and the patients who volunteered to share their data for research. "Hopefully, this will take us to the next level," she said. "We want new therapies that improve the lives of [people] with kidney [diseases]." ■

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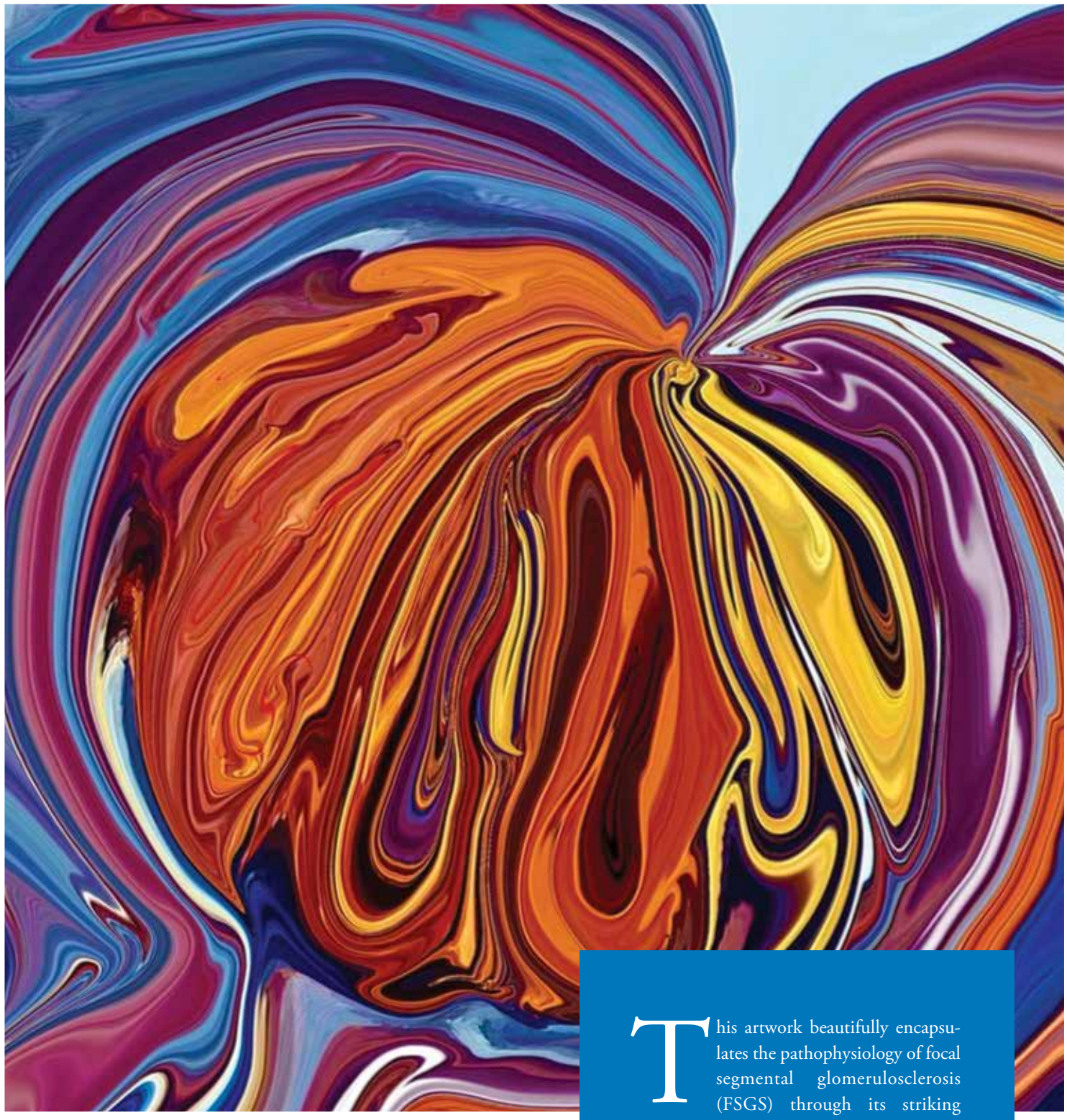
Scarred Filtration

https://doi.org/10.62716/kn.000442025



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

This artwork beautifully encapsulates the pathophysiology of focal segmental glomerulosclerosis (FSGS) through its striking interplay of colors and movement. The yellow and white hues symbolize sclerosis, representing the hardened, scarred glomeruli losing their vital filtration ability. The red swirls evoke inflammation and injury, mirroring podocyte damage and protein leakage. The chaotic distortions reflect the patchy, segmental destruction seen in FSGS, in which some areas struggle while others persist—an artistic testament to both loss and resilience.

ASN's 2025 Policy Priorities: Advancing Kidney Health for All Americans Through STAND

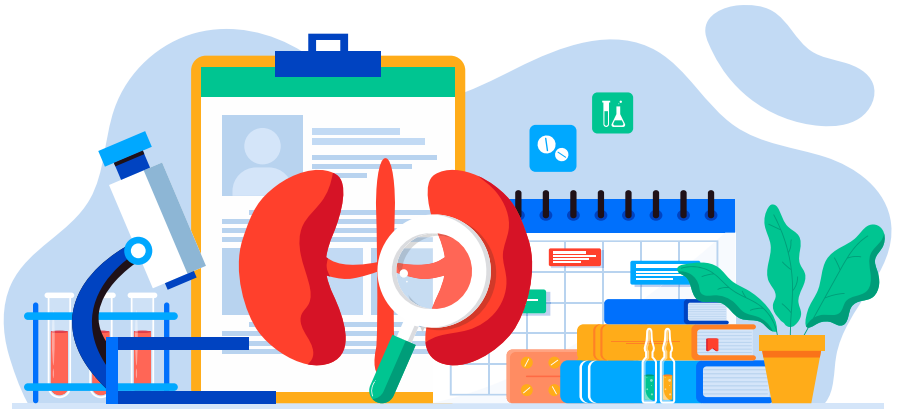
By Ryan Murray

https://doi.org/10.62716/kn.000512025

As kidney care faces evolving challenges in health care policy, research funding, and workforce development, ASN will continue to advocate for kidney health policies that ensure optimal care for patients and support for professionals in the field. As a leading voice in the health care policy arena, ASN is leveraging expertise of its Policy and Advocacy Committee, Quality Committee, and Transplant Policy Committee to shape its annual policy priorities. ASN will embark on an ambitious policy agenda in 2025, structured around two primary goals: 1) establishing an Office of Kidney Health and Transplantation within the Department of Health and Human Services (HHS) and 2) advancing the "STAND" for Kidney Health framework.

At least 10 components across the federal government (including the Agency for Healthcare Research and Quality, Centers for Disease Control and Prevention, Centers for Medicare & Medicaid Services, Department of Defense, Food and Drug Administration, Health Resources and Services Administration [HRSA], Indian Health Service, National Institutes of Health [and National Institute of Diabetes and Digestive and Kidney Diseases in particular], and Department of Veterans Affairs) play an important role in advancing the nation's kidney health, and ASN believes an opportunity exists for stronger coordination on kidney and transplant research across the federal government and in particular within HHS. ASN is advocating for an HHS Officer of Kidney Health and Transplantation, situated in the HHS Secretary's Office, to ensure all components within the department that have a role in kidney health work in coordination to uphold the commitment made by Congress to people living with kidney diseases by setting a strategic vision, fostering coordination, and aligning kidney health policy.

ASN will also operate legislative and regulatory levers to advance its comprehensive STAND for Kidney Health framework of its 2025 policy priorities.



ASN Annual Spring Hill Day

On March 19, members of the ASN Policy and Advocacy Committee and the newly established ASN Transplant Policy Committee met with members of Congress to highlight opportunities to improve efficiency, drive innovation, and foster access to the optimal therapy in kidney care. In addition to continuing to foster relationships and forging new ones with their congressional delegations, committee members urged Congress to:

- Enact the Honor Our Living Donors Act: Simplifying access to federal financial support for living donors by ensuring eligibility is based only upon the donor's income, instead of the recipient's income.
- Advance the Expanding Support for Living Donors Act: Increasing eligibility for reimbursement of donation-related costs to up to 700% of the federal poverty line and covering expenses up to $10,000.
- Support $25 million for KidneyX in Fiscal Year (FY) 26.
  - Catalyzing development of new therapies and products for people with kidney diseases (prevention, diagnosis, and treatment)
- Invest in $67 million for HRSA in FY26.
  - Ensuring funds (and expertise) to implement the bipartisan Securing the US OPTN Act, particularly emphasizing investments in data and information technology to make the system more efficient and navigable
  - Including the clarification that HRSA has the authority to collect and use patient waitlist registration fees in the FY26 appropriations bill

Stay tuned for a summary of Hill Day in an upcoming issue of *Kidney News*.

S Start earlier to prevent, diagnose, and treat kidney diseases.

ASN will continue to advocate for early detection and intervention to mitigate the progression of kidney diseases by:

- Advocating for screening people most at risk for kidney diseases, such as people living with:
  - Diabetes mellitus
  - Hypertension
- Encouraging the collection of high-quality data to justify screening the US population most at risk for kidney diseases, including glomerular diseases
- Addressing earlier care for kidney diseases by:
  - Developing pathways or guidance
  - Funding research and advocating for others to do so
  - Monitoring implementation efforts by health systems and researchers
  - Ensuring that every American has access to high-quality kidney care

T Transform kidney transplant to expand access to the optimal therapy.

Ensuring greater access to kidney transplantation is a cornerstone of ASN's policy efforts. Objectives in this area include:

- Advancing priorities to maximize access to kidney transplantation for every American who would benefit, particularly by:
  - Championing reforms to make the transplant system more transparent to people with kidney failure and their care teams
  - Influencing the Organ Procurement and Transplantation Network (OPTN) Modernization Initiative and Increasing Organ Transplant Access
  - Resolving the challenges with the kidney allocation system including the growing "discard" rate and number of out-of-sequence offers
- Enacting legislation to better support living donors
- Fighting for robust appropriations to modernize the transplant infrastructure and fund the living donor reimbursement program

A Accelerate research, discovery, and innovation to advance American kidney health.

ASN is committed to fostering innovation in kidney disease treatment. Key efforts include:

- Supporting robust appropriations for kidney research, which includes:
  - Promoting the success of federal agencies supporting basic, clinical, and translational research
  - Incentivizing innovators to fill unmet needs, increasing the pace of disruptive approaches, and adopting existing approaches by supporting programs like KidneyX (Kidney Innovation Accelerator)
  - Issuing Transform Kidney Health Research's final report to bolster the kidney community's efforts to increase federal funding for kidney research
- Collaborating with the kidney community to improve regulatory pathways for bringing new therapies to market
- Making data available to the research community in a timely fashion, in as close to real-time as possible (for example, from the End Stage Renal Disease Quality Reporting System)

N Nurture a nephrology workforce to meet patient needs.

In 2025, ASN will address the nephrology workforce crisis by:

- Articulating a plan for increasing compensation for nephrologists, including transplant nephrologists
- Partnering with the American Nephrology Nurses Association, National Kidney Foundation, and Renal Physicians Association to identify, prioritize, and develop recommendations for strengthening the dialysis care team, including advanced practice practitioners
- Monitoring efforts to address immigration issues in nephrology, which includes:
  - Considering the impact of visa restrictions/changes in immigration policy on nephrology training and the nephrology workforce
  - Addressing issues related to physician licensure, such as the Advisory Commission on Additional Licensing Models' draft guidance document
  - Ensuring that the entire country, including underserved rural and urban America, has access to high-quality kidney care

D Drive efficiency to deliver value in kidney health.

Enhancing efficiency in kidney care ensures better patient outcomes and cost-effective treatment. ASN is focused on:

- Improving kidney health programs in the federal government by:
  - Reimagining the Medicare End-Stage Renal Disease bundle
  - Guaranteeing access to innovation and data in Medicare Advantage
  - Advocating for programs that advance kidney care, research, and education within the context of efforts to reorganize the federal government
- Addressing data challenges in kidney health, such as:
  - Accessing affordable data
  - Increasing interoperability in electronic health records
- Ensuring appropriate quality parameters, including the longitudinal measurement of the care for all Americans living with kidney diseases regardless of payor

ASN's 2025 policy agenda, structured around the STAND framework, is a robust plan to address the challenges facing nephrology. However, strategic partnerships are necessary to effectively improve kidney health policies, support research funding, and strengthen the kidney care workforce. ASN is collaborating with policymakers and other major medical organizations to ensure that kidney care remains a priority in federal health care policymaking. By building off of prior success and through legislative and regulatory advocacy, ASN aims to make meaningful progress in kidney health this year.

To keep track of ASN's policy efforts throughout the year, follow coverage in *Kidney News* and the ASN podcast feed, and visit ASN's new Kidney Health Advocacy webpage by scanning the QR code. For real-time updates from ASN Policy, follow @ASNAdvocacy on X. ■

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

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.

https://doi.org/10.62716/kn.000332025

Nephron It's been a while, Mac. What do you have for me?

Mac I have a 68-year-old male with an allogeneic stem cell transplant and now with unexplained lactic acidosis.

Nephron (*excited*) Whoa! Stop right there. Why is that a nephrology consult?

Mac Trust me, you are going to love this one! You are like a king when it comes to figuring out non-nephrology stuff. Aren't nephrologists the wizards of internal medicine?

Nephron Well, in that case, we may have to put on our onconephrology hat or call a friend over for some New York-style coffee. I think I shall invite my friend Dr. Car T. He is just a phone call away.

Mac Hmm…oh well. I can totally relate to that one.

Pause as Dr. Car T enters

Car T Dear Nephron and Mac, please continue to discuss the case. What do we have in store for "The Car"?

Mac This is a 68-year-old male with a history of an allogeneic stem cell transplant for leukemia earlier this year. He is doing well for being post-transplant for the last 5 months on a non-CNI [calcineurin inhibitor]-based GvHD [graft-versus-host disease] regimen. He was admitted and sent for a full laboratory workup, as his care team noticed a low bicarbonate level on recent laboratory results, and he has been experiencing some fatigue. Just to lay it out: His arterial pH was 7.31, and base excess was −12.8 mEq/L. His serum electrolytes and kidney function are normal with an anion gap of 18. His serum lactate level came back at 18 mmol/L.

Nephron Stop! This is ridiculous. This is likely sepsis and/or hypotension. Just hydrate him, and he can go home.

Mac (*laughing out loud*) Can we move on? I would not be here if it was that simple.

Car T (*angry at Nephron*) Oh, come on! Please continue, Mac.

Mac His vitals are normal, and he has not been hypotensive. In the last 4 days, his blood cultures have been negative. After small doses of sodium bicarbonate treatment, fluid replacement, and 2 good days of hydration, his lactate levels increased to 30 mmol/L and are now 45 mmol/L.

Nephron (*bored, rolling his eyes*) Oh yes, you just nailed point number 1: This is still a boring case. If this isn't type A lactic acidosis, this is type B. Come on!

Car T Interesting. I was thinking you might say that his anion gap is normal. Lactic acidosis is the most common cause of metabolic acidosis in patients who are hospitalized. Although the acidosis is usually associated with an elevated anion gap, moderately increased lactate levels can be observed with a normal anion gap. When lactic acidosis exists as an isolated acid-base disturbance, the arterial pH is reduced. Mac, can you tell us a bit about what you understand about lactate production in our body?

Nephron (*winking*) Dr. Car T, are we done with your medicine lecture yet?

Mac Lactate generation and metabolism play a key role in understanding lactic acidosis, which results from both overproduction and impaired metabolism of lactate. Cellular lactate production is influenced by a redox state, reflected in the nicotinamide adenine dinucleotide (NAD^+/NADH [NAD plus hydrogen]) ratio. A low NAD^+/NADH ratio shifts the balance toward lactate production, often due to factors such as inadequate oxygen delivery or rapid oxidation of substances like ethanol. Lactate dehydrogenase catalyzes the conversion between pyruvate and lactate, primarily producing L-lactate, the dominant isomer in humans. Normal metabolism generates 15–20 mmol/kg of lactate daily, primarily through glycolysis. The liver, kidneys, and heart metabolize lactate by oxidizing it to CO_2 and water (70%–80%) or converting it back to glucose (15%–20%) via the Cori cycle.

Lactic acid accumulation is buffered by extracellular bicarbonate, and its metabolism helps restore bicarbonate levels.

Nephron (*yawning*) This is really boring me. It reminds me of those complex lectures in medical school that make students not want to go into kidney medicine.

Car T Why is this not lactic acidosis type A? Lactic acidosis is classified as L-lactic acidosis and D-lactic acidosis; L comes in two types: A and B. Type A is caused by impaired tissue oxygenation, and type B occurs without obvious oxygenation issues. However, overlaps exist, such as in sepsis, in which both increased lactate production and reduced clearance contribute.

Type A lactic acidosis results from severe tissue hypoperfusion due to hypovolemia, cardiac failure, sepsis, or cardiopulmonary arrest. Clearly you are telling me this is not type A.

Nephron Hmm, I like the way you split L into A and B. So much alphabet play here. So, what about D?

Mac (*trying to remember*) D-Lactic acidosis is a rare condition seen in short bowel syndrome and gastrointestinal malabsorption. Excess glucose and starch fermentation by gut bacteria produce D-lactate, which accumulates due to slow human metabolism, leading to metabolic acidosis and neurological symptoms like weakness, cerebellar dysfunction, and confusion.

Sometimes we see this in high-dose intravenous propylene glycol and diabetic ketoacidosis, in which D-lactate forms from lactaldehyde and methylglyoxal, respectively.

Car T (*jumping in*) Standard lactate tests do not detect D-lactate, requiring specialized analysis. From an onconephrology perspective, I doubt this is D-lactate. I assume a CT [computed tomography] scan was done looking for infections, and it was negative.

Silence

Mac Hmm. Yes, of course.

Nephron (*shocked*) Let me guess; it's cancer or some strange new cancer drug causing this?

Mac (*smirking*) Clearly this is type B lactic acidosis. Now what do we think is causing this? The patient is not diabetic, and the medication list does not include metformin, if that is what you are thinking.

Let's get rid of the obvious: There were no seizures or carbon monoxide poisoning that could lead to increased oxygen requirements and decreased delivery issues. Urine toxicology was done but a day late. It was negative for cocaine or toxic alcohols, and the patient is not getting any major form of propylene glycol. He is not on salicylates, albuterol, or any nucleoside reverse-transcriptase inhibitors. Phew! I think I covered most causes of type B lactic acidosis…. Oh, and his cancer is in remission per the recent bone marrow and scans.

Car T Linezolid?

Silence

Mac (*confidently*) No!

Car T Hmmm…. Fascinating. Just to remind you, inherited mitochondrial disorders, such as MELAS [mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes], which result from defects in mitochondrial DNA, lead to lactic acidosis and stroke-like episodes. Thiamine deficiency can also cause lactic acidosis by impairing key enzymes in the tricarboxylic acid cycle. This condition worsens with high glucose loads but resolves with intravenous thiamine. Certain drugs, particularly HIV nucleoside reverse-transcriptase inhibitors, disrupt mitochondrial function, leading to lactic acidosis and lipid accumulation in the liver and muscles.

Nephron (*showing off*) He did mention something regarding the HIV-related medications, but thiamine is a very good point.

Mac Thiamine infusion was given but led to no change in lactate levels.

Car T I think the patient may have a malignancy. Are you sure the scan was good quality?

Mac (*nodding up and down*) So, what do we do here?

Nephron (*boastfully*) There is also an entity called stress hyperlactatemia.

Mac I know that entity. Stress hyperlactatemia, seen in exercise and disease, predicts mortality but remains controversial in literature. Traditionally linked to anaerobic glycolysis from hypoxia, newer evidence suggests increased aerobic lactate production, often due to adrenergic stimulation. Lactate aids energy efficiency, supports gluconeogenesis, and acts hormonally to enhance the metabolism. But he doesn't seem to have a stressful disease right now.

Nephron Mac, what are you going to do? The ball is in your court.

Mac I am going to ask for more imaging, as his lactate dehydrogenase is high as well, and make sure a lymphoma is not brewing here. The time course for post-transplant lymphoma fits, given he received a stem cell transplant.

A few days later

Mac I guess there is a reason Car T is here. Repeat scans with intravenous contrast confirmed new retroperitoneal and inguinal lymph nodes. A lymph node biopsy confirmed lymphoma.

Car T (*jumping in*) Lactic acidosis is rare in leukemia, lymphoma, and solid tumors, with an unclear cause. Proposed mechanisms include anaerobic metabolism in tumor clusters, liver metastases, and increased lactate production via the Warburg effect. Even patients with small tumor burdens can develop lactic acidosis. Thiamine or riboflavin deficiency may contribute, along with impaired lactate clearance. I would check for Epstein-Barr virus by PCR [polymerase chain reaction].

Mac (*confident*) We did, and it was very high. He has Epstein-Barr virus plus post-transplant lymphoproliferative disorder. That is likely what is driving the type B lactic acidosis.

Car T Superbly done, my friend. Quick diagnosis!

Nephron (*jumping in*) Yes, of course. Tell your team your plan to give some "vitamin R."

Car T Although you use rituximab for all diseases in nephrology, it's not the only treatment hematologists have in store.

Nephron (*laughing*) There you go again, Car T! Fascinating diagnosis and treatment, Mac. Special thanks to our onconephrologist in helping us figure out this tough case. I must say, this was a true learning experience.

Car T takes a bow and winks. ■

Detective Nephron was developed by Kenar D. Jhaveri, MD, FASN, professor of medicine at the Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, Hempstead, NY. Special thanks are given to Rimda Wanchoo, MD, professor of medicine at the Donald and Barbara Zucker School of Medicine at Hofstra/Northwell; Sam Kant, MD, FASN, attending nephrologist and transplant physician at St. Vincent's University Hospital, University College Dublin, Ireland; and Prakash Gudsoorkar, MD, FASN, assistant professor of medicine at the University of Cincinnati, OH, for their editorial assistance. Send correspondence regarding this column to kjhaveri@kidneynews.org.

KRYSTEXXA **can change the course** of uncontrolled gout[1]

In the MIRROR trial, KRYSTEXXA with methotrexate:

DEMONSTRATED EFFICACY

71% (n=71/100) vs 39% (n=20/52) patient response* compared to KRYSTEXXA alone during Month 6 (*P*<0.0001)[1]

ESTABLISHED SAFETY PROFILE

4% (n=4/96) of patients experienced infusion reactions vs 31% (n=15/49) of patients treated with KRYSTEXXA alone

6-12 months of KRYSTEXXA may reverse years of urate deposition[1]

Best results were seen at 6-12 months.[1] Optimal treatment duration has not been established.[1] Individual results may vary.

KRYSTEXXA has not been studied to reverse damage to the kidneys, heart, or any of the body's organs.

*The primary efficacy endpoint was the proportion of responders, defined by patients achieving and maintaining sUA <6 mg/dL for at least 80% of the time during Month 6.[1]

The MIRROR RCT was a 52-week, randomized, double-blind, placebo-controlled trial conducted in adult patients with chronic gout refractory to conventional therapy to evaluate administration of KRYSTEXXA (8 mg Q2W) coadministered with 15 mg/week oral methotrexate and 1 mg/day oral folic acid (n=100) vs KRYSTEXXA with placebo (n=52).[1,2]

Q2W, once every 2 weeks; sUA, serum uric acid.

INDICATION

KRYSTEXXA® (pegloticase) is indicated for the treatment of chronic gout in adult patients who have failed to normalize serum uric acid and whose signs and symptoms are inadequately controlled with xanthine oxidase inhibitors at the maximum medically appropriate dose or for whom these drugs are contraindicated.

Limitations of Use: KRYSTEXXA is not recommended for the treatment of asymptomatic hyperuricemia.

IMPORTANT SAFETY INFORMATION

WARNING: ANAPHYLAXIS AND INFUSION REACTIONS, G6PD DEFICIENCY ASSOCIATED HEMOLYSIS AND METHEMOGLOBINEMIA

- **Anaphylaxis and infusion reactions have been reported to occur during and after administration of KRYSTEXXA.**
- **Anaphylaxis may occur with any infusion, including a first infusion, and generally manifests within 2 hours of the infusion. Delayed hypersensitivity reactions have also been reported.**
- **KRYSTEXXA should be administered in healthcare settings and by healthcare providers prepared to manage anaphylaxis and infusion reactions.**
- **Premedicate with antihistamines and corticosteroids and closely monitor for anaphylaxis for an appropriate period after administration of KRYSTEXXA.**
- **Monitor serum uric acid levels prior to each infusion and discontinue treatment if levels increase to above 6 mg/dL, particularly when 2 consecutive levels above 6 mg/dL are observed.**
- **Screen patients at risk for glucose-6-phosphate dehydrogenase (G6PD) deficiency prior to starting KRYSTEXXA. Hemolysis and methemoglobinemia have been reported with KRYSTEXXA in patients with G6PD deficiency. KRYSTEXXA is contraindicated in patients with G6PD deficiency.**

CONTRAINDICATIONS:

- In patients with G6PD deficiency.
- In patients with history of serious hypersensitivity reactions, including anaphylaxis, to KRYSTEXXA or any of its components.

KRYSTEXXA can dissolve years of systemic urate deposition[3,4]

ChangeTheCourse.com

WARNINGS AND PRECAUTIONS

Gout Flares: An increase in gout flares is frequently observed upon initiation of anti-hyperuricemic therapy, including KRYSTEXXA. Gout flare prophylaxis with a non-steroidal anti-inflammatory drug (NSAID) or colchicine is recommended starting at least 1 week before initiation of KRYSTEXXA therapy and lasting at least 6 months, unless medically contraindicated or not tolerated.

Congestive Heart Failure: KRYSTEXXA has not been formally studied in patients with congestive heart failure, but some patients in the pre-marketing placebo-controlled clinical trials experienced exacerbation. Exercise caution in patients who have congestive heart failure and monitor patients closely following infusion.

ADVERSE REACTIONS

The most commonly reported adverse reactions (≥5%) are:

KRYSTEXXA co-administration with methotrexate trial:
KRYSTEXXA with methotrexate: gout flares, arthralgia, COVID-19, nausea, and fatigue; KRYSTEXXA alone: gout flares, arthralgia, COVID-19, nausea, fatigue, infusion reaction, pain in extremity, hypertension, and vomiting.

KRYSTEXXA pre-marketing placebo-controlled trials:
gout flares, infusion reactions, nausea, contusion or ecchymosis, nasopharyngitis, constipation, chest pain, anaphylaxis, and vomiting.

Please see Brief Summary of Prescribing Information for KRYSTEXXA on following page.

References: 1. KRYSTEXXA (pegloticase) [prescribing information] Horizon. **2.** Botson JK, et al. *Arthritis Rheumatol.* 2023;75:293-304. **3.** Sundy JS, et al. *JAMA.* 2011;306:711-720. **4.** Dalbeth N, et al. *Joint Bone Spine.* 2024;91:105715.

AMGEN Rare Disease

KRYSTEXXA® pegloticase

KRYSTEXXA® (pegloticase) injection, for intravenous use

Brief Summary - Please see the KRYSTEXXA package insert for Full Prescribing Information.

WARNING: ANAPHYLAXIS and INFUSION REACTIONS, G6PD DEFICIENCY ASSOCIATED HEMOLYSIS and METHEMOGLOBINEMIA

See full prescribing information for complete boxed warning.

- **Anaphylaxis and infusion reactions have been reported to occur during and after administration of KRYSTEXXA.**
- **Anaphylaxis may occur with any infusion, including a first infusion, and generally manifests within 2 hours of the infusion. However, delayed hypersensitivity reactions have also been reported.**
- **KRYSTEXXA should be administered in healthcare settings and by healthcare providers prepared to manage anaphylaxis and infusion reactions.**
- **Pre-medicate with antihistamines and corticosteroids and closely monitor for anaphylaxis for an appropriate period of time after administration of KRYSTEXXA.**
- **Monitor serum uric acid levels prior to each infusion and discontinue treatment if levels increase to above 6 mg/dL, particularly when 2 consecutive levels above 6 mg/dL are observed.**
- **Screen patients at risk for G6PD deficiency prior to starting KRYSTEXXA. Hemolysis and methemoglobinemia have been reported with KRYSTEXXA in patients with G6PD deficiency. KRYSTEXXA is contraindicated in patients with G6PD deficiency.**

INDICATIONS AND USAGE

KRYSTEXXA® (pegloticase) is indicated for the treatment of chronic gout in adult patients refractory to conventional therapy.

Gout refractory to conventional therapy occurs in patients who have failed to normalize serum uric acid and whose signs and symptoms are inadequately controlled with xanthine oxidase inhibitors at the maximum medically appropriate dose or for whom these drugs are contraindicated.

Limitations of Use:
KRYSTEXXA is not recommended for the treatment of asymptomatic hyperuricemia.

CONTRAINDICATIONS

KRYSTEXXA is contraindicated in:

- Patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency *[see Warnings and Precautions]*
- Patients with history of serious hypersensitivity reactions, including anaphylaxis, to KRYSTEXXA or any of its components

WARNINGS AND PRECAUTIONS

Anaphylaxis

In a 52-week controlled trial, which evaluated KRYSTEXXA co-administered with methotrexate compared to KRYSTEXXA alone, patients were pre-treated with standardized infusion reaction prophylaxis and were discontinued from treatment with KRYSTEXXA if serum uric acid levels increased to above 6 mg/dL at 2 consecutive visits after the initiation of KRYSTEXXA therapy to reduce the risk of anaphylaxis. One patient randomized to the group treated with KRYSTEXXA co-administered with methotrexate (1%) experienced anaphylaxis during the first infusion and no patients experienced anaphylaxis in the group treated with KRYSTEXXA alone *[see Adverse Reactions]*.

During pre-marketing clinical trials with KRYSTEXXA alone, KRYSTEXXA was not discontinued following 2 consecutive serum uric acid levels above 6 mg/dL. Anaphylaxis was reported with a frequency of 6.5% (8/123) of patients treated with KRYSTEXXA every 2 weeks and 4.8% (6/126) for the every 4-week dosing regimen. There were no cases of anaphylaxis in patients receiving placebo. Anaphylaxis generally occurred within 2 hours after treatment.

Diagnostic criteria of anaphylaxis were skin or mucosal tissue involvement, and, either airway compromise, and/or reduced blood pressure with or without associated symptoms, and a temporal relationship to KRYSTEXXA or placebo injection with no other identifiable cause. Manifestations included wheezing, peri-oral or lingual edema, or hemodynamic instability, with or without rash or urticaria, nausea or vomiting. Cases occurred in patients being pre-treated with one or more doses of an oral antihistamine, an intravenous corticosteroid and/or acetaminophen. This pre-treatment may have blunted or obscured symptoms or signs of anaphylaxis and therefore the reported frequency may be an underestimate.

KRYSTEXXA should be administered in a healthcare setting by healthcare providers prepared to manage anaphylaxis. Patients should be pre-treated with antihistamines and corticosteroids. Anaphylaxis may occur with any infusion, including a first infusion, and generally manifests within 2 hours of the infusion. However, delayed type hypersensitivity reactions have also been reported. Patients should be closely monitored for an appropriate period of time for anaphylaxis after administration of KRYSTEXXA. Patients should be informed of the symptoms and signs of anaphylaxis and instructed to seek immediate medical care should anaphylaxis occur after discharge from the healthcare setting.

The risk of anaphylaxis is higher in patients whose uric acid level increases to above 6 mg/dL, particularly when 2 consecutive levels above 6 mg/dL are observed. Monitor serum uric acid levels prior to infusions and discontinue treatment if levels increase to above 6 mg/dL. Because of the possibility that concomitant use of oral urate-lowering therapy and KRYSTEXXA may potentially blunt the rise of serum uric acid levels, it is recommended that before starting KRYSTEXXA patients discontinue oral urate-lowering medications and not institute therapy with oral urate-lowering agents while taking KRYSTEXXA.

Infusion Reactions

In a 52-week, controlled trial which evaluated KRYSTEXXA co-administered with methotrexate compared to KRYSTEXXA alone *[see Adverse Reactions]*, patients were pre-treated with standardized infusion reaction prophylaxis and were discontinued from treatment with KRYSTEXXA if serum uric acid levels increased to above 6 mg/dL at 2 consecutive visits after the initiation of KRYSTEXXA therapy to reduce the risk of infusion reactions. Infusion reactions were reported in 4% of patients in the KRYSTEXXA co-administered with methotrexate group compared to 31% of patients treated with KRYSTEXXA alone experienced infusion reactions *[see Adverse Reactions]*. In both treatment groups, the majority of infusion reactions occurred at the first or second KRYSTEXXA infusion and during the time of infusion. Manifestations of these infusion reactions were similar to that observed in the pre-marketing trials.

During pre-marketing 24-week controlled clinical trials with KRYSTEXXA alone, KRYSTEXXA was not discontinued following 2 consecutive serum uric acid levels above 6 mg/dL. Infusion reactions were reported in 26% of patients treated with KRYSTEXXA 8 mg every 2 weeks, and 41% of patients treated with KRYSTEXXA 8 mg every 4 weeks, compared to 5% of patients treated with placebo. These infusion reactions occurred in patients being pre-treated with an oral antihistamine, intravenous corticosteroid and/or acetaminophen. This pre-treatment may have blunted or obscured symptoms or signs of infusion reactions and therefore the reported frequency may be an underestimate.

Manifestations of these reactions included urticaria (frequency of 10.6%), dyspnea (frequency of 7.1%), chest discomfort (frequency of 9.5%), chest pain (frequency of 9.5%), erythema (frequency of 9.5%), and pruritus (frequency of 9.5%). These manifestations overlap with the symptoms of anaphylaxis, but in a given patient did not occur together to satisfy the clinical criteria for diagnosing anaphylaxis. Infusion reactions are thought to result from release of various mediators, such as cytokines. Infusion reactions occurred at any time during a course of treatment with approximately 3% occurring with the first infusion, and approximately 91% occurred during the time of infusion.

KRYSTEXXA should be administered in a healthcare setting by healthcare providers prepared to manage infusion reactions. Patients should be pre-treated with antihistamines and corticosteroids. KRYSTEXXA should be infused slowly over no less than 120 minutes. In the event of an infusion reaction, the infusion should be slowed, or stopped and restarted at a slower rate.

The risk of infusion reaction is higher in patients whose uric acid level increases to above 6 mg/dL, particularly when 2 consecutive levels above 6 mg/dL are observed. Monitor serum uric acid levels prior to infusions and discontinue treatment if levels increase to above 6 mg/dL. Because of the possibility that concomitant use of oral urate-lowering therapy and KRYSTEXXA may potentially blunt the rise of serum uric acid levels, it is recommended that before starting KRYSTEXXA patients discontinue oral urate-lowering medications and not institute therapy with oral urate-lowering agents while taking KRYSTEXXA.

G6PD Deficiency Associated Hemolysis and Methemoglobinemia

Life threatening hemolytic reactions and methemoglobinemia have been reported with KRYSTEXXA in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency. Because of the risk of hemolysis and methemoglobinemia, do not administer KRYSTEXXA to patients with G6PD deficiency *[see Contraindications]*. Screen patients at risk for G6PD deficiency prior to starting KRYSTEXXA. For example, patients of African, Mediterranean (including Southern European and Middle Eastern), and Southern Asian ancestry are at increased risk for G6PD deficiency.

Gout Flares

In a 52-week, randomized, double-blind trial which evaluated KRYSTEXXA co-administered with methotrexate compared to KRYSTEXXA alone, patients were administered gout flare prophylaxis similar to that in the pre-marketing, placebo-controlled trials.

In this trial, the percentages of patients with any flare for the first 3 months were 66% and 69% for the group treated with KRYSTEXXA co-administered with methotrexate and the group treated with KRYSTEXXA alone, respectively. In the group treated with KRYSTEXXA co-administered with methotrexate, the percentages of patients with any flare for the subsequent 3 month increments of treatment were 27% during Month 6, 8% during Month 9 and 9% during Month 12. In the group treated with KRYSTEXXA alone, the percentages of patients with any flare were 14% during Month 6, 9% during Month 9 and 21% during Month 12.

During pre-marketing, 24-week controlled clinical trials with KRYSTEXXA alone, the frequencies of gout flares were high in all treatment groups, but more so with KRYSTEXXA treatment during the first 3 months of treatment, and decreased in the subsequent 3 months of treatment. The percentages of patients with any flare for the first 3 months were 74%, 81%, and 51%, for KRYSTEXXA 8 mg every 2 weeks, KRYSTEXXA 8 mg every 4 weeks, and placebo, respectively. The percentages of patients with any flare for the subsequent 3 months were 41%, 57%, and 67%, for KRYSTEXXA 8 mg every 2 weeks, KRYSTEXXA 8 mg every 4 weeks, and placebo, respectively. Patients received gout flare prophylaxis with colchicine and/or nonsteroidal anti-inflammatory drugs (NSAIDs) starting at least one week before receiving KRYSTEXXA.

Gout flares may occur after initiation of KRYSTEXXA. An increase in gout flares is frequently observed upon initiation of anti-hyperuricemic therapy, due to changing serum uric acid levels resulting in mobilization of urate from tissue deposits. Gout flare prophylaxis with a non-steroidal anti-inflammatory drug (NSAID) or colchicine is recommended starting at least 1 week before initiation of KRYSTEXXA therapy and lasting at least 6 months, unless medically contraindicated or not tolerated. KRYSTEXXA does not need to be discontinued because of a gout flare. The gout flare should be managed concurrently as appropriate for the individual patient *[see Dosage and Administration]*.

Congestive Heart Failure

KRYSTEXXA has not been formally studied in patients with congestive heart failure, but some patients in the pre-marketing, 24-week controlled clinical trials experienced exacerbation of congestive heart failure. Two cases of congestive heart failure exacerbation occurred during the trials in patients receiving treatment with KRYSTEXXA 8 mg every 2 weeks. No cases were reported in placebo-treated patients. Four subjects had exacerbations of pre-existing congestive heart failure while receiving KRYSTEXXA 8 mg every 2 weeks during the open-label extension study.

Exercise caution when using KRYSTEXXA in patients who have congestive heart failure and monitor patients closely following infusion.

Re-treatment with KRYSTEXXA

No controlled trial data are available on the safety and efficacy of re-treatment with KRYSTEXXA after stopping treatment for longer than 4 weeks. Due to the immunogenicity of KRYSTEXXA, patients receiving re-treatment may be at increased risk of anaphylaxis and infusion reactions. Therefore, patients receiving re-treatment after a drug-free interval should be monitored carefully *[see Adverse Reactions]*.

ADVERSE REACTIONS

The following serious adverse reactions are discussed in greater detail in other sections of the label:

- Anaphylaxis *[see Warnings and Precautions]*
- Infusion Reactions *[see Warnings and Precautions]*
- G6PD Deficiency Associated Hemolysis and Methemoglobinemia *[see Warnings and Precautions]*
- Gout Flares *[see Warnings and Precautions]*
- Congestive Heart Failure *[see Warnings and Precautions]*

Clinical Trials Experience

Because clinical studies are conducted under widely varying and controlled conditions, adverse reaction rates observed in clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug, and may not predict the rates observed in a broader patient population in clinical practice.

Co-administration with Methotrexate

A 52-week, randomized, double-blind trial was conducted in adult patients with chronic gout refractory to conventional therapy to evaluate administration of KRYSTEXXA 8 mg every 2 weeks co-administered with weekly administration of oral methotrexate 15 mg, compared to KRYSTEXXA alone. In this trial, patients who were able to tolerate two weeks on methotrexate 15 mg were then randomized to receive four additional weeks on either methotrexate 15 mg or matching placebo prior to initiating KRYSTEXXA therapy. A total of 152 subjects were randomized, and of these, 145 subjects completed the 4-week methotrexate run-in period and received KRYSTEXXA (96 subjects received KRYSTEXXA co-administered with methotrexate and 49 received KRYSTEXXA plus placebo) during the treatment period. All patients received pre-treatment with an oral antihistamine, intravenous corticosteroid and acetaminophen. These patients were between the ages of 24 and 83 years (average 55 years); 135 patients were male and 17 and were female; 105 patients were White/Caucasian, 22 were Black/African American,

14 were Asian, 5 were Native Hawaiian/Other Pacific Islander and 5 identified as Other; 28 were Hispanic or Latino. Common co-morbid conditions among the enrolled patients included hypertension (63%), osteoarthritis (25%), hyperlipidemia (24%), gastroesophageal reflux disease (22%), obesity (20%), type 2 diabetes (18%) and depression (16%). Patients with an eGFR <40 mL/min/1.73 m² were excluded from this trial.

The most commonly reported adverse reaction during the methotrexate pre-treatment periods was gout flare. The most commonly reported adverse reactions that occurred in ≥ 5% in either treatment group during the KRYSTEXXA co-administered with methotrexate or KRYSTEXXA alone period are provided in Table 1.

Table 1. Adverse Reactions Occurring in 5% or More of Patients in Either the KRYSTEXXA Co-administered with Methotrexate or KRYSTEXXA Alone Treatment Period

Adverse Reaction	KRYSTEXXA with Methotrexate (N=96) n (%)	KRYSTEXXA Alone (N=49) n (%)
Gout flare	64 (67%)	35 (71%)
Arthralgia	13 (14%)	5 (10%)
COVID-19	9 (9%)	3 (6%)
Nausea	5 (5%)	6 (12%)
Fatigue	5 (5%)	2 (4%)
Infusion reaction	4 (4%)[a]	15 (31%)
Pain in extremity	1 (1%)	3 (6%)
Hypertension	1 (1%)	3 (6%)
Vomiting	0	4 (8%)

[a] Included one case of anaphylaxis

KRYSTEXXA ALONE

The data described below reflect exposure to KRYSTEXXA in patients with chronic gout refractory to conventional therapy in two replicate randomized, placebo-controlled, double-blind 24-week clinical trials: 85 patients were treated with KRYSTEXXA 8 mg every 2 weeks; 84 patients were treated with KRYSTEXXA 8 mg every 4 weeks; and 43 patients were treated with placebo. These patients were between the ages of 23 and 89 years (average 55 years); 173 patients were male and 39 were female; and 143 patients were White/Caucasian, 27 were Black/African American, 24 were Hispanic/Latino and 18 were all other ethnicities. Common co-morbid conditions among the enrolled patients included hypertension (72%), dyslipidemia (49%), chronic kidney disease (28%), diabetes (24%), coronary artery disease (18%), arrhythmia (16%), and cardiac failure/left ventricular dysfunction (12%).

During the pre-marketing placebo-controlled clinical trials, the most commonly reported adverse reactions that occurred in greater than or equal to 5% of patients treated with KRYSTEXXA 8 mg every 2 weeks are provided in Table 2.

Table 2. Adverse Reactions Occurring in 5% or More of Patients Treated with KRYSTEXXA Compared to Placebo

Adverse Reaction	KRYSTEXXA 8 mg every 2 weeks (N=85) n[a] (%)	Placebo (N=43) n (%)
Gout flare	65 (77%)	35 (81%)
Infusion reaction	22 (26%)	2 (5%)
Nausea	10 (12%)	1 (2%)
Contusion[b] or Ecchymosis[b]	9 (11%)	2 (5%)
Nasopharyngitis	6 (7%)	1 (2%)
Constipation	5 (6%)	2 (5%)
Chest Pain	5 (6%)	1 (2%)
Anaphylaxis	4 (5%)	0 (0%)
Vomiting	4 (5%)	1 (2%)

[a] If the same subject in a given group had more than one occurrence in the same preferred term event category, the subject was counted only once.

[b] Most did not occur on the day of infusion and could be related to other factors (e.g., concomitant medications relevant to contusion or ecchymosis, insulin dependent diabetes mellitus).

Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. The observed incidence of antibody positivity in an assay is highly dependent on several factors including assay sensitivity and specificity and assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, the comparison of the incidence of antibodies to pegloticase with the incidence of antibodies to other products may be misleading.

In a 52-week, randomized, double-blind trial which evaluated KRYSTEXXA co-administered with methotrexate compared to KRYSTEXXA alone, approximately 26% of patients had pre-existing antibodies to pegloticase. Patients with an increase in titer from baseline or who were negative at baseline and developed an anti-pegloticase response at one or more post dose time points was 30% and 51%, for the KRYSTEXXA co-administered with methotrexate and KRYSTEXXA alone treatment groups, respectively. Patients with higher antibody titers were more likely to have faster clearance and lower efficacy.

During pre-marketing 24-week controlled clinical trials with KRYSTEXXA alone, anti-pegloticase antibodies developed in 92% of patients treated with KRYSTEXXA every 2 weeks, and 28% for placebo. Anti-PEG antibodies were also detected in 42% of patients treated with KRYSTEXXA. High anti-pegloticase antibody titer was associated with a failure to maintain pegloticase-induced normalization of uric acid. The impact of anti-PEG antibodies on patients' responses to other PEG-containing therapeutics is unknown.

There was a higher incidence of infusion reactions in patients with high anti-pegloticase antibody titer: 53% (16 of 30) in the KRYSTEXXA every 2 weeks group compared to 6% in patients who had undetectable or low antibody titers.

Postmarketing Experience

The following adverse reactions have been identified during postapproval use of KRYSTEXXA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship.

General disorders and administration site conditions: asthenia, malaise, peripheral swelling

DRUG INTERACTIONS

Methotrexate

KRYSTEXXA 8 mg every 2 weeks has been studied in patients with chronic gout refractory to conventional therapy taking concomitant oral methotrexate 15 mg weekly. Co-administration of methotrexate with KRYSTEXXA may increase pegloticase concentration compared to KRYSTEXXA alone.

PEGylated products

Because anti-pegloticase antibodies appear to bind to the PEG portion of the drug, there may be potential for binding with other PEGylated products. The impact of anti-PEG antibodies on patients' responses to other PEG-containing therapeutics is unknown.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

There are no adequate and well-controlled studies of KRYSTEXXA in pregnant women. Based on animal reproduction studies, no structural abnormalities were observed when pegloticase was administered by subcutaneous injection to pregnant rats and rabbits during the period of organogenesis at doses up to 50 and 75 times, respectively, the maximum recommended human dose (MRHD). Decreases in mean fetal and pup body weights were observed at approximately 50 and 75 times the MRHD, respectively *[see Data]*.

All pregnancies have a background risk of birth defect, loss or other adverse outcomes. In the US general population, the estimated background risk of major birth defects and miscarriage in clinical recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Animal Data

In 2 separate embryo-fetal developmental studies, pregnant rats and rabbits received pegloticase during the period of organogenesis at doses up to approximately 50 and 75 times the maximum recommended human dose (MRHD), respectively (on a mg/m² basis at maternal doses up to 40 and 30 mg/kg twice weekly, in rats and rabbits, respectively). No evidence of structural abnormalities was observed in rats or rabbits. However, decreases in mean fetal and pup body weights were observed at approximately 50 and 75 times the MRHD in rats and rabbits, respectively (on a mg/m² basis at maternal doses up to 40 and 30 mg/kg every other day, in rats and rabbits, respectively). No effects on mean fetal body weights were observed at approximately 10 and 25 times the MRHD in rats and rabbits, respectively (on a mg/m² basis at maternal doses up to 10 mg/kg twice weekly in both species).

Lactation

Risk Summary

It is not known whether this drug is excreted in human milk. Therefore, KRYSTEXXA should not be used when breastfeeding unless the clear benefit to the mother can overcome the unknown risk to the newborn/infant.

Pediatric Use

The safety and effectiveness of KRYSTEXXA in pediatric patients less than 18 years of age have not been established.

Geriatric Use

Of the total number of patients treated with KRYSTEXXA 8 mg every 2 weeks in the controlled studies, 34% (29 of 85) were 65 years of age and older and 12% (10 of 85) were 75 years of age and older. No overall differences in safety or effectiveness were observed between older and younger patients, but greater sensitivity of some older individuals cannot be ruled out. No dose adjustment is needed for patients 65 years of age and older.

Renal Impairment

No dose adjustment is required for patients with renal impairment. In a 52-week, randomized, double-blind trial which evaluated KRYSTEXXA co-administered with methotrexate compared to KRYSTEXXA alone, 85% of patients had chronic kidney disease based on estimated glomerular filtration rate (eGFR) of ≥ 40 to < 90 mL/min/1.73 m² at baseline. In the pre-marketing 24-week controlled clinical trials with KRYSTEXXA alone, a total of 32% (27 of 85) of patients treated with KRYSTEXXA 8 mg every 2 weeks had a creatinine clearance of ≤62.5 mL/min. No overall differences in efficacy were observed.

OVERDOSAGE

No reports of overdosage with KRYSTEXXA have been reported. The maximum dose that has been administered as a single intravenous dose is 12 mg as uricase protein. Patients suspected of receiving an overdose should be monitored, and general supportive measures should be initiated as no specific antidote has been identified.

PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Anaphylaxis and Infusion Reactions

- Anaphylaxis and infusion reactions can occur at any infusion while on therapy. Counsel patients on the importance of adhering to any prescribed medications to help prevent or lessen the severity of these reactions.
- Educate patients on the signs and symptoms of anaphylaxis, including wheezing, peri-oral or lingual edema, hemodynamic instability, and rash or urticaria, nausea or vomiting.
- Educate patients on the most common signs and symptoms of an infusion reaction, including urticaria (skin rash), erythema (redness of the skin), dyspnea (difficulty breathing), flushing, chest discomfort, chest pain, and rash.
- Advise patients to seek medical care immediately if they experience any symptoms of an allergic reaction during or at any time after the infusion of KRYSTEXXA *[see Warnings and Precautions, Adverse Reactions]*
- Advise patients to discontinue any oral urate-lowering agents before starting on KRYSTEXXA and not to take any oral urate-lowering agents while on KRYSTEXXA.

Glucose-6-phosphate dehydrogenase (G6PD) Deficiency

Inform patients not to take KRYSTEXXA if they have a condition known as G6PD deficiency. Explain to patients that G6PD deficiency is more frequently found in individuals of African, Mediterranean, or Southern Asian ancestry and that they may be tested to determine if they have G6PD deficiency, unless already known *[see Warnings and Precautions, Contraindications]*.

Gout Flares

Explain to patients that gout flares may initially increase when starting treatment with KRYSTEXXA, and that medications to help reduce flares may need to be taken regularly for the first few months after KRYSTEXXA is started *[see Warnings and Precautions, Adverse Reactions]*. Advise patients that they should not stop KRYSTEXXA therapy if they have a flare.

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Should Patients Receiving Induction for Lupus Nephritis Receive PJP Prophylaxis? An Opportunistic Discussion Between Nephrology and Rheumatology

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Pneumocystis jirovecii pneumonia (PJP) is a serious opportunistic fungal infection in patients with compromised or suppressed immune systems. While clear guidelines exist for the use of PJP prophylaxis in those with underlying malignancy and in solid organ transplant recipients, there are no published consensus guidelines for patients with rheumatologic diseases receiving immunosuppressive medications, including those with systemic lupus erythematosus (SLE) (1–3).

Up to 65% of patients with SLE develop lupus nephritis over the course of their disease, requiring potent induction and maintenance immunosuppressive therapies (4). Thus, there is strong crosstalk and collaboration between nephrologists and rheumatologists when caring for this patient population. Advances in immunosuppressive therapies have been growing at an impressive rate, leading to improved control of autoimmune diseases, although also raising critical questions about risk for opportunistic infections, including PJP. Among rheumatologists, this movement has lent itself to increasing literature and discussion regarding the indications for and appropriateness of a routine PJP prophylaxis prescription in patients with SLE undergoing induction therapy (2, 3). Adding to concern with advancing immunosuppression is the high mortality rate among patients with PJP and with an autoimmune disease, which is estimated to be 40% to 50% (5).

A pivotal *Cochrane Database of Systematic Reviews* in 2014 concluded that PJP prophylaxis is warranted when the risk of infection exceeds 6%, which corresponds to a number needed to treat (NNT) of approximately 20 (1). A similar meta-analysis suggested a threshold of 3.5% (corresponding to an NNT of approximately 30), recognizing the high mortality of PJP infections (6). However, the frequency of PJP varies greatly among autoimmune diseases, and even within a single condition, the frequency of PJP can depend on multiple factors, complicating clinicians' ability to assess patient risk relative to these thresholds. Additionally, recommendations based on common practice, such as steroid dosing and duration to guide PJP prophylaxis, may not be appropriate in isolation when considering patients with SLE or other autoimmune diseases. Key to the question of prophylaxis therefore becomes the balance of risk and benefit.

In the case of SLE, recent data have consistently suggested a low infection rate (3, 7, 8). Studies considering both those who do and do not receive prophylaxis have demonstrated a relatively low incidence, on the order of two per every 1000 person-years, when all patients with SLE are considered in aggregate (3).

Nephrologists and rheumatologists must work in concert with one another as we collaborate in the care of these patients with medical complexities.

In the field of rheumatology, there is a growing movement toward conditional prescription of PJP prophylaxis in patients with SLE, based on risk factors associated with a lower NNT weighed against potential adverse effects from added medications. Studies have demonstrated that more than 10% of patients with SLE experience side effects, including development of rash, drug allergy, cytopenias, and even worsening disease flares in association with antibiotic prophylaxis, particularly trimethoprim-sulfamethoxazole, which is most frequently used (9–11). Additionally, polypharmacy associated with increased pill burden in this setting and resultant decreased medication adherence remains a very real threat to the treatment of SLE (2). A more targeted or conditional approach allows one to ensure that these possible harms are counterbalanced by greater potential benefit to PJP prophylaxis. Specific conditions that appear to increase the risk of infection and warrant prophylaxis include:

- low absolute lymphocyte count (no consensus exists yet on the exact threshold)
- low $CD4^+$ count (<200 cells/mm^3)
- presence of concomitant structural lung disease (2, 12, 13).

The use of cytotoxic induction therapies with high-dose steroids interestingly remains up for debate. A survey of rheumatologists in the United States found that 50% of physicians self-report prescribing antibiotic prophylaxis along with induction therapy consisting of cyclophosphamide and high-dose steroids (14). This same study found a low frequency of PJP infection in patients with SLE, at less than 0.2% (14), in keeping with an NNT that has been estimated as greater than 100 (2).

Ultimately, the decision to prescribe PJP prophylaxis will likely continue to be a moving target, requiring individual case considerations to help quantify risk. Indeed, the newest 2024 guidelines from the American College of Rheumatology now recommend that patients with new-onset class III/IV lupus nephritis receive an induction regimen consisting of triple immunosuppressive therapy—a change that may further shift the conversation regarding infection risk (15). Recommended triple immunosuppressive therapy includes pulse IV steroids with high-dose taper thereafter plus 1) a mycophenolic acid analogue and belimumab, 2) a mycophenolic acid analogue and a calcineurin inhibitor, or 3) a cyclophosphamide with belimumab (15).

Today, many questions remain regarding the choice to prescribe PJP prophylaxis in patients with lupus nephritis. It will continue to be crucial that nephrologists remain aware of the evolving discussions and guidelines among rheumatologists, with whom we share a large and growing patient population. Nephrologists and rheumatologists must work in concert with one another as we collaborate in the care of these patients with medical complexities. ■

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The authors report no conflicts of interest.

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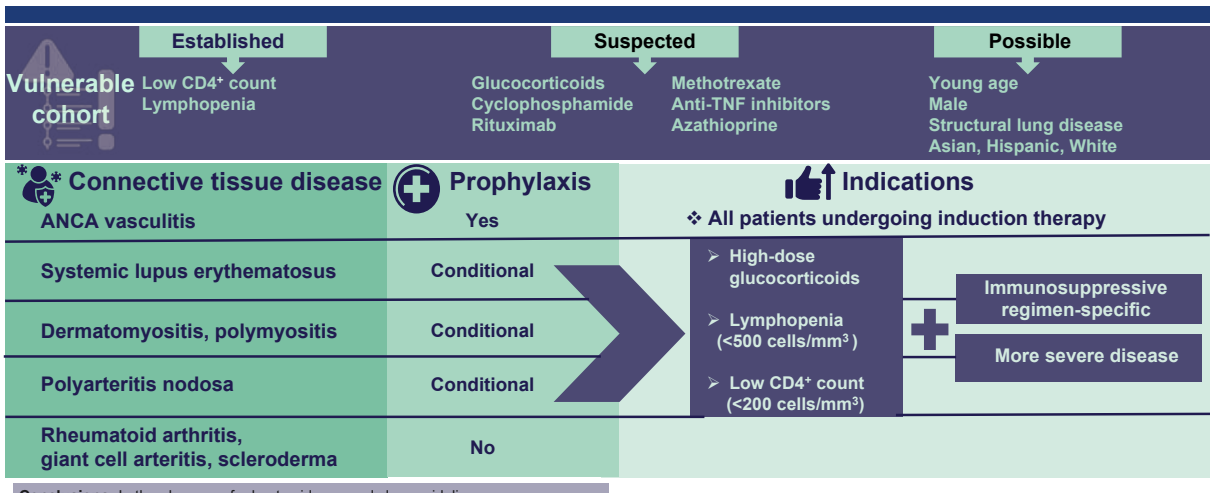
Evolving strategies for *Pneumocystis* pneumonia prophylaxis in connective tissue diseases

KidneyNews



Conclusions: In the absence of robust evidence and clear guidelines on *Pneumocystis* pneumonia prophylaxis in connective tissue disease, patients must rely on cautious, data-informed judgment. Clinical decisions should balance available data with individualized patient risk analysis. ANCA, antineutrophil cytoplasmic antibody; TNF, tumor necrosis factor.

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Furosemide Versus Torsemide: May the Highest Dose Win!

By Donnchadh Reidy and Sam Kant

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Since furosemide first gained US Food and Drug Administration approval in 1966, loop diuretics have been central to the role of the management of heart failure. In nearly 60 years, there has been significant development in the pharmacologic treatment of heart failure. However, furosemide remains the dominant loop diuretic on the market, followed by bumetanide and torsemide (1). There has been accumulating data that torsemide has a superior pharmacologic profile to furosemide, including increased and more consistent bioavailability, a significantly longer half-life, and favorable effects on neurohormones such as decreased aldosterone (2). This has led to speculation as to the superiority of torsemide compared with other available loop diuretics. The recently published TRANSFORM-HF (Torsemide Comparison With Furosemide for Management of Heart Failure) trial sought to answer this question by examining all-cause mortality in 2859 patients who were hospitalized across 60 hospitals in the United States in cohorts randomized to torsemide versus furosemide, demonstrating no significant difference (3). This culminated into reconsideration of the possible pharmacologic benefits of torsemide over furosemide. The TRANSFORM-Mechanism (Torsemide Comparison With Furosemide for Management of Patients With Stable Heart Failure) trial was designed to investigate the pharmacodynamic differences between these two drugs (4).

The TRANSFORM-Mechanism substudy randomized patients 1:1 to oral furosemide versus oral torsemide. Eighty-eight patients were enrolled from July 2019 to March 2022 via the TRANSFORM-HF trial and the TRANSFORM-Outpatient parent study (3). During the TRANSFORM-Mechanism study, clinicians largely used a 2:1 dosing conversion for furosemide to torsemide. In the study, excretion of the unchanged diuretic was measured using liquid chromatography with more furosemide (median, 24.8% [interquartile range, 16.6%–34.1%]) recovered in the urine than torsemide (median, 17.1% [interquartile range, 12.3%–23.5%]), suggesting higher kidney bioavailability of furosemide. As expected, furosemide had a slower onset of action and prolonged delivery versus torsemide, with a greater percentage of drug excreted after the initial 2 hours ($p = 0.003$). Notably, oral dosing equivalence was found to be 4:1 when comparing the natriuretic effect of furosemide versus torsemide rather than the 2:1 conversion used in the study. Higher torsemide doses did result in higher natriuresis, but this was accompanied by higher neurohormonal activation with significant increases in aldosterone ($p = 0.002$), renin ($p < 0.001$), and norepinephrine ($p = 0.039$). In other words, the neurohormonal activation negated the diuretic effects of torsemide, as there was an absence of differences in blood volume or body weight at 30 days compared with furosemide.

The TRANSFORM-Mechanism trial demonstrated the importance of kidney-specific bioavailability. Despite greater availability of torsemide in the blood, this did not reflect delivery of the drug to the luminal side of the kidney tubular epithelium, which determines the natriuretic effect. This may be secondary to the hepatic metabolism of torsemide affecting its overall delivery to the tubule. Furthermore, furosemide's slower gastrointestinal absorption may prove advantageous, given that it minimizes the effect of its short half-life. A prior study with extended-release preparations of torsemide demonstrated greater natriuretic effects with greater preservation of kidney function (5). Furosemide's slower onset of action may be beneficial compared with torsemide's rapid onset of action. In terms of real-world clinical use, TRANSFORM-Mechanism demonstrated that furosemide's diuretic effects were similar to torsemide when dosed in a 4:1 ratio.

The limitations of the study were that this was an open-label trial, influencing clinician and patient bias, involving both hospitalized and stable outpatients (which could affect pharmacodynamic results), and had unsupervised 24-hour urine collection. Overall, this study dispels the belief that torsemide is superior to furosemide and reiterates that ultimately, it is the dosing of the diuretic that should take precedence over the choice of the loop diuretic. ■

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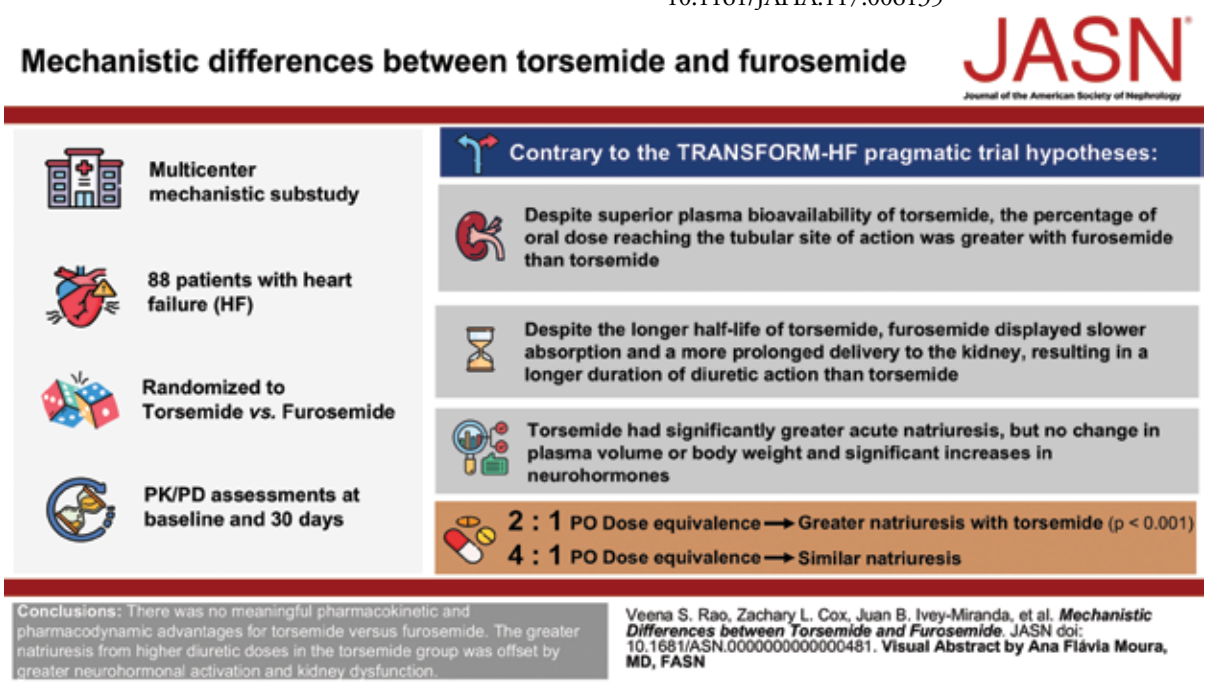

PK/PD, pharmacokinetic/pharmacodynamic; PO, oral.

ASN Transplant Policy Committee Advocates for Maximizing Transplant Access

By Karen Blum

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Rachel Patzer, PhD, MPH

Sumit Mohan, MD, MPH, FASN

ASN recently established a Transplant Policy Committee to advocate across government and professional sectors, aiming to maximize access to transplant in the United States. Committee members Rachel Patzer, PhD, MPH, president and chief executive officer of the Regenstrief Institute in Indianapolis, IN, and a professor at Indiana University, and Sumit Mohan, MD, MPH, FASN, professor of medicine and epidemiology at Columbia University in New York, spoke with *Kidney News* (*KN*) about some of the committee's efforts.

KN: Last year, the Health Resources and Services Administration (HRSA) released for public comment a proposed expansion of the Organ Procurement and Transplantation Network (OPTN) data collection to include pre-waitlist data for all patients with solid organ transplants. The committee submitted feedback and published your thoughts (1). What do pre-waitlist data constitute?

Patzer: [Pre-waitlist data include] any step occurring prior to when a patient is placed on the national waiting list, including referral and evaluation for transplant. Typically, there is a referral form that has to go from their physician to the transplant center; that date of referral, any information about the patient at the time of referral, and aspects of the evaluation are considered part of pre-waitlisting data.

Once the patient is referred by their clinician, typically a nephrologist, they then start the evaluation process at the transplant center. That process varies by transplant center but typically includes education, a financial evaluation, a psychosocial evaluation, and a medical evaluation. Usually, the patient goes through multiple appointments before a multidisciplinary team determines transplant eligibility at the waitlist selection conference. All of these steps are considered pre-waitlisting steps.

KN: How will it be helpful to have that information?

Patzer: For so long, we haven't understood the true demand for transplant because existing national surveillance data only capture data on patients placed on the waiting list. There are patients who were referred and did not start the evaluation or patients who started the evaluation but did not complete it, but we don't know—it's a black box. There's a lot in terms of quality improvement that a transplant center, the referring physician, or the dialysis facility might want to do to improve access to transplant. But if we don't know what's going on in the black box of waitlisting, it's really challenging to do that.

For example, research has shown that barriers to getting a transplant may be different than barriers to getting placed on the waiting list, which may be different than the barriers to even starting the evaluation. It's challenging to try to intervene or address those issues unless we know, for a particular patient population or region, what the specific challenges are. Is it that they have high rates of referral but low rates of starting the evaluation? That might tell us that we need to look more at the transplant center process. If they have high rates of starting the evaluation but low rates of listing, that might tell us that we need to focus on a different part of the process. We've seen so much research around variation in access to some of these early transplant steps that we know there's substantial variation in practice. We don't have national data on this now, but we've looked at this in the southeast, primarily in Georgia, North Carolina, South Carolina, and other regions—and other researchers have done this in smaller-scale studies—and found that there are a lot of inequities in access or variation in access at the transplant center level or dialysis facility level that we really need to understand before we can address the issues.

Mohan: More than half a million people are on dialysis, but the proportion of patients on the waitlist is decreasing, so access to the transplant waitlist is actually decreasing. We don't fully understand why. Rachel's work has shown very clearly that access to the waitlist varies. As a patient, you may go to one transplant center and get declined as a candidate for waitlisting, but if you go to another center, that other center may actually accept you as a candidate. That variation is significant, and we don't fully understand the reasons for it. Patients have no visibility of that process, so if we want to change access to transplant, we have to change access to the waitlist. And if we want to change access to the waitlist, we have to know why people are not making it onto the list. Is it because people aren't being referred, or is it because centers have different thresholds?

KN: In your comments to HRSA, you supported this data collection but recommended a phased-in approach. Can you elaborate?

Patzer: This is a significant change in data collection, and that does have a potential burden on transplant centers. So, we recommended a potential phased-in approach to collecting that data, in which submission might be voluntary for a certain period of time. We don't know how this will be rolled out. HRSA announced this directive and solicited one round of public comments, but there hasn't yet been the second round of public comments, so it's not entirely clear what implementation may look like. We don't know what's going to happen, but it's important to recognize that this is a potential unfunded mandate. HRSA did recommend it being paired with removing some data elements and forms at the same time.

Mohan: There's reluctance from some quarters in the transplant community about collecting more data, and a hesitation that these are data that are going to inform research but create a burden on transplant centers. It's important to emphasize that this is not research data, and the proposed collection approach is cognizant of the current data burden. We proposed using data that already exist in the electronic medical record and a collection approach that is less time and resource intensive because it's batched data reporting. We're starting with the most basic critical elements that we think will give us at least some understanding of what is happening. This will evolve and be informed by what we learn. So, if we learn that there's a lot of variation in evaluation time, then we may want more granular data to understand why there is so much variation. But as a first step, we need to understand, after people are referred to a transplant center, how many people start an evaluation or how many people finish. We only know how many people make it onto the waitlist.

KN: What is the status? When could a final decision be rendered?

Patzer: We are in a little bit of a wait-and-see pattern for next steps from HRSA. HRSA is going through all of the public comments that it received by early January and then will put forward more specific information and ask for public comment one more time—this time with a 30-day time period. After that, we'll have more details of when and how this will be implemented, and what specific data elements will be included. The ASN Transplant Policy Committee has advocated for this. This workgroup that was actually part of OPTN had all of these recommendations for how this should work and what data elements should be collected. There's a lot going on at the federal government, so it is possible that HRSA may hold off on this last public comment period for a little bit longer, until things settle.

Mohan: We haven't heard anything from HRSA on this front, although the next step is another comment period from the Office of Management and Budget before it's formally implemented by OPTN. It's unclear to what extent the current proposals for data elements or the collection cadence will change during the process prior to implementation, so it's clearly a wait and see for now.

KN: What are some of the barriers that would need to be overcome for this to happen successfully? You mentioned technology as one hurdle.

Patzer: The OPTN Modernization Initiative calls for modernizing the transplant data system. There's a lot that we could do to improve data collection processes to reduce that burden. Unfortunately, we don't know all of the specifics of the OPTN Modernization Initiative, including specific task orders and priorities for technology. The potential barriers are slower rollout of modernizing the data system, so if we're relying on antiquated ways to collect these data, that does cause more burden on transplant center staff. It comes down to time and staff, and transplant centers will bear the brunt of that.

Other potential barriers are that people may not understand the value of how these data could be used, since they're newer data elements. There's a lot we need to do to educate our community about that value. The Transplant Policy Committee has been trying to focus on how this is really beneficial, primarily for patients and their families. It's also been called for by experts in the field for many years. Collecting pre-waitlisting data is named in the NASEM (National Academies of Science, Engineering, and Medicine) report for more transparency in this process. Patients want to know where the best place is for them to get a transplant or to get on the list, and these data would help inform that decision.

Mohan: Transplant centers have to be willing to do this. There's some misunderstanding in the community about what the goals are and why this would help. It's important that people understand that this is valuable for patients and valuable for us to evaluate the underlying need. For kidney diseases, we have a population with kidney failure, so we have some sense of what the needs are or the scope of the problem. In the other organ transplant systems, there's no denominator. We have no idea how many patients with cirrhosis or how many patients with heart failure exist out there with end-stage heart failure who would benefit from a heart transplant. The waitlisting data proposal is organ-agnostic, so it would actually help us develop a better sense, for the first time, of what the transplant need is in all of the other organ systems, which is information that's been lacking.

KN: What else are you actively working on?

Patzer: One main priority is coordinating with other ASN committees. I serve as the liaison between the Transplant Policy Committee and the ASN Policy and Advocacy Committee, forming collaborative relationships to shape transplant policy, helping our members understand what implementation might look like and understand how transplant-related policies might impact their practices, and then trying to increase access to donor kidneys as well. If I were to brainstorm what we think they're going to be, it's things like focusing on the Center for Medicare & Medicaid Services' (CMS') Increasing Organ Transplant Access (IOTA) model and building awareness around it. Last year, we spent a lot of time trying to get more resources around implementation for the OPTN Modernization Initiative, so we'll be closely following that as well. The pre-waitlisting data will be another priority of ours, ensuring that implementation of this policy moves forward.

Mohan: I think there's also going to be an increased focus on allocation policy because of the ongoing rise in out-of-sequence kidney allocation (2). I'm hoping that will be a major focus so that we can figure out that piece. At the end of last year, HRSA put a stop to all out-of-sequence allocation work from the Expeditious Task Force, but that hasn't stopped the practice. We're waiting to see what it looks like.

KN: IOTA will start this July. What do you expect we will see or learn from that?

Mohan: CMS has randomized half of the country into the IOTA model. There are 103 transplant centers that are in it, and they're all incentivized to grow volume-wise. What I expect to see is that those centers will really grow. In fact, between 2023 and 2024, there was essentially no increase in the number of kidney transplants that happened year over year. Hopefully that will change. That's one goal. The other goal is allocation efficiency. If they are able to move the needle on allocation efficiency, as measured by a higher organ offer acceptance rate, we should see fewer discarded organs and more effective organ allocation.

Patzer: We're not going to see major results yet, but all of the transplant centers that were allocated or randomized to be in the model are starting to have a lot of conversations and thinking about what they could be doing right now to prepare for this.

KN: If you could implement a single change in transplant policy tomorrow, what would it be?

Mohan: A better allocation system. I think our allocation system is the root cause of many of the challenges in transplantation today. If there is something we could change more quickly, it would be much more transparency. There needs to be transparency in terms of how centers accept or list patients and how centers accept organs or don't. Not having that transparency has allowed centers to become selective in terms of which patients they accept for waitlisting and which organs they're willing to accept, to the detriment of patient access to transplant and presumably to patient outcomes.

Patzer: I'm going to come at it from the data side, which is having one system in which all of these data live, and there is real-time access to that data, and it's interoperable, and it's standardized, so that we didn't spend so much time and effort chasing it. It's pie in the sky, a little bit, but it is technically feasible.

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

This interview has been edited for length and clarity.

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More on *Kidney News Online*

Resolving the challenges with the kidney allocation system including the growing discard rate and number of out-of-sequence offers is a top ASN transplant policy priority in 2025. Read more on the society's efforts by scanning the QR code.

Are We Entering a New Era in Treatment of Thrombotic Microangiopathy?

By Arash Rashidi and Himabindu Yerneni

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Acquired thrombotic thrombocytopenic purpura (TTP) is a potentially life-threatening event resulting from systemic microvascular thrombosis leading to profound thrombocytopenia, hemolytic anemia, and organ failure of varying severity (1). Acquired immune TTP (iTTP) is caused by a severe deficiency of a disintegrant and metalloproteinase with a thrombospondin type 1 motif, member 13 (ADAMTS13) due to the presence of inhibitory autoantibody anti-cysteine-spacer antibody or other antibodies directed against other domains of ADAMTS13 such as thrombospondin type 1 doamain, and C-terminal domains. This process further contributes to the accumulation of ultra large von Willebrand factor (vWF) multimers, which bind to platelets and induce aggregation (2). Advancements in the management of iTTP over the past three decades have dramatically transformed the management and outcome of this previously fatal disease. A 90% mortality rate of thrombotic microangiopathy (TMA) in the 1980s has been reduced to approximately 10% in 2024 alone (3).

The groundbreaking TITAN (Study to Assess Efficacy and Safety of Anti-von Willebrand Factor [vWF] Nanobody in Patients With Acquired Thrombotic Thrombocytopenic Purpura [aTTP]) study using caplacizumab, an anti-vWF-humanized single variable domain immunoglobulin, showed promising results in the management of iTTP (Nanobody and Nanobodies [Ablynx NV] target the A1 domain of the vWF, which prevents interaction with the platelet glycoprotein Ib-IX-V receptor). Caplacizumab with a plasma exchange showed accelerated resolution of TTP and platelets stabilization; however, it produced a higher bleeding risk (4). Later, HERCULES (Phase III Trial With Caplacizumab in Patients With Acquired Thrombotic Thrombocytopenic Purpura) and post-HERCULES (Follow-Up Study for Patients Who Completed Study ALX0681-C301) studies showed similar outcomes (5, 6). Other treatments like recombinant ADAMTS13 (rADAMTS13), N-acetyl cysteine, and anfibatide, which inhibits platelet aggregation by binding to glycoprotein Ib and inhibiting its interaction with vWF, have been tested in animal models and showed efficacious results; however, they were only seen in case reports (7). Based on these studies, an expert panel for the International Society on Thrombosis and Haemostasis released 11 comprehensive recommendations on TTP in 2018. For a first acute episode and relapses of iTTP, the panel made a strong recommendation for adding corticosteroids to therapeutic plasma exchange (TPE) and a conditional recommendation for adding rituximab and caplacizumab (8).

iTTP treatment with TPE may lead to a prolonged hospital stay, including multiple sessions of daily TPE and the associated costs of plasma, equipment, nursing care, and medical supervision. Recently, Kühne and colleagues evaluated the treatment of acute iTTP with caplacizumab and immunosuppression without TPE in comparison with management with TPE, caplacizumab, and immunosuppression (9). The main objective of the retrospective study was to reduce the therapeutic burden without compromising the overall clinical outcome or patient safety. In the study, the authors used the Austrian Thrombotic Microangiopathy Registry and the German REACT-2020 TTP registry. A total of 42 patients with acute iTTP who received a TPE-free treatment regimen of immunosuppression and upfront caplacizumab were compared with a control group of 59 patients with iTTP who received frontline treatment with caplacizumab, in addition to TPE and immunosuppression. Clinical outcomes were evaluated based on daily complete blood count, serum chemistry, and ADAMTS13 activity testing done weekly. Subsequent initiation of TPE was based on a missing increase in platelet count, a worsening clinical condition, or new organ damage. Time-to-platelet count normalization was considered the primary outcome, and key secondary outcomes included clinical response, clinical exacerbation, refractory TTP, TTP-related deaths, and the time-to-platelet count doubling.

The parameters of the initial clinical presentation—duration and dose of caplacizumab—and the use of rituximab within 72 hours did not differ between the two groups, except for a significantly higher initial lactate dehydrogenase level in the TPE group (median, 703 vs 1052 U/L; $p < 0.01$). The primary outcome time-to-platelet count normalization was not significantly different between TPE-free and TPE-based management. Clinical exacerbations occurred in two patients (4.8%) in the TPE-free cohort and in nine patients (15.3%) in the TPE cohort. Exacerbations in the TPE-free cohort were linked to concomitant cytomegalovirus, active HIV and hepatitis B virus coinfection, concomitant antiplatelet antibodies in association with an ovarian teratoma, and multiple platelet transfusions before the correct diagnosis of TTP was made and early termination of caplacizumab before ADAMTS13 remission was acquired. In the TPE group, refractory TTP was observed due to active diseases that may have impaired the platelet count response, namely, the diagnosis of pancreatic cancer, pneumonic sepsis, and aspiration pneumonia. There was no significant difference in the time-to-platelet count doubling between the two cohorts with a median time of 1 day in both cohorts. Reported time to recovery of ADAMTS13 activity to 20% or more after treatment initiation was shorter in the TPE-free cohort. The duration of hospital stay was significantly shorter in the TPE-free cohort, and fewer patients were admitted to the intensive care unit. Complications were observed in 11 patients (26.2%) in the TPE-free group and 16 patients (27.1%) in the TPE group, excluding complications of iTTP.

To our knowledge, the study by Kühne et al. (9) is the largest real-world cohort with acute iTTP, managed by anti-VWF treatment and omitting TPE. Due to the retrospective nature of the study, selection bias, such as the tendency to recruit patients with milder iTTP symptoms for TPE-free management, may be present in the current study, but differences in initial lactate dehydrogenase levels did not show any differences in primary outcome based on stratified analysis. In most instances, exacerbations were attributed to the early termination of caplacizumab when ADAMTS13 activity remained below 10%. This highlights that the ADAMTS13-guided approach is successful in acute iTTP management with caplacizumab.

There are many other ongoing studies for treatment of iTTP. The MAYARI (Caplacizumab and Immunosuppressive Therapy Without Firstline Therapeutic Plasma Exchange in Adults With Immune-Mediated Thrombotic Thrombocytopenic Purpura) trial (10) is an open-label, single-group, phase III multicenter trial of caplacizumab with immunosuppressive therapy without frontline use of TPE for iTTP. The study is aiming to recruit 61 adult patients with recurrent iTTP confirmed by low ADAMTS13 activity and absence of signs or symptoms consistent with other TMA syndromes such as atypical hemolytic uremia syndrome. The primary objective of the study is to find the proportion of participants achieving remission without TPE.

The assessment of safety and efficacy for rADAMTS13 as a treatment for iTTP is the objective of another study (A Study of TAK-755 [rADAMTS13] With Little to No Plasma Exchange [PEX] Treatment in Adults With Immune-Mediated Thrombotic Thrombocytopenic Purpura) (11). In this phase II study, 40 adult patients with de novo or recurrent iTTP are given random, two dose levels of intravenous rADAMTS13 for the acute treatment period combined with immunosuppressive therapy. The primary outcome in this trial is incidence of adverse events over a 12-week period.

Despite potential limitations arising from the retrospective design and possible selection bias, the key findings from the study by Kühne et al. (9) suggest that caplacizumab without TPE is efficacious in controlling TMA and achieving a clinical response in acute iTTP. In addition to the short-term control of microvascular thrombosis and subsequent organ damage, the modified treatment regimen was efficacious in achieving ADAMTS13 remission and allows for the cessation of anti-VWF medication with caplacizumab. Kühne et al. (9) showed efficacy and safety of a TPE-free approach in patients with iTTP. This can be the beginning of a TPE-free era in the treatment of iTTP. ■

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The authors report no conflicts of interest.

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Bridging the Gap in AKI Follow-Up: From Research to Implementation

By Jia Hwei Ng

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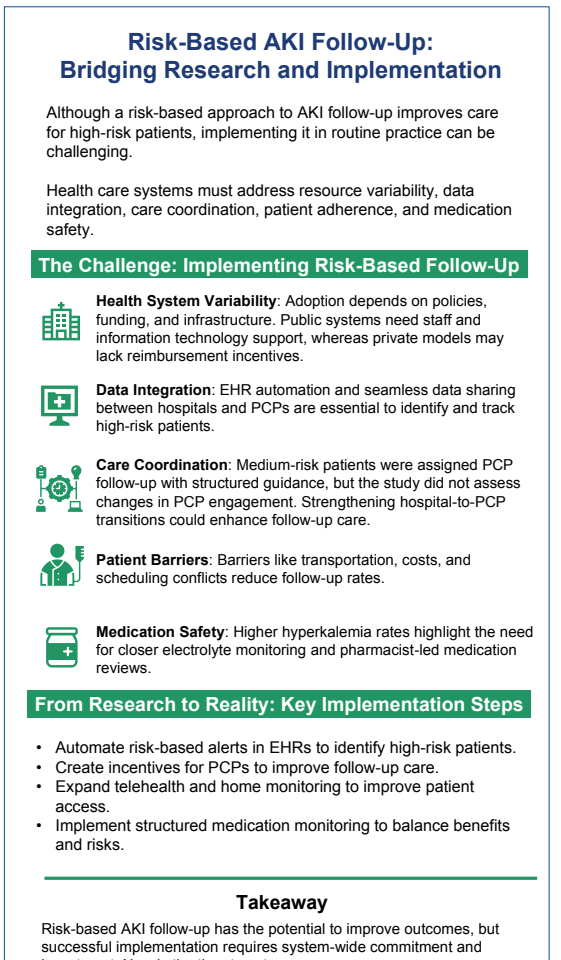
Acute kidney injury (AKI) increases the risk of chronic kidney disease and cardiovascular complications, yet postdischarge care remains inconsistent. Many survivors of AKI do not receive timely nephrology referrals or guideline-based medications, increasing their risk of disease progression and hospital readmission. A recent study by Pannu et al., evaluating a risk-based follow-up approach, demonstrates a promising strategy to address these gaps and improve long-term outcomes (1).

The study implemented a risk-guided model, in which survivors of AKI were stratified by chronic kidney disease risk. Low-risk patients received education alone, medium-risk patients had additional clinical guidance for their primary care physicians (PCPs), and high-risk patients were referred to nephrology. The intervention significantly increased nephrology follow-ups (from 9% to 29%) and improved adherence to angiotensin-converting enzyme inhibitors (ACEis), angiotensin II receptor blockers (ARBs), and statins. In addition, the study showed that the intervention was feasible across multiple hospitals.

A key strength of this model is its ability to target care where it is needed most, ensuring that specialty resources are used efficiently. Although the intervention group had higher rates of hyperkalemia, this was likely due to increased ACEi/ARB use, reinforcing the importance of medication monitoring (2, 3).

Although this targeted approach optimizes resource allocation and enhances care for high-risk patients, there are opportunities to further build on these findings. Given that this is a smaller study, larger trials are needed to evaluate long-term outcomes. Additionally, although medium-risk patients were assigned to PCPs with structured follow-up guidance, the study did not specifically assess changes in PCP engagement. Strengthening structured transitions between hospitals and primary care could further support comprehensive follow-up for survivors of AKI.

Implementing optimal follow-up care for AKI in real-world health care systems requires overcoming logistical barriers (4). Automated risk alerts in electronic health records (EHRs) are necessary to flag high-risk patients and trigger referrals. Stronger PCP involvement, supported by financial incentives or dedicated transitional care teams, is crucial for sustained follow-up. Patient adherence must also be addressed through expanded telehealth options and improved access to monitoring. Additionally, safer medication protocols are needed to balance the benefits of ACEis/ARBs with the risk of hyperkalemia (2).



This study provides a framework for improving AKI follow-up and highlights the potential of a risk-based approach to enhance postdischarge care. The findings are an important step forward in addressing gaps in AKI management, and although larger studies are needed to fully assess long-term outcomes, the evidence presented is compelling. Now is the time to build on this progress and start the conversation on how health care systems can implement this approach and whether they are ready to operationalize it. Bridging the post-AKI care gap will require commitment, coordination, and investment—but this study provides a foundation for future implementation. ■

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The author reports no conflicts of interest.

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Blood Pressure Goals in Kidney Transplant Recipients: More Progress, but a Target Remains Elusive

By Dearbhail Ni Cathain and Sam Kant

https://doi.org/10.62716/kn.000232025

Kidney transplant recipients remain at higher risk than the general population of significant morbidity and mortality related to cardiovascular disease (1). This increased risk can partly be attributed to traditional cardiovascular risk factors such as diabetes, dyslipidemia, and hypertension—the latter being particularly prevalent in the kidney transplant population. Mechanistically, hypertension in this population can be associated with donor factors or recipient factors, including post-transplant renal artery stenosis, allograft rejection, and immunosuppressive medications (2). Although a common problem, there is no established optimum blood pressure (BP) target in this population; the general paradigm shift toward lower BP targets has not yet been adopted in this group due to unsubstantiated concerns of acute kidney injury.

The Collaborative Transplant Study proposed to investigate BP targets in the transplant population using large-scale retrospective data available on over 60,000 kidney transplant recipients (3). Data on BP were collected at year 1 after transplant and then at follow-up. Adults undergoing transplant between 2000 and 2021 included in the Collaborative Transplant Study were analyzed. Hypertension was classified using the 2017 American College of Cardiology/American Heart Association parameters (4). The primary outcomes studied were death-censored graft failure and patient mortality from years 1 to 6 after transplantation.

The population of kidney transplant recipients included mainly males (62%) in receipt of their first kidney transplant (89%) from deceased donors (69%) with no detectable human leukocyte antigen (HLA) antibodies before transplantation (81%). Results showed that 77% of recipients had stage 1 hypertension. There was an association between older age at the time of transplantation and an increased risk of hypertension (77% in those >50 years old versus 66% in those ages 18–24 years). The study showed an increased risk of death-censored graft failure in recipients with hypertension with a hazard ratio of 1.11 in those with stage 1 hypertension (95% confidence interval [CI], 1.02–1.2; p = 0.018) and 1.55 in those with stage 2 hypertension (95% CI, 1.43–1.68; p < 0.001). There was also an increased risk of mortality with stage 2 hypertension (hazard ratio, 1.13 [95% CI, 10.5–1.22]; p = 0.002). The following subanalysis was performed:

- Recipient sex: Females had an increased risk of death-censored graft failure with both stages 1 and 2 hypertension. However, males only had an increased risk with stage 2 hypertension.
- Age: Younger patients appeared more vulnerable to the impact of stages 1 and 2 hypertension.
- Transplant status (i.e., graft number and HLA status): Those who underwent retransplantation and those who had HLA antibodies were at higher risk of death-censored graft failure.

To our knowledge, this study is the largest to date in this patient cohort and reaffirms the relationship between hypertension and death-censored graft failure and mortality in the transplant population (3). The study failed to demonstrate a benefit of targeting BPs lower than 130/80 in contrast to the current Kidney Disease: Improving Global Outcomes (KDIGO) recommendations (5). As a retrospective cross-sectional analysis, which used nonstandardized clinic BP readings, it is unsurprising that this was a limited study and unable to establish a clear BP goal. This study contributes to the growing literature in support of early intervention and optimization in post-transplant hypertension and also re-emphasizes the need for clinicians to be seeking accurate BP assessment to make appropriate clinical decisions (6–8). To progress, we need to seek randomized control trials with rigorous protocols akin to the Systolic Blood Pressure Intervention Trial (SPRINT) to best serve our patients who have undergone kidney transplants (9). ■

Dearbhail Ni Cathain, MD, and Sam Kant, MD, FASN, are with the Division of Nephrology, Department of Medicine, St. Vincent's University Hospital, University College Dublin, Ireland. Dr. Kant is a deputy editor for Kidney News.

The authors report no conflicts of interest.

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On a Mission to Fill a Void in Pediatric Nephrology

By Lisa Schwartz

https://doi.org/10.62716/kn.000422025

Christel Wekon-Kemeni, MD

For Christel Wekon-Kemeni, MD, 2025 has been quite unforgettable. He kicked off the year on national television as a contestant on "Wheel of Fortune," an experience he described as surreal, exciting, and once-in-a-lifetime. Only a few weeks later, he was speaking to members of Congress as part of his advocacy efforts, fighting for the needs of children with chronic kidney disease (CKD) and kidney failure. This year marks another milestone in his journey: the start of his final year of fellowship training in pediatric nephrology and a future defined by many pivotal moments.

As a first-generation American with Cameroonian roots, Wekon-Kemeni believed he was destined for the field of medicine. Born in Boston and raised in Virginia, his mother was a nurse and his father a pharmacist. He was inspired and encouraged at a young age to pursue medicine, not just as a profession but as a calling.

Initially, Wekon-Kemeni dreamed of becoming an ophthalmologist, motivated by his own vision impairment. It was during high school, when his father became extremely ill with malaria, that his decision to go into medicine was solidified. "When my dad was in the hospital, I remember feeling helpless. I wanted to know why he got sick, how the human body worked, and how to heal him. It was after this experience that I committed to going into medicine to care for the health of others," he recalled.

A blog is born

As he was finishing his premedical studies at the University of Miami, Wekon-Kemeni began applying to medical school. After graduating from college and subsequently being accepted to medical school, he realized that his future was filled with unknowns, barriers, and hope. He wondered, "What did the road ahead have in store?"

Unable to find resources or first-hand accounts of the medical school experience online, he started his blog, *Black Man, M.D.* (1), in 2015. As a first-year medical student at Wake Forest University School of Medicine, he wanted to document his journey and provide insight for others navigating medical school, particularly underrepresented minorities, and as he writes in his blog, "to crush negative stereotypes."

His weekly posts offered a candid look at life as a Black medical student going through the challenges of getting through medical school, earning his degree, and later completing his residency training and chief resident year in pediatrics at The University of North Carolina at Chapel Hill. Many of his posts repeatedly addressed the question, "Why do I want to be a doctor?"

The road to pediatrics

Although he always thought that he would become an ophthalmologist, it was in his third year of medical school that he discovered pediatrics and a new path. "When I got to my pediatric rotation, I realized that I loved working with the kids," he recalled. "It was one of the only specialties where I felt excited to go and learn. It was fun and challenging. Everyone was passionate about delivering the very best care for the children. I knew there was a real opportunity to make a difference in children's lives."

Rotating through different pediatric subspecialties, he became intrigued by nephrology and the complexities of kidney physiology. When he started his fellowship training in pediatric nephrology at Emory University/Children's Healthcare of Atlanta, the specialty perfectly combined his two interests working with children on kidney health.

In his 2023 blog post, "Launching a New Life," Wekon-Kemeni shared the eye-opening experiences of his first year as a pediatric nephrology fellow—from the rigors of training and the wonder of attending his first pediatric kidney transplant surgery to partaking in Camp Independence, a summer camp for children with chronic illnesses (2). He wrote in this entry:

> "I was in awe of how much fun the kids were having at camp and how resilient they were at such a young age. As I talked with some of them, I listened to how they had to go about taking multiple medications on a daily basis.... I also learned what conditions they had and how it led them to have to receive organ transplants at such young ages, altering the way they could live their lives. What really amazed me was how nonchalant they described what they were saying, as if it was a simple fact of life. The thing is, it was a simple fact of life to them."

Addressing the shortage of specialists in the field

Throughout this first year of fellowship, Wekon-Kemeni recognized the enormous need for pediatric nephrologists to care for the specialized needs of young patients who were fragile. "There is a severe shortage of pediatric nephrologists," he noted. "Not many residents think about going into this specialty, and it is only going to get worse as people retire from the profession."

Concerted efforts to attract more specialists to the field have been developed to support the next generation of pediatric nephrologists. The Pediatric Subspecialty Loan Repayment Program (3) is an example of these efforts, offering up to $100,000 in loan repayment for clinicians providing pediatric medical, surgical, or behavioral care in underserved communities.

Additionally, initiatives like ASN's Loan Mitigation Program (4), which provides funding to decrease the loan burden of those entering the field of nephrology, and Kidney STARS (Students and Residents) Program (5), which provides funding for medical students, residents, and graduate students interested in nephrology to attend ASN Kidney Week to immerse themselves in the nephrology community and connect with mentors, have been designed to increase interest in pursuing a career in nephrology. Wekon-Kemeni not only benefited from ASN's Loan Mitigation Program but also from the Kidney STARS Program, attending Kidney Week virtually in 2021 and again in 2024 when he returned as a group mentor, guiding and encouraging medical students interested in pediatric nephrology.

Advocating for the needs of children with kidney diseases

The need for more research and kidney failure treatments specifically focused on children also inspired Wekon-Kemeni to become active with the American Society of Pediatric Nephrology's Public Policy Committee and ASN's advocacy efforts during his training. "Adult research and findings are often extrapolated to pediatric patients, but kids are not just little adults. We need medical professionals who are focused on them uniquely," he stated.

He regularly attends virtual ASN Hill Days, working to bring greater awareness to members of Congress about the needs of children with CKD, specifically the necessity for more pediatric nephrologists and policy solutions to address the complex Medicare and Medicaid challenges many families face.

An evolution of a mission

Wekon-Kemeni's journey into pediatric nephrology has transformed him over the years. His *Black Man, M.D.*, blog reflects how far he has come since he was a high school student with a dream to become a doctor. To help others realize a similar future in medicine, he created a scholarship for minority high school students, which he has supported through crowdfunding over the past 6 years. To date, 15 Desire to Inspire scholarships, totaling nearly $15,000, have been awarded, and he plans to continue and expand on those efforts.

Whether he meant to or not, Wekon-Kemeni has become a source of inspiration for others who follow his path. As he embarks on the next phase of his career, his mission remains clear: to continue caring and advocating for pediatric patients and their health care needs; inspiring, mentoring, and teaching the next generation of pediatric nephrologists; and making a lasting impact on the lives of children with kidney diseases.

To read Dr. Wekon-Kemeni's blog, *Black Man, M.D.*, and learn more about the Desire to Inspire Scholarship, visit https://blackmanmd.com/.

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"Yo-Yo Dieting" Linked to Increased Kidney Events in Type 1 Diabetes

https://doi.org/10.62716/kn.000492025

For patients with type 1 diabetes, body-weight cycling—sometimes called "yo-yo dieting"—is associated with a higher long-term risk of kidney events, suggests a study in *The Journal of Clinical Endocrinology & Metabolism*.

The retrospective observational study included 1432 patients with type 1 diabetes enrolled in the Diabetes Control and Complications Trial (DCCT) and the follow-up Epidemiology of Diabetes Interventions and Complications (EDIC) study. Patients ranged in age from 13 to 39 years; the average duration of follow-up across both studies was 21 years. In the initial DCCT report from 1993, intensive glycemic control delayed the onset and slowed the progression of diabetic retinopathy, nephropathy, and neuropathy.

For analysis of body-weight cycling, four measures of individual body-weight variability were calculated, with variability independent of the mean (VIM) as the primary index. Six criteria for decline in kidney function and progression to chronic kidney disease (CKD) were analyzed for their association with body-weight variability.

Participants with high VIM were more likely to experience a 40% decline in the estimated glomerular filtration rate from baseline to follow-up: hazard ratio (HR), 1.25. The association was independent of baseline and follow-up CKD risk factors and use of nephroprotective medications. High VIM was also associated with doubling of serum creatinine (HR, 1.34), stage 3 CKD (HR, 1.36), and rapid decline in the estimated glomerular filtration rate (>3 mL/min/m^2 per year; HR, 1.39).

Patients with high VIM were more likely to have moderate to severe increases in albuminuria, although the association was not significant after adjustment for covariates during follow-up. Other measures of body-weight cycling showed similar associations with diabetic kidney disease outcomes.

In the general population, yo-yo dieting is a CKD risk factor. In a previous study of the DCCT/EDIC cohort, the authors found that body-weight cycling is associated with increased risk of major cardiovascular events in patients with type 1 diabetes.

The new analysis shows increased long-term risk of kidney events associated with body-weight cycling in type 1 diabetes, independent of traditional risk factors and body mass index. The researchers discuss possible mechanisms of the observed associations. They conclude: "Clinically, strategies aimed at weight reduction in people with type 1 diabetes should focus on promoting long-term weight maintenance, as weight stability may have a positive impact on health outcomes" [Camoin N, et al. Body-weight cycling and risk of diabetic kidney disease in people with type 1 diabetes in the DCCT/EDIC population. *J Clin Endocrinol Metab*, published online February 4, 2025. doi: 10.1210/clinem/dgae852]. ■

Similar Outcomes of Nonsteroid Options for Childhood Nephrotic Syndrome

https://doi.org/10.62716/kn.000502025

Two classes of nonsteroid immunosuppressive drugs—cyclophosphamides and calcineurin inhibitors—have comparable effects on relapse rates in children with nephrotic syndrome, according to a target trial emulation study in *JAMA Pediatrics*.

Using data from the prospective INSIGHT (Insight Into Nephrotic Syndrome: Investigating Genes, Health, and Therapeutics) study, the researchers emulated a "pragmatic, open-label clinical trial" of treatment for childhood nephrotic syndrome. The analysis included children diagnosed with nephrotic syndrome from 1996 through 2019. The median age at diagnosis was 3.7 years; 64% of patients were boys. Treatment consisted of cyclophosphamide in 252 patients, calcineurin inhibitors in 131, and both medications sequentially in 87.

Randomization was emulated by overlap weighting propensity scores. The primary outcome of interest was time to relapse after initiation of cyclophosphamide or calcineurin inhibitor treatment. Median follow-up after treatment initiation was 5.5 years.

Relapses occurred in 71% of children with cyclophosphamide and 88% with calcineurin inhibitors. Time to relapse was similar between groups, before and after propensity score weighting. In weighted cohorts, relapse rates were 73% with cyclophosphamide and 85% with calcineurin inhibitors; the difference was not significant.

With both treatments, no more than 5% of patients had incident chronic kidney disease. Subsequent relapse rates, use of nonsteroid immunosuppression, and kidney function were similar between groups. Calcineurin inhibitor use was associated with increased hospitalizations and intravenous albumin use: hazard ratios, 1.83 and 2.81, respectively.

One-half of children with nephrotic syndrome are treated with nonsteroid immunosuppressive medications to prevent relapse. In the absence of comparative effectiveness data, the use of cyclophosphamide versus calcineurin inhibitors varies significantly.

This emulated clinical trial suggests similar relapse rates in children with nephrotic syndrome initiating treatment with these two drugs. Given its lower cost, shorter duration of treatment, and greater accessibility, cyclophosphamide is the preferred initial choice for nonsteroid immunosuppressive medication in childhood nephrotic syndrome, the researchers suggest [Robinson CH, et al. Comparative efficacy of nonsteroid immunosuppressive medications in childhood nephrotic syndrome. *JAMA Pediatr* 2025; 179:321–331. doi: 10.1001/jamapediatrics.2024.5286]. ■

Sex Disparities in Kidney Transplantation Narrow, but Persist

https://doi.org/10.62716/kn.000462025

Recent decades have seen progress in correcting sex inequities in access to kidney transplantation, although significant disparities remain, reports a pre-proof study in the *American Journal of Kidney Diseases*.

The retrospective cohort study included data on 2.3 million adults initiating kidney replacement therapy between 1997 and 2020, drawn from the US Renal Data System. Trends in sex inequities in transplant waitlisting and living and deceased donor kidney transplantation (LDKT and DDKT) were analyzed. Outcomes were analyzed in 3-year eras, beginning from 1997 to 2000 and ending from 2017 to 2020, with adjustment for patient- and neighborhood-level characteristics.

"Sex inequities in waitlisting became less pronounced over time," the researchers write. After adjustment for clinical factors, the disparity in waitlist placement for women compared with men decreased from 19% in 1997 to 2000 to 14% in 2017 to 2020. Among patients with diabetes, the disparity decreased from 25% to 22%. Patients aged 60 to 79 years saw a greater reduction in waitlist disparities: from 35% in 1997 to 2000 to 18% in 2017 to 2020.

Among patients on the waitlist, sex disparity in LDKT increased significantly across eras: from 11% to 21%. There was a small decrease in disparity among women aged 60 to 79 years: from 25% to 23%. Meanwhile, the inequity in DDKT flipped from an 8% disparity favoring men in 1997 to 2000 to a 16% disparity favoring women in 2017 to 2020. Similar patterns were noted for patients with diabetes and for those aged 60 to 79 years.

The findings suggest improvement in inequities in kidney transplant waitlisting for women compared with men. However, women face persisting disparities, particularly those aged 60 years or older or with diabetes-attributed kidney failure. Sex disparities in LDKT among women have worsened over time.

For reasons that are unclear, access to DDKT shifted from a disparity favoring men to a substantial disparity favoring women. Further efforts to mitigate sex inequities should emphasize a "multi-level, multifactorial approach encompassing all phases of the complex transplant care continuum," the researchers write [Harding JL, et al. Trends in sex disparities in access to kidney transplantation: A nationwide US cohort study. *Am J Kidney Dis*, published online February 27, 2025. doi: 10.1053/j.ajkd.2024.12.008]. ■

SGLT2 Inhibitor Reduces Need for Insulin in Diabetic Kidney Disease

https://doi.org/10.62716/kn.000482025

For people with chronic kidney disease (CKD) and type 2 diabetes, treatment with the sodium-glucose cotransporter-2 (SGLT2) inhibitor canagliflozin can reduce insulin requirements, according to clinical trial data reported in *Nephrology Dialysis Transplantation*.

The researchers present a post hoc analysis of data from the CREDENCE (Canagliflozin and Renal Events in Diabetes With Established Nephropathy Clinical Evaluation) study, a randomized, placebo-controlled trial of canagliflozin in people with type 2 diabetes and CKD. In the original CREDENCE report, canagliflozin was associated with reduced risk of kidney failure and cardiovascular events.

The analysis included 4401 randomized patients. Study treatments were compared for their effects on insulin use, including initiation, dose adjustments, and discontinuation. Kidney, cardiovascular, and safety outcomes were evaluated as well.

At baseline, 65.5% of patients were receiving insulin. This group had a lower estimated glomerular filtration rate, higher albuminuria, and longer duration of diabetes.

At a median follow-up of 2.0 years, patients assigned to canagliflozin had a significant reduction in the primary outcome of insulin initiation or dose intensification of over 25%: hazard ratio, 0.81. Reductions in insulin requirement were independent of baseline kidney function or albuminuria. Patients receiving canagliflozin were also more likely to have sustained insulin dose reductions of greater than 50%. Rates of insulin discontinuation were low: approximately 4% in both groups.

With their unique glycosuric effect, SGLT2 inhibitors are a strongly recommended therapy for type 2 diabetes and CKD. This treatment may help to reduce the burdens associated with insulin use. However, there are few data on the extent of reduction in insulin requirement associated with SGLT2 inhibition.

The new analysis suggests "clinically meaningful" reductions in insulin initiation and dose intensification with canagliflozin in people with CKD and type 2 diabetes. The study "supports the use of canagliflozin in people with CKD, not only for end organ protection, but also to...reduce exposure to insulin and its associated adverse

effects," the investigators conclude [Beal B, et al. Effects of SGLT2 inhibition on insulin use in CKD and type 2 diabetes: Insights from the CREDENCE trial. *Nephrol Dial Transpl*, published online February 28, 2025. doi: 10.1093/ndt/gfaf044].

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