ASN American Society of Nephrology

Kidney News

July 2022 | Vol. 14, Number 7

Vaccination, Treatment Decisions Studied in Adults with Kidney Diseases during COVID-19

By Tracy Hampton

Two recent studies published in the *CJASN* address different aspects of the COVID-19 pandemic in adults with advanced kidney diseases: one examines whether prior COVID-19 vaccination affected the outcomes of individuals on dialysis who became infected with SARS-CoV-2 (1), and the other assesses the pandemic's impact on treatment decision-making for older patients with chronic kidney disease (CKD) (2).

People with CKD or other severe chronic medical conditions are at higher risk for more serious COVID-19 illness, and patients with kidney failure who rely on in-center hemodialysis face an elevated risk of becoming exposed to the SARS-CoV-2 virus. Research has shown that individuals undergoing hemodialysis have impaired immune responses to COVID-19 vaccines, but few studies have described the efficacy of COVID-19 vaccination in such patients.

To investigate, scientists conducted a multi-center observational study of patients who were receiving hemodialysis in London and who were regularly tested for COVID-19 during the period of vaccine rollout with Pfizer-BioNTech's mRNA-based BNT162b2 and AstraZeneca's adenovirus-based AZD1222. SARS-CoV-2 infection was identified in 1323 patients of different ethnicities (Asian/other, 30%; Black, 38%; and White, 32%), including 1047 (79%) unvaccinated, 86 (7%) after first-dose vaccination, and 190 (14%) after second-dose vaccination. Most patients who tested positive had a mild course of COVID-19, but 515 (39%) were hospitalized, and 172 (13%) died.

Results indicated that older age, diabetes, and immune suppression were associated with greater illness severity. After adjustments, prior two-dose vaccination was associated with a 75% lower risk of hospital admission and an 88% lower risk of death compared with no vaccination. The researchers found it notable that no loss of protection against COVID-19 was seen in patients older than 65 years or with increasing time since vaccination, and no difference was seen between vaccine types.

Continued on page 7

Update on the Task Force on the Future of Nephrology

Reimagining Nephrology Fellowship Training

By Mark Rosenberg

The ASN Task Force on the Future of Nephrology was charged in April 2022 to reconsider all aspects of the future of nephrology and determine how to best prepare nephrology fellows for the challenges and opportunities the future will bring. Consisting of a diverse cross-section of ASN members, the task force will provide recommendations to the ASN Council by September 2022. The timeline will meet the commitment made by ASN to the American Board of Internal Medicine (ABIM) and the Accreditation Council for Graduate Medical Education (ACGME), as these organizations determine what changes should be made to nephrology certification and recertification (ABIM) and fellowship training program (ACGME) requirements. To learn more about the task force, its charge, and membership, please refer to the April and June 2022 *Kidney News* articles (1–3).

Through weekly meetings, the task force has received input from multiple stakeholders, including representatives from ABIM and ACGME, the ASN Workforce and Training Committee (WTC) leadership, and people with kidney diseases. As this work progresses, plans are in place to engage other stakeholders, such as nephrology fellows, training pro-

Continued on page 11

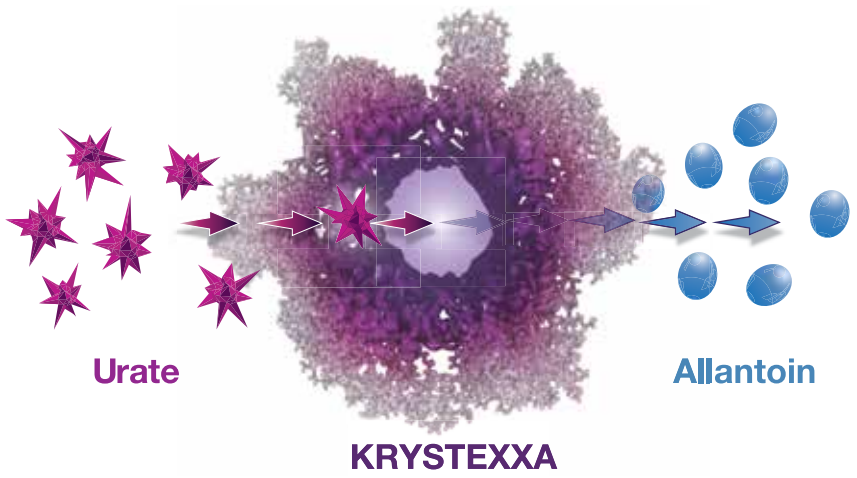
Inside

Transplantation
Advances in kidney transplantation are pushing the barriers of science and society.

ISCHEMIA CKD trial
New data on cardiovascular procedures in patients with advanced CKD

Stem cell transplant
Improving kidney outcomes after allogeneic hematopoietic stem cell transplant

KRYSTEXXA (PEGLOTICASE) IS A RECOMBINANT INTO ALLANTOIN[1]



Artist's renditions.

RENAL EXCRETION OF ALLANTOIN IS UP TO 10 TIMES MORE EFFICIENT THAN EXCRETION OF URIC ACID[2]

INDICATION AND IMPORTANT SAFETY INFORMATION

INDICATIONS AND USAGE

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.

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

IMPORTANT SAFETY INFORMATION

WARNING: ANAPHYLAXIS AND INFUSION REACTIONS

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-type hypersensitivity reactions have also been reported. KRYSTEXXA should be administered in healthcare settings and by healthcare providers prepared to manage anaphylaxis and infusion reactions. Patients should be premedicated with antihistamines and corticosteroids. Patients should be closely monitored for an appropriate period of time for anaphylaxis after administration of KRYSTEXXA. Monitor serum uric acid levels prior to infusions and consider discontinuing treatment if levels increase to above 6 mg/dL, particularly when 2 consecutive levels above 6 mg/dL are observed.

The risk of anaphylaxis and infusion reactions is higher in patients who have lost therapeutic response.

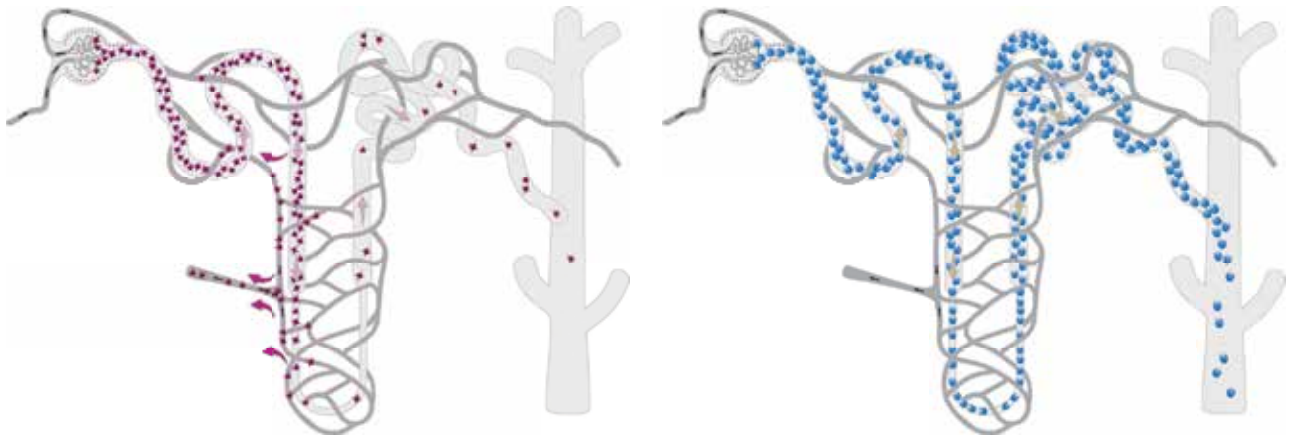
Concomitant use of KRYSTEXXA and oral urate-lowering agents may blunt the rise of sUA levels. Patients should discontinue oral urate-lowering agents and not institute therapy with oral urate-lowering agents while taking KRYSTEXXA.

In the event of anaphylaxis or infusion reaction, the infusion should be slowed, or stopped and restarted at a slower rate.

References: 1. KRYSTEXXA (pegloticase) [prescribing information] Horizon. **2.** McDonagh EM, et al. *Pharmacogenet Genomics*. 2014;24:464-476. **3.** Terkeltaub R, et al. *Arthritis Res Ther*. 2006;8(suppl 1):S4.

HORIZON

URICASE ENZYME THAT CONVERTS URATE



Only 10% of uric acid filtered through the kidney is excreted[3]

vs

Nearly all of allantoin filtered through the kidney is excreted[2,3]

TO LEARN MORE, VISIT KRYSTEXXAHCP.COM

Inform patients of the symptoms and signs of anaphylaxis, and instruct them to seek immediate medical care should anaphylaxis occur after discharge from the healthcare setting.

CONTRAINDICATIONS: G6PD DEFICIENCY ASSOCIATED HEMOLYSIS AND METHEMOGLOBINEMIA

Screen patients for G6PD deficiency prior to starting KRYSTEXXA. Hemolysis and methemoglobinemia have been reported with KRYSTEXXA in patients with G6PD deficiency. Do not administer KRYSTEXXA to these patients.

GOUT FLARES

An increase in gout flares is frequently observed upon initiation of anti-hyperuricemic therapy, including treatment with KRYSTEXXA. If a gout flare occurs during treatment, KRYSTEXXA need not be discontinued. 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 studied in patients with congestive heart failure, but some patients in the clinical trials experienced exacerbation. Exercise caution when using KRYSTEXXA in patients who have congestive heart failure and monitor patients closely following infusion.

ADVERSE REACTIONS

The most commonly reported adverse reactions in clinical trials with KRYSTEXXA are gout flares, infusion reactions, nausea, contusion or ecchymosis, nasopharyngitis, constipation, chest pain, anaphylaxis and vomiting.

Please see Brief Summary of Prescribing Information, including Boxed Warning, for KRYSTEXXA on the following page.

KRYSTEXXA®
pegloticase

KRYSTEXXA® pegloticase

(pegloticase injection), for intravenous infusion

Brief Summary - Please see the KRYSTEXXA package insert for Full Prescribing 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. However, delayed-type hypersensitivity reactions have also been reported.**
- **KRYSTEXXA should be administered in healthcare settings and by healthcare providers prepared to manage anaphylaxis and infusion reactions.**
- **Patients should be pre-medicated with antihistamines and corticosteroids.**
- **Patients should be closely monitored for an appropriate period of time for anaphylaxis after administration of KRYSTEXXA.**
- **Monitor serum uric acid levels prior to infusions and consider discontinuing 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. Do not administer KRYSTEXXA to patients with G6PD deficiency.**

INDICATIONS AND USAGE

KRYSTEXXA® (pegloticase) is a PEGylated uric acid specific enzyme 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.

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

CONTRAINDICATIONS

Glucose-6-phosphate dehydrogenase (G6PD) deficiency

WARNINGS AND PRECAUTIONS

Anaphylaxis

During pre-marketing clinical trials, 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. 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 consider discontinuing 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

During pre-marketing controlled clinical trials, 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 consider discontinuing 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

During the controlled treatment period with KRYSTEXXA or placebo, 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.

Congestive Heart Failure

KRYSTEXXA has not been formally studied in patients with congestive heart failure, but some patients in the clinical trials experienced exacerbation. 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.

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

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 6-month 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.

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.

The most common adverse reactions that occurred in ≥5% of patients treated with KRYSTEXXA 8 mg every 2 weeks are provided in Table 1.

Table 1. Adverse Reactions Occurring in 5% or More of Patients Treated with KRYSTEXXA Compared to Placebo

Adverse Reaction (Preferred Term)	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

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.

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.

Postmarketing Experience

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

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.

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. 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).

General Information

Provide and instruct patients to read the accompanying Medication Guide before starting treatment and before each subsequent treatment.

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.
- 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.
- 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.

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. Advise patients that they should not stop KRYSTEXXA therapy if they have a flare.

Manufactured by:
Horizon Therapeutics Ireland DAC
Dublin, Ireland
US License Number 2022

Distributed by:
Horizon Therapeutics
Deerfield, IL 60015

ASN American Society of Nephrology

KidneyNews

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

www.asn-online.org

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

Publications mail agreement No. 40624074. Return undeliverable Canadian addresses to PO Box 503, RPO West Beaver Creek, Richmond Hill ON L4B 4R6

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

★ WINNER OF 3 DESIGN AWARDS ★

GD USA 2018 WINNER — WINNER 2019 APEX AWARDS FOR PUBLICATION EXCELLENCE — GD USA 2020 WINNER

CORPORATE SUPPORTERS 2021

ASN gratefully acknowledges the Society's Diamond and Platinum Corporate Supporters for their contributions in 2021.

DIAMOND LEVEL

Akebia Therapeutics

AstraZeneca

natera

Otsuka | Visterra — Otsuka Group of Companies

PLATINUM LEVEL

Bayer

CareDx

Fresenius Medical Care

Travere Therapeutics

Vifor Pharma

Vaccination, Treatment Decisions Studied

Continued from cover

"COVID-19 continues to be common in patients on dialysis, causing hospital admissions and death, but fortunately it is milder with two doses of the vaccine," said senior author Debasish Banerjee, MD, FRCP, of St George's University Hospitals, National Health Service (NHS) Foundation Trust, London.

An accompanying editorial (3) noted that the study's encouraging results may prove the effectiveness of COVID-19 vaccines for patients on dialysis, but there is still much work to be done. The authors—Matthew J. Oliver, MD, MHS, FRCPC, and Peter G. Blake, MB, MSc, FRCPC, of Ontario Health—emphasized the importance of looking back and carefully evaluating the clinical effect of decisions made during the pandemic, including the early decision to offer vaccination to patients without high-level evidence of benefit. "While the COVID-19 pandemic is ever changing, making vaccine studies challenging, it also provides new opportunities to examine vaccine effectiveness from many different angles," they wrote.

In an accompanying Patient Voice article (4), Uwe K. H. Korst, a patient consultant and a co-chair of ERKNet, The European Rare Kidney Disease Reference Network, advocates for additional education for patients, nurses, doctors, and the public to increase vaccine acceptance. He also stressed the need to ensure that patients' voices are heard.

Another concern during the COVID-19 pandemic relates to how uncertainty surrounding the evolving pandemic influences shared decision-making among clinicians, patients with advanced CKD, and their care partners. To investigate this issue, researchers of this second recent study (2) interviewed 76 adults (39 older patients with advanced CKD, 17 care partners, and 20 nephrology clinicians) from Boston, Portland (Maine), San Diego, and Chicago from August to December 2020. The interviews revealed that clinicians perceived greater vulnerability among older patients with CKD and more readily encouraged home-based modalities for these patients during the COVID-19 pandemic, but their discussions of vulnerability, advanced care planning, and conservative management remained limited.

Lack of discussions of COVID-19-related risks, fewer education options, and inconsistent discussions of advanced care planning and conservative management left patients with unaddressed concerns and the need to navigate the emerging COVID-19 guidance on their own. Despite heightened uncertainty, patient preferences for treatment modality (such as dialysis) remained stable, and most perceived their chosen modality to be the safest, the researchers found. Importantly, clinicians reported burnout caused by the pandemic, increased time demands, and workforce limitations.

"To improve shared decision-making during the pandemic and its aftermath, clinicians should promote and encourage conversations with patients who want to talk about COVID-19, with an emphasis on safety and quality of life, including the risks posed to them by COVID-19 and the impact of COVID-19 on treatment options. These discussions should present all options, including conservative management, and incorporate advanced care planning," said senior author Keren Ladin, PhD, MSc, of Tufts University. "Also, clinician burnout must be addressed with adequate resources and appropriate training."

The authors noted that their findings suggest an openness to telemedicine, which can be a convenient form of care for patients and their care partners and can help improve work-life balance for nephrologists and other health care providers.

References

1. Ashby DR, et al. Severity of COVID-19 after vaccination among hemodialysis patients: An observational cohort study. *Clin J Am Soc Nephrol* [published online ahead of print June 1, 2022]. doi: 10.2215/CJN.16621221; https://cjasn.asnjournals.org/content/early/2022/06/01/CJN.16621221
2. Porteny T, et al. Treatment decision making for older kidney patients during COVID-19. *Clin J Am Soc Nephrol* [published online ahead of print June 1, 2022]. https://cjasn.asnjournals.org/content/early/2022/06/07/CJN.13241021
3. Oliver MJ, Blake PG. Clinical utility of COVID-19 vaccination in patients undergoing hemodialysis. *Clin J Am Soc Nephrol* [published online ahead of print June 1, 2022]. doi: 10.2215/CJN.04930422; https://cjasn.asnjournals.org/content/early/2022/06/01/CJN.04930422
4. Korst UKH. COVID-19 vaccination for patients undergoing long-term hemodialysis (Patient Voice). *Clin J Am Soc Nephrol* [published online ahead of print June 1, 2022]. doi: 10.2215/CJN.04460422; https://cjasn.asnjournals.org/content/early/2022/06/01/CJN.04460422

Top 10 Predictions about US Nephrologists in 2035

ASN Executive Vice President's Update

By Tod Ibrahim

During the past few months, I have participated in several meetings that included in-depth discussions about the future of the health care workforce in the United States. Each time, the discussion started with predictions about shortages of every kind of health professional—from physicians to nurses to physician assistants/associates to other clinicians—and then shifted to concerns about the ability to provide high-quality patient care in the future as a result.

Although this editorial will focus on the future of nephrologists in the United States, I recognize that the situation is dire throughout the world, particularly for nurses. Earlier this year, the International Centre on Nurse Migration—in partnership with CGFNS (Commission on Graduates of Foreign Nursing Schools) International and the International Council of Nurses—estimated "up to 13 million more nurses will be required over the next decade, the equivalent of almost half of the world's current 28 million-strong workforce" of nurses (1, 2). Another recent report predicted that the United States will have "a gap of between 200,000 and 450,000 nurses available for direct patient care" by 2025 (3).

The reasons for the global shortage of nurses and the shortage of other health professionals, including nephrologists, in the United States are similar. The COVID-19 pandemic has taken a toll on health professionals individually and collectively, exposing broader issues within health care systems. Already low before the pandemic, staffing ratios for health professionals have become worse, causing more overwork, dissatisfaction, hopelessness, and burnout. Nearly one-third of health professionals "surveyed intend to reduce work hours," and one in five physicians and two in five nurses "intend to leave their practice altogether" during the next year, a recent report noted (4).

According to the Association of American Medical Colleges (AAMC), the United States "could see an estimated shortage of between 37,800 and 124,000 physicians by 2034" (5). More specifically, AAMC projects a "shortage of primary care physicians of between 17,800 and 48,000" and a "shortage across the nonprimary care specialties of between 21,000 and 77,100 physicians," including nephrologists.

"If underserved populations had health care use patterns like populations with fewer access barriers, demand would rise such that the nation would be short by about 102,400 (13%) to 180,400 (22%) physicians relative to the current supply," the AAMC report added. AAMC defines underserved as "minority populations, people living in rural communities, and people without medical insurance." It is important to highlight the fact that the United States must address a shortage of physicians overall as well as a maldistribution of physicians across geography, race and ethnicity, economic status, and specialties.

An estimated 10,370 to 12,939 nephrologists currently practice in the United States (6, 7). From 2008 to 2020, the number of US nephrologists doubled, even though only 52% of tracks offered by nephrology fellowship training programs, accredited by the Accreditation Council for Graduate Medical Education (ACGME), filled all their positions through the National Resident Matching Program (NRMP) Medical Specialties Matching Program in the appointment year 2022 Match (8, 9). (NRMP is rebranding this program in 2022 as the Medicine and Pediatrics Specialties Match, because the matches for adult and pediatric specialties are now on the same timeline.)

Because of this history during the past decade and the projected shortages among other internal medicine specialties, it is highly unlikely that the number of nephrology fellows will increase much in the near future. If anything, the number of nephrology fellows may decrease, given the current mismatch between the number of internal medicine residents who matched into nephrology in December 2020 (345) and the number who started fellowship training in July 2021 (454) (10).

As a new cadre of physicians start their nephrology fellowships this month, it is fair to ask, "What are the top 10 predictions about US nephrologists in 2035?"

1. **Like most countries, the United States will face massive shortages of health professionals.** Because undergraduate and graduate medical education takes at least 7 years for primary care physicians, 9 years for adult nephrologists, 10 years for pediatric nephrologists, and longer for several other specialists, this is the time to implement a strategy for addressing these shortages as well as the maldistribution across geography, race and ethnicity, economic status, and specialties.

2. **Other health professionals will have a greater role, responsibility, and authority in much of the United States.** At least three forces are blurring the lines among health professionals, including nephrologists: Legislatures in states unable to attract physicians are expanding scope of practice for other health professionals, efforts to contain soaring health care costs are creating incentives to shift responsibilities, and technology is forcing a re-evaluation of how best to deploy the workforce.

3. **The public will rely more on both episodic care and omnichannel health delivery via retailers, such as Amazon, CVS Health, Walgreens, and Walmart.** This year, all four of these companies "accelerated their investments in healthcare," focusing on "new areas from primary care to telehealth" (11). Among the Fortune 500, these companies rank first (Walmart), second (Amazon), fourth (CVS Health), and 18th (Walgreens) (12). In 2018, CVS Health launched CVS Kidney Care "to fundamentally transform the treatment paradigm" for the millions of people with kidney diseases by focusing "on early identification of kidney disease, targeted patient engagement, and ongoing education to help slow disease progression" (13).

4. **Patients will depend even more on information from unregulated social media channels to inform their care.** "Increasing numbers of Americans have turned to internet sources for health and medical information in recent years, with approximately three out of four searching for health information online today," observed the National Academy of Medicine (14). Because few of these channels "differentiate between credible and non-credible sources of information," the quality, accuracy, and truthfulness vary. This reality forces patients to "make their own judgments about how much trust to place in a source and the quality of the information it shares," and these decisions are "influenced by their level of health and digital literacy, prior knowledge, personal situations, and personal beliefs." As the leadership of the American Board of Internal Medicine recently stated, "If enough people like, share, or choose to believe something, others will accept it as true" (15).

5. **Local, state, and federal governments will insert themselves more between physicians and patients.** In "Confronting disinformation, polarization, and demagoguery," I tried to describe this issue in the May 2022 edition of ASN *Kidney News* (16). Since then, this situation has worsened, resulting in a recent perspective, "Physicians as political pawns—the Texas directive on gender-affirming care and other moves" that prophesied: "These political and legal challenges to the profession will be felt unequally, but the reverberations of politicized mistrust will harm everyone who needs to be able to tell a doctor the truth about themselves, as well as any doctor who needs to hear it" (17).

6. **Nearly all US physicians will be born between 1965 and 2005.** This 40-year span includes three generations: Generation X (born between 1965 and 1980), Millennials (1981–1996), and Generation Z (1997–2012). Each of these generations will be progressively more racially and ethnically diverse, socially engaged, and politically active (18).

7. **Facing considerable debt, physicians will also be more likely to retire earlier from medicine than previous generations.** The first half of this prediction is based on fact: The average medical student debt is projected to exceed $300,000 by 2024, whereas "Black and African American medical students owe more, on average, than their peers of any race or ethnicity" (19). These projections predate the

current reality of rising inflation and higher interest rates, so debt is likely to be even greater. The second half of this prediction is informed speculation: Physicians have embraced the "Great Resignation"; both Generation X and Millennials value work-life balance, freedom, and flexibility; and the specialties that currently have the earliest retirement age (anesthesia, emergency medicine, and interventional radiology) were at the forefront of the influx of private equity and employed physicians, which is currently happening in nephrology (20).

8 **Nearly 100% of US physicians will be employed.** The number of physicians employed by hospitals, health systems, or corporate entities has increased from 42% in 2012 to 74% in 2021 (21, 22). Additionally, more than 90% of physicians who accepted new positions last year were "as employees and not as independent practice owners/partners," up from 60% in 2001 (23). In this year's January issue of ASN *Kidney News*, Katherine Westin Kwon, MD, FASN, and Eugene Lin, MD, MS, FASN, described how "Start-up companies, larger for-profit healthcare providers, and venture capital firms have formed a marketplace of new products aimed at helping nephrologists improve their management of CKD [chronic kidney disease] at a population level," which often involves employing nephrologists (24).

9 **Current physician specialties will be more specialized, and current subspecialties will be more sub-subspecialized.** On the one hand, greater shortages of health professionals could result in more generalization. For example, each nephrologist will be responsible for more patients (especially in underserved parts of the country), necessitating a broader range of skills, knowledge, and experience. On the other hand, every trend in medicine is toward greater specialization, which is incentivized by the current reimbursement system. Moreover, if the future of health care is employed nephrologists working in large, integrated delivery systems (including retailers), then the ideal role for a nephrologist is treating the most challenging cases across the spectrum of kidney diseases, failure, and transplantation, which likely necessitates some sort of structured subspecialization.

10 **Physician-scientists will be fewer, older, and more endangered than ever.** Concerns about the future of physician-scientists started in 1979 and continue today (25). As illustrated in "Physician-scientists in the United States at 2020: Trends and concerns," the "disincentives to research careers—unstable research funding, financial pressures on medical institutions, and student debt—remain," whereas the gap between when physician-scientists complete research training and receive their first grants from the National Institutes of Health has widened (26). As is well documented, the future physicians in the United States—people who identify as underrepresented in medicine, including women—are less likely to pursue careers as physician-scientists. The future for physician-scientists in nephrology is worse than in nearly every other discipline: "Underfunding of kidney disease research impedes scientific opportunities and innovation and prevents the collaboration of young investigators with research faculty that can accelerate the exodus of talent within the nephrology research workforce" (27).

Earlier this year, the American Society of Nephrology established the Task Force on the Future of Nephrology. The task force is charged with envisioning how best the specialty can meet the needs of people with kidney diseases. By focusing on what is best for patients, the task force will articulate a strategy for accomplishing Robert Frost's wise advice in "A Servant to Servants": "… the best way out is always through" (28). Nephrology is well-positioned to be a stronger specialty in 2035 than it is today if we are purposeful during the next 13 years and beyond. ■

Tod Ibrahim, MLA, is Executive Vice President, American Society of Nephrology, Washington, DC.

Acknowledgment: Mr. Ibrahim thanks ASN Data Science Officer Kurtis Pivert for his help with this editorial.

References

1. International Council of Nurses. New report calls for global action plan to address nursing workforce crisis and prevent an avoidable healthcare disaster. January 24, 2022. https://www.icn.ch/news/new-report-calls-global-action-plan-address-nursing-workforce-crisis-and-prevent-avoidable
2. Buchan J, et al. Sustain and retain in 2022 and beyond. The global nursing workforce and the COVID-19 pandemic. International Council of Nurses, CGFNS International, and International Centre on Nurse Migration. January 2022. https://www.icn.ch/system/files/2022-01/Sustain%20and%20Retain%20in%202022%20and%20Beyond-%20The%20global%20nursing%20workforce%20and%20the%20COVID-19%20pandemic.pdf
3. Berlin G, et al. Assessing the lingering impact of COVID-19 on the nursing workforce. McKinsey & Company. May 11, 2022. https://www.mckinsey.com/industries/healthcare-systems-and-services/our-insights/assessing-the-lingering-impact-of-covid-19-on-the-nursing-workforce
4. Sinsky CA, et al. COVID-related stress and work intentions in a sample of US health care workers. *Mayo Clin Proc Innov Qual Outcomes* 2021; 5:1165–1173. doi: 10.1016/j.mayocpiqo.2021.08.007
5. Association of American Medical Colleges. The complexities of physician supply and demand: Projections from 2019 to 2034. IHS Markit, Ltd. June 2021. https://www.aamc.org/media/54681/download?attachment
6. Centers for Medicare & Medicaid Services. National downloadable file. May 21, 2022. https://data.cms.gov/provider-data/dataset/mj5m-pzi6
7. American Board of Internal Medicine. Candidates certified—all candidates. May 1, 2021. https://www.abim.org/Media/vaqdilmh/1_candidates-certified-all-candidates-050121.pdf
8. Association of American Medical Colleges. Physician specialty data report. 2020. https://www.aamc.org/data-reports/workforce/report/physician-specialty-data-report
9. National Resident Matching Program. Results and data. Specialties Matching Service. The Match. March 2022. https://www.nrmp.org/wp-content/uploads/2022/03/2022-SMS-Results-Data-FINAL.pdf
10. National Resident Matching Program. Results and data. Specialties Matching Service. The Match. February 2021. https://www.nrmp.org/wp-content/uploads/2022/04/SMS_Result_and_Data_2021.pdf
11. Torrence R. 2022 forecast: Competition in retail healthcare will heat up. Here's what to expect from Amazon, CVS and Walgreens. Fierce Healthcare. December 22, 2021. https://www.fiercehealthcare.com/practices/5-predictions-for-retail-healthcare-industry-2022
12. Fortune 500. *Fortune*. 2022. https://fortune.com/fortune500/
13. CVS Health. Kidney Care. 2022. https://www.cvshealth.com/our-services/health-and-wellness-services/kidney-care
14. Kington RS, et al. Identifying credible sources of health information in social media: Principles and attributes. National Academy of Medicine. July 16, 2021. https://nam.edu/identifying-credible-sources-of-health-information-in-social-media-principles-and-attributes/
15. Baron RJ, Ejnes YD. Physicians spreading misinformation on social media—do right and wrong answers still exist in medicine? *N Engl J Med* [published online ahead of print May 18, 2022]. doi: 10.1056/NEJMp2204813; https://www.nejm.org/doi/full/10.1056/NEJMp2204813
16. Ibrahim T. Confronting disinformation, polarization, and demagoguery. *Kidney News* 2022; 14(5):8–9. https://www.kidneynews.org/view/journals/kidney-news/14/5/article-p8_3.xml
17. Kirkland A. Physicians as political pawns—the Texas directive on gender-affirming care and other moves. *N Engl J Med* 2022; 386:2161–2164. doi: 10.1056/NEJMp2203746
18. Fry R, Parker K. Early benchmarks show 'post-millennials' on track to be most diverse, best-educated generation yet. A demographic portrait of today's 6- to 21-year-olds. Pew Research Center. November 15, 2018. https://www.pewresearch.org/social-trends/2018/11/15/early-benchmarks-show-post-millennials-on-track-to-be-most-diverse-best-educated-generation-yet/
19. Education Data Initiative. Average medical school debt. December 9, 2021. https://educationdata.org/average-medical-school-debt
20. Nabity J. Which physician specialties retire early? Physicians Thrive. April 6, 2021. https://physiciansthrive.com/retirement-planning/specialty-retirement/
21. Kane CK, Emmons DW. Policy research perspectives. New data on physician practice arrangements: Private practice remains strong despite shifts toward hospital employment. American Medical Association. 2013. https://www.ama-assn.org/sites/ama-assn.org/files/corp/media-browser/premium/health-policy/prp-physician-practice-arrangements_0.pdf
22. Physicians Advocacy Institute. COVID-19's impact on acquisitions of physician practices and physician employment 2019–2021. Prepared by Avalere Health. April 2022. http://www.physiciansadvocacyinstitute.org/Portals/0/assets/docs/PAI-Research/PAI%20Avalere%20Physician%20Employment%20Trends%20Study%202019-21%20Final.pdf?ver=ksWkgjKXB_yZfImFdXlvGg%3d%3d
23. Miller P. A growing number of physicians are employed. Physician staffing blog. Merritt Hawkins. May 6, 2022. https://www.merritthawkins.com/news-and-insights/blog/healthcare-news-and-trends/increase-of-employed-physicians/
24. Kwon KW, Lin E. Shifting practice landscape. For-profit companies move into CKD care. *Kidney News* 2022; 14(1):11. https://www.kidneynews.org/view/journals/kidney-news/14/1/article-p11_5.xml?tab_body=fulltext
25. Wyngaarden JB. The clinical investigator as an endangered species. *N Engl J Med* 1979; 301:1254–1259. doi: 10.1056/NEJM197912063012303
26. Garrison HH, Ley TJ. Physician-scientists in the United States at 2020: Trends and concerns. *FASEB J* 2022; 36:e22253. doi: 10.1096/fj.202200327
27. Murray R, Kramer H. Realizing the goals of the Advancing American Kidney Health initiative: Toward a better future for kidney disease research funding. *Adv Chronic Kidney Dis* 2022; 29:76–82. doi: 10.1053/j.ackd.2022.01.005
28. Frost R. A Servant to servants. Bartleby.com. 1915. https://www.bartleby.com/118/9.html

PHAIRIFY

Take Control of Your Career with Phairify

ASN is partnering with Phairify to provide members with new career management tools. Get complimentary access to Phairify's exclusive nephrology-specific compensation and productivity data that can level the negotiation playing field for physicians.

Learn more at www.asn-online.org/phairify or scan the QR code with your mobile device.

Update on the Task Force on the Future of Nephrology

Continued from cover

grams, private practice nephrology groups, and nephrology professional organizations. The task force is taking a data-driven approach to the current state of nephrology training and practice that includes data from the ABIM Nephrology Procedures Survey Study of diplomates; questions assessing fellows' perspectives on nephrology procedures included in ASN's 2022 Nephrology Fellow Survey; and the ASN Data Resource Center's reports regarding the current and future workforce, nephrology practice patterns, and fellow assessments of educational needs.

The challenge of reimagining nephrology fellowship training to meet future practice requirements is determining what that future will look like. Recommendations need to account for the changing landscape of undergraduate and graduate medical education, including a greater emphasis on competency-based medical education, and changes that are happening in health care and nephrology practice. The task force will identify core strategies to ensure current and future nephrology fellows are prepared to best meet the needs of people with kidney diseases.

Key issues that the task force is considering include:

- **Procedural requirements for nephrology certification.** These requirements currently include temporary vascular access placement for hemodialysis and kidney biopsy. Of importance, the ABIM 2021 procedural frequency survey sent to over 10,000 nephrologists (19.7% response rate) indicated 70.9% of respondents no longer performed temporary vascular access, and 14.7% performed between one and five procedures per year. For kidney biopsy, 83.1% of respondents no longer performed kidney biopsies, and 6.9% performed between one and five biopsies per year.
- **Subspecialization in nephrology.** Although there will always be a need for "generalist" nephrologists, especially in rural areas, the trend is for increasing subspecialization whether in transplant nephrology, interventional nephrology, glomerular disease, or other emerging subspecialties, such as onconephrology, women's health, and cardiorenal. Nephrology has previously taken a "big tent" approach to training and practice, but is it time to consider embracing subspecialization and adjusting our training models to more effectively support subspecialization? Related to this issue is how to best recognize subspecialization.
- **Flexibility in the current fellowship training model—the "other 12 months."** Based on the current ACGME nephrology program requirements, fellowship length must be 24 months with a minimum of 12 months devoted to clinical experiences. This structure provides an opportunity for individualized pathways based on fellow interests, future practice goals, and the expertise available in the training program. Such pathways should have standardized outcomes. In a 2015–2016 needs assessment, nephrology fellows indicated interest in additional instruction in home hemodialysis, peritoneal dialysis, kidney ultrasound, pathology, glomerulonephritis, toxicology, and obstetric nephrology (4).
- **Changing landscape of nephrology.** Changes include new and emerging therapies, a greater focus on home therapy, patient-centered care, health care justice, population health, and team-based care (see this edition's *Kidney News* article by Tod Ibrahim, entitled "Top 10 predictions about US nephrologists in 2035").
- **Training program variability.** Variability exists among the 148 ACGME-accredited fellowship programs that span both small and large programs as well as academic and community settings. The resources and training opportunities vary considerably based on this variability.

As the work of the task force continues, regular updates will be provided in *Kidney News*. To provide your thoughts and ideas on the future of nephrology, please email Melissa West, ASN's Senior Director for Strategic Relations and Patient Engagement, at mwest@asn-online.org. ■

Mark Rosenberg, MD, FASN, is a nephrologist, Professor of Medicine, and Vice Dean for Education at the University of Minnesota Medical School, Minneapolis.

References

1. Seaborg E. US Preventive Services Task Force will consider CKD screening recommendation. USPSTF responds positively to request from Coalition for Kidney Health. *Kidney News* 2022; 14(4):1, 8. https://www.kidneynews.org/view/journals/kidney-news/14/4/article-p1_1.xml
2. Quaggin SE. ASN president's update. Close the gap—time for a kidney health check. *Kidney News* 2022; 14(4):8–9. https://www.kidneynews.org/view/journals/kidney-news/14/4/article-p8_4.xml?rskey=nnicWh&result=4
3. West M. Reconsidering all aspects of nephrology's future. *Kidney News* 2022; 14(6):29. https://www.kidneynews.org/view/journals/kidney-news/14/6/article-p29_17.xml
4. Rope RW, et al. Education in nephrology fellowship: A survey-based needs assessment. *J Am Soc Nephrol* 2017; 28:1983–1990. doi: 10.1681/ASN.2016101061

UNITED TO MAKE A DIFFERENCE.

WE'RE UNITED 4 KIDNEY HEALTH

Join the kidney health professionals who are embracing four priorities to move us closer to our goal of a world without kidney diseases.

www.4KidneyHealth.org

ASN
American Society of Nephrology

I'LL DO ALL I CAN TO PRESCRIBE WHAT I BELIEVE IS RIGHT FOR MY PATIENT.

There's more than one reason why Parsabiv® is prescribed by nephrologists for their clinically appropriate patients.

Indication

Parsabiv® (etelcalcetide) is indicated for the treatment of secondary hyperparathyroidism (HPT) in adult patients with chronic kidney disease (CKD) on hemodialysis.

Limitations of Use:

Parsabiv® has not been studied in adult patients with parathyroid carcinoma, primary hyperparathyroidism, or with CKD who are not on hemodialysis and is not recommended for use in these populations.

Important Safety Information for Parsabiv®

Contraindication: Parsabiv® is contraindicated in patients with known hypersensitivity to etelcalcetide or any of its excipients. Hypersensitivity reactions, including face edema and anaphylactic reaction, have occurred.

Hypocalcemia: Parsabiv® lowers serum calcium and can lead to hypocalcemia, sometimes severe. Significant lowering of serum calcium can cause QT interval prolongation and ventricular arrhythmia. Patients with conditions that predispose to QT interval prolongation and ventricular arrhythmia may be at increased risk for QT interval prolongation and ventricular arrhythmias if they develop hypocalcemia due to Parsabiv®. Closely monitor corrected serum calcium and QT interval in patients at risk on Parsabiv®.

Significant reductions in corrected serum calcium may lower the threshold for seizures. Patients with a history of seizure disorder may be at increased risk for seizures if they develop hypocalcemia due to Parsabiv®. Monitor corrected serum calcium in patients with seizure disorders on Parsabiv®.

Concurrent administration of Parsabiv® with another oral calcimimetic could result in severe, life-threatening hypocalcemia. Patients switching from cinacalcet to Parsabiv® should discontinue cinacalcet for at least 7 days prior to initiating Parsabiv®. Closely monitor corrected serum calcium in patients receiving Parsabiv® and concomitant therapies known to lower serum calcium.

Measure corrected serum calcium prior to initiation of Parsabiv®. Do not initiate in patients if the corrected serum calcium is less than the lower limit of normal. Monitor corrected serum calcium within 1 week after initiation or dose adjustment and every 4 weeks during treatment with Parsabiv®. Measure PTH 4 weeks after initiation or dose adjustment of Parsabiv®. Once the maintenance dose has been established, measure PTH per clinical practice.

Worsening Heart Failure: In Parsabiv® clinical studies, cases of hypotension, congestive heart failure, and decreased myocardial performance have been reported. Closely monitor patients treated with Parsabiv® for worsening signs and symptoms of heart failure.

Upper Gastrointestinal Bleeding: In clinical studies, 2 patients treated with Parsabiv® in 1253 patient years of exposure had upper gastrointestinal (GI) bleeding at the time of death. The exact cause of GI bleeding in these patients is unknown and there were too few cases to determine whether these cases were related to Parsabiv®.

Patients with risk factors for upper GI bleeding, such as known gastritis, esophagitis, ulcers or severe vomiting, may be at increased risk for GI bleeding with Parsabiv®. Monitor patients for worsening of common Parsabiv® GI adverse reactions and for signs and symptoms of GI bleeding and ulcerations during Parsabiv® therapy.

Adynamic Bone: Adynamic bone may develop if PTH levels are chronically suppressed.

Adverse Reactions: In clinical trials of patients with secondary HPT comparing Parsabiv® to placebo, the most common adverse reactions were blood calcium decreased (64% vs. 10%), muscle spasms (12% vs. 7%), diarrhea (11% vs. 9%), nausea (11% vs. 6%), vomiting (9% vs. 5%), headache (8% vs. 6%), hypocalcemia (7% vs. 0.2%), and paresthesia (6% vs. 1%).

Please see Brief Summary of full Prescribing Information on adjacent page.

Visit **ParsabivHCP.com/efficacy** to see how Parsabiv® performed in clinical trials and real-world settings.

Parsabiv®
(etelcalcetide) Injection for intravenous use
2.5mg/0.5mL | 5mg/1mL | 10mg/2mL

BRIEF SUMMARY OF PRESCRIBING INFORMATION

Parsabiv®
(etelcalcetide) Injection for intravenous use

2.5mg/0.5mL | 5mg/1mL | 10mg/2mL

Please see package insert for full Prescribing Information.

INDICATIONS AND USAGE

PARSABIV is indicated for the treatment of secondary hyperparathyroidism (HPT) in adult patients with chronic kidney disease (CKD) on hemodialysis.

Limitations of Use:

PARSABIV has not been studied in adult patients with parathyroid carcinoma, primary hyperparathyroidism, or with chronic kidney disease who are not on hemodialysis and is not recommended for use in these populations.

CONTRAINDICATIONS

Hypersensitivity

PARSABIV is contraindicated in patients with known hypersensitivity to etelcalcetide or any of its excipients. Hypersensitivity reactions, including face edema and anaphylactic reaction, have occurred with PARSABIV *[see Adverse Reactions (6) in PARSABIV full prescribing information]*.

WARNINGS AND PRECAUTIONS

Hypocalcemia

PARSABIV lowers serum calcium *[see Adverse Reactions (6.1) in PARSABIV full prescribing information]* and can lead to hypocalcemia, sometimes severe. Significant lowering of serum calcium can cause paresthesias, myalgias, muscle spasms, seizures, QT interval prolongation, and ventricular arrhythmia.

QT Interval Prolongation and Ventricular Arrhythmia

In the combined placebo-controlled studies, more patients treated with PARSABIV experienced a maximum increase from baseline of greater than 60 msec in the QTcF interval (0% placebo versus 1.2% PARSABIV). In these studies, the incidence of a maximum post-baseline predialysis QTcF > 500 msec in the placebo and PARSABIV groups was 1.9% and 4.8%, respectively *[see Adverse Reactions (6.1) in PARSABIV full prescribing information]*. Patients with congenital long QT syndrome, history of QT interval prolongation, family history of long QT syndrome or sudden cardiac death, and other conditions that predispose to QT interval prolongation and ventricular arrhythmia may be at increased risk for QT interval prolongation and ventricular arrhythmias if they develop hypocalcemia due to PARSABIV. Closely monitor corrected serum calcium and QT interval in patients at risk receiving PARSABIV.

Seizures

Significant reductions in corrected serum calcium may lower the threshold for seizures. Patients with a history of seizure disorder may be at increased risk for seizures if they develop hypocalcemia due to PARSABIV. Monitor corrected serum calcium in patients with seizure disorders receiving PARSABIV.

Risk of Hypocalcemia with Other Serum Calcium Lowering Products

Concurrent administration of PARSABIV with another oral calcium-sensing receptor agonist could result in severe, life-threatening hypocalcemia. Patients switching from cinacalcet to PARSABIV should discontinue cinacalcet for at least 7 days prior to initiating PARSABIV *[see Dosage and Administration (2.4) in PARSABIV full prescribing information]*. Closely monitor corrected serum calcium in patients receiving PARSABIV and concomitant therapies known to lower serum calcium.

Monitoring Serum Calcium and Patient Education

Measure corrected serum calcium prior to initiation of PARSABIV. Do not initiate in patients if the corrected serum calcium is less than the lower limit of normal. Monitor corrected serum calcium within 1 week after initiation or dose adjustment and every 4 weeks during treatment with PARSABIV *[see Dosage and Administration (2.2) in PARSABIV full prescribing information]*. Educate patients on the symptoms of hypocalcemia and advise them to contact a healthcare provider if they occur.

Management of Hypocalcemia

If corrected serum calcium falls below the lower limit of normal or symptoms of hypocalcemia develop, start or increase calcium supplementation (including calcium, calcium-containing phosphate binders, and/or vitamin D sterols or increases in dialysate calcium concentration). PARSABIV dose reduction or discontinuation of PARSABIV may be necessary *[see Dosage and Administration (2.2) in PARSABIV full prescribing information]*.

Worsening Heart Failure

In clinical studies with PARSABIV, cases of hypotension, congestive heart failure, and decreased myocardial performance have been reported. In clinical studies, heart failure requiring hospitalization occurred in 2% of PARSABIV-treated patients and 1% of placebo-treated patients. Reductions in corrected serum calcium may be associated with congestive heart failure, however, a causal relationship to PARSABIV could not be completely excluded. Closely monitor patients treated with PARSABIV for worsening signs and symptoms of heart failure.

Upper Gastrointestinal Bleeding

In clinical studies, two patients treated with PARSABIV in 1253 patient-years of exposure had upper gastrointestinal (GI) bleeding noted at the time of death while no patient in the control groups in 384 patient-years of exposure had upper GI bleeding noted at the time of death. The exact cause of GI bleeding in these patients is unknown, and there were too few cases to determine whether these cases were related to PARSABIV.

Patients with risk factors for upper GI bleeding (such as known gastritis, esophagitis, ulcers, or severe vomiting) may be at increased risk for GI bleeding while receiving PARSABIV treatment. Monitor patients for worsening of common GI adverse reactions of nausea and vomiting associated with PARSABIV *[see Adverse Reactions (6.1) in PARSABIV full prescribing information]* and for signs and symptoms of GI bleeding and ulcerations during PARSABIV therapy. Promptly evaluate and treat any suspected GI bleeding.

Adynamic Bone

Adynamic bone may develop if PTH levels are chronically suppressed. If PTH levels decrease below the recommended target range, the dose of vitamin D sterols and/or PARSABIV should be reduced or therapy discontinued. After discontinuation, resume therapy at a lower dose to maintain PTH levels in the target range *[see Dosage and Administration (2.1) in PARSABIV full prescribing information]*.

ADVERSE REACTIONS

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

- Hypocalcemia *[see Warnings and Precautions (5.1) in PARSABIV full prescribing information]*
- Worsening Heart Failure *[see Warnings and Precautions (5.2) in PARSABIV full prescribing information]*
- Upper Gastrointestinal Bleeding *[see Warnings and Precautions (5.3) in PARSABIV full prescribing information]*
- Adynamic Bone *[see Warnings and Precautions (5.4) in PARSABIV full prescribing information]*

Clinical Trials 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 clinical practice.

The data in Table 2 are derived from two placebo-controlled clinical studies in patients with chronic kidney disease and secondary hyperparathyroidism on hemodialysis. The data reflect exposure of 503 patients to PARSABIV with a mean duration of exposure to PARSABIV of 23.6 weeks. The mean age of patients was approximately 58 years, and 60% of the patients were male. Of the total patients, 67% were Caucasian, 28% were Black or African American, 2.6% were Asian, 1.2% were Native Hawaiian or Other Pacific Islander, and 1.6% were categorized as Other.

Table 2 shows common adverse reactions associated with the use of PARSABIV in the pool of placebo-controlled studies. These adverse reactions occurred more commonly on PARSABIV than on placebo and were reported in at least 5% of patients treated with PARSABIV.

Table 2: Adverse Reactions Reported in ≥ 5% of PARSABIV-Treated Patients

Adverse Reaction*	Placebo (N = 513)	PARSABIV (N = 503)
Blood calcium decreased[a]	10%	64%
Muscle spasms	7%	12%
Diarrhea	9%	11%
Nausea	6%	11%
Vomiting	5%	9%
Headache	6%	8%
Hypocalcemia[b]	0.2%	7%
Paresthesia[c]	1%	6%

*Included adverse reactions reported with at least 1% greater incidence in the PARSABIV group compared to the placebo group

[a] Asymptomatic reductions in calcium below 7.5 mg/dL or clinically significant asymptomatic reductions in corrected serum calcium between 7.5 and < 8.3 mg/dL (that required medical management)

[b] Symptomatic reductions in corrected serum calcium < 8.3 mg/dL

[c] Paresthesia includes preferred terms of paresthesia and hypoesthesia

Other adverse reactions associated with the use of PARSABIV but reported in < 5% of patients in the PARSABIV group in the two placebo-controlled clinical studies were:

- Hyperkalemia: 3% and 4% for placebo and PARSABIV, respectively.
- Hospitalization for Heart Failure: 1% and 2% for placebo and PARSABIV, respectively.
- Myalgia: 0.2% and 2% for placebo and PARSABIV, respectively.
- Hypophosphatemia: 0.2% and 1% for placebo and PARSABIV, respectively.

Description of Selected Adverse Reactions

Hypocalcemia

In the combined placebo-controlled studies, a higher proportion of patients on PARSABIV developed at least one corrected serum calcium value below 7.0 mg/dL (7.6% PARSABIV, 3.1% placebo), below 7.5 mg/dL (27% PARSABIV, 5.5% placebo), and below 8.3 mg/dL (79% PARSABIV, 19% placebo). In the combined placebo-controlled studies, 1% of patients in the PARSABIV group and 0% of patients in the placebo group discontinued treatment due to an adverse reaction attributed to a low corrected serum calcium.

Hypophosphatemia

In the combined placebo-controlled studies, 18% of patients treated with PARSABIV and 8.2% of patients treated with placebo had at least one measured phosphorus level below the lower normal limit (i.e., 2.2 mg/dL).

QTc Interval Prolongation Secondary to Hypocalcemia

In the combined placebo-controlled studies, more patients treated with PARSABIV experienced a maximum increase from baseline of greater than 60 msec in the QTcF interval (0% placebo versus 1.2% PARSABIV). The patient incidence of maximum post-baseline predialysis QTcF > 500 msec in the placebo and PARSABIV groups was 1.9% and 4.8%, respectively.

Hypersensitivity

In the combined placebo-controlled studies, the subject incidence of adverse reactions potentially related to hypersensitivity was 4.4% in the PARSABIV group and 3.7% in the placebo group. Hypersensitivity reactions in the PARSABIV group were pruritic rash, urticaria, and face edema.

Immunogenicity

As with all peptide therapeutics, there is potential for immunogenicity. The detection of anti-drug binding antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody positivity in an assay may be influenced by several factors, including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to etelcalcetide with the incidence of antibodies to other products may be misleading.

In clinical studies, 7.1% (71 out of 995) of patients with secondary hyperparathyroidism treated with PARSABIV for up to 6 months tested positive for binding anti-etelcalcetide antibodies. Fifty-seven out of 71 had pre-existing anti-etelcalcetide antibodies.

No evidence of altered pharmacokinetic profile, clinical response, or safety profile was associated with pre-existing or developing anti-etelcalcetide antibodies.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

There are no available data on the use of PARSABIV in pregnant women. In animal reproduction studies, effects were seen at doses associated with maternal toxicity that included hypocalcemia. In a pre- and post-natal study in rats administered etelcalcetide during organogenesis through delivery and weaning, there was a slight increase in perinatal pup mortality, delay in parturition, and transient effects on pup growth at exposures 1.8 times the human exposure for the clinical dose of 15 mg three times per week. There was no effect on sexual maturation, neurobehavioral, or reproductive function in the rat offspring. In embryo-fetal studies, when rats and rabbits were administered etelcalcetide during organogenesis, reduced fetal growth was observed at exposures 2.7 and 7 times exposures for the clinical dose, respectively.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data

Animal Data

There were no effects on embryo-fetal development in Sprague-Dawley rats when etelcalcetide was dosed at 0.75, 1.5, and 3 mg/kg/day by the intravenous route during organogenesis (pre-mating to gestation day 17) at exposures up to 1.8 times human exposures at the clinical dose of 15 mg three times per week based on AUC. No effects on embryo-fetal development were observed in New Zealand White rabbits at doses of etelcalcetide of 0.375, 0.75, and 1.5 mg/kg by the intravenous route (gestation day 7 to 19), representing up to 4.3 times human exposures based on AUC. In separate studies at higher doses of 4.5 mg/kg in rats (gestation days 6 to 17) and 2.25 mg/kg in rabbits (gestation days 7 to 20), representing 2.7- and 7-fold clinical exposures, respectively, there was reduced fetal growth associated with maternal toxicities of hypocalcemia, tremoring, and reductions in body weight and food consumption.

In a pre- and post-natal development study in Sprague-Dawley rats administered etelcalcetide at 0.75, 1.5, and 3 mg/kg/day by the intravenous route (gestation day 7 to lactation day 20), there was a slight increase in perinatal pup mortality, delay in parturition, and transient reductions in post-natal growth at 3 mg/kg/day (representing 1.8-fold human exposures at the clinical dose of 15 mg three times per week based on AUC), associated with maternal toxicities of hypocalcemia, tremoring, and reductions in body weight and food consumption. There were no effects on sexual maturation, neurobehavioral, or reproductive function at up to 3 mg/kg/day, representing exposures up to 1.8-fold human exposure based on AUC.

Lactation

Risk Summary

There are no data regarding the presence of PARSABIV in human milk or effects on the breastfed infant or on milk production. Studies in rats showed [^{14}C]-etelcalcetide was present in the milk at concentrations similar to plasma. Because of the potential for PARSABIV to cause adverse effects in breastfed infants including hypocalcemia, advise women that use of PARSABIV is not recommended while breastfeeding.

Data

Presence in milk was assessed following a single intravenous dose of [^{14}C]-etelcalcetide in lactating rats at maternal exposures similar to the exposure at the human clinical dose of 15 mg three times per week. [^{14}C]-etelcalcetide-derived radioactivity was present in milk at levels similar to plasma.

Pediatric Use

The safety and efficacy of PARSABIV have not been established in pediatric patients.

Geriatric Use

Of the 503 patients in placebo-controlled studies who received PARSABIV, 177 patients (35.2%) were ≥ 65 years old and 72 patients (14%) were ≥ 75 years old.

No clinically significant differences in safety or efficacy were observed between patients ≥ 65 years and younger patients (≥ 18 and < 65 years old). No differences in plasma concentrations of etelcalcetide were observed between patients ≥ 65 years and younger patients (≥ 18 and < 65 years old).

OVERDOSAGE

There is no clinical experience with PARSABIV overdosage. Overdosage of PARSABIV may lead to hypocalcemia with or without clinical symptoms and may require treatment. Although PARSABIV is cleared by dialysis, hemodialysis has not been studied as a treatment for PARSABIV overdosage. In the event of overdosage, corrected serum calcium should be checked and patients should be monitored for symptoms of hypocalcemia, and appropriate measures should be taken *[see Warnings and Precautions (5.1) in PARSABIV full prescribing information]*.

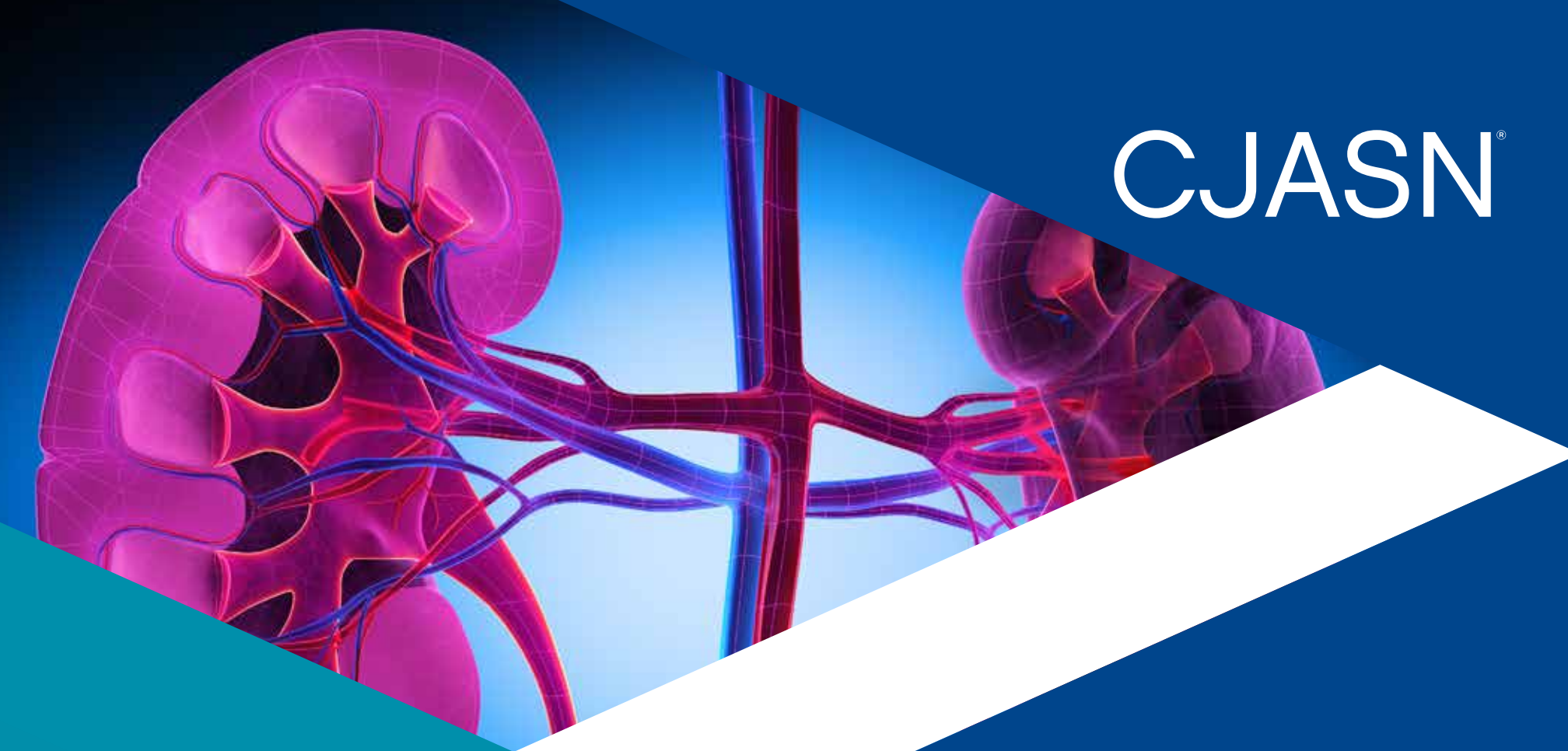
AMGEN®

PARSABIV® (etelcalcetide)

Manufactured for:
KAI Pharmaceuticals, Inc., a wholly owned subsidiary of Amgen, Inc.
One Amgen Center Drive
Thousand Oaks, California 91320-1799

Patent: http://pat.amgen.com/Parsabiv/

USA-416-80951 02/21



Access the special reviews from the Kidney Transplantation: Long-Term Management Challenges Series.

These comprehensive reviews cover:

- Contemporary immunosuppression regimens
- Innovative immune-monitoring strategies
- Posttransplant complications & clinical conditions
- Pediatric transplant recipients
- Pregnancy, fertility, and contraception
- And more

Download the free collection today.

KIDNEY TRANSPLANTATION
Arrival of the Next Frontier
PART I

By Sam Kant, Daniel C. Brennan, and Samira Farouk

The short period of 2020 to 2022 has felt like its own era in the field of kidney transplantation, with significant advances in the field on various fronts. The next two editions of *Kidney News* will highlight some of these advances in kidney transplantation, which push the barriers of science and society. This first and current edition will focus on racial inequities in transplantation and measures to address them, the new kidney transplant allocation system, updates from the *Apolipoprotein L1* (*APOL1*) Long-term Kidney Transplantation Outcomes (APOLLO) study, and groundbreaking advances in xenotransplantation and finally, will review increasingly encountered oxalosis in patients with kidney transplantation.

Structural racism impedes equitable access to transplantation. Drs. Chan and McElroy provide a background on how racial inequities afflict transplantation. They propose the use of social determinants of health data (social conditions with broad-ranging effects on individuals' health, functioning, and quality of life) to begin to address these inequities and outline suggestions for improving data infrastructure. These recommendations align with a report from the National Academies of Sciences, Engineering, and Medicine to improve equitable organ allocation (1).

The recognition of the association of *APOL1* kidney-risk variants and chronic kidney disease has been one of most significant discoveries in nephrology in the past decade (2). Living kidney donors with *APOL1* high-risk variants have reduced kidney function post-donation and higher risk of progression to end stage kidney disease. In addition, the Kidney Donor Risk Index (KDRI) scores improve dramatically with replacement of race with the donor *APOL1* genotype (3). As high KDRI organs are more likely to be discarded, changes in its calculation are likely to impact organ allocations. Dr. Freedman et al. summarize the APOLLO study, which seeks to determine outcomes in recipients of deceased donor kidneys based on *APOL1* genotypes.

…2020 to 2022 has felt like its own era in the field of kidney transplantation, with significant advances in the field…

The United Network for Organ Sharing/Organ Procurement and Transplantation Network kidney allocation policy has undergone significant changes to improve equitable distribution of deceased donor allografts (4). Dr. Vella discusses these changes, with a focus on the Kidney Donor Profile Index and Estimated Post Transplant Survival scores, as well as the elimination of regional allocation rule variations.

This issue of *Kidney News* would be incomplete without discussion of the groundbreaking advances in xenotransplantation. Albeit first done in 1964, xenotransplantation has not become standard practice, given significant immunologic barriers, concern for zoonoses, and lack of a steady organ source (5). Dr. Killian et al. describe how these challenges may potentially be overcome with the use of genetically edited porcine allografts. They share their preliminary experience with this novel practice in a human model, along with associated issues and potential measures to mitigate them (6).

This issue concludes with a discussion of hyperoxaluria—an increasingly recognized cause of delayed graft function in kidney allografts (7). Dr. Krishnamoorthy discusses various clinical scenarios, including primary hyperoxaluria, enteric oxalosis, and delayed graft function, in patients with kidney transplants, along with recommended management strategies.

Significant strides of kidney transplantation have continued not only in the areas described here but also in the realm of genomics, biomarkers, new insights into thrombotic microangiopathy, focal segmental glomerulosclerosis recurrence in transplantation, and updates on the use of belatacept. Stay tuned for the August edition of *Kidney News*, where we turn our attention to these topics. ■

Sam Kant, MD, and Daniel C. Brennan, MD, are with the Comprehensive Transplant Center, Johns Hopkins University School of Medicine, Baltimore, MD. Samira Farouk, MD, MS, FASN, is with the Barbara T. Murphy Division of Nephrology, Department of Medicine, Icahn School of Medicine at Mount Sinai, New York, NY.

Drs. Kant and Farouk report no conflicts of interest. Dr. Brennan reports grants and research support from AlloVir, Amplyx, CareDx, and Natera and serving as a consultant with CareDx, Hansa, Medeor, Sanofi, and Vera Therapeutics and on the editorial board of *Transplantation* and UpToDate.

References

1. National Academies of Sciences, Engineering, and Medicine. Research Council. Realizing the promise of equity in the organ transplantation system. Consensus Study Report. 2022. https://nap.nationalacademies.org/catalog/26364/realizing-the-promise-of-equity-in-the-organ-transplantation-system
2. Genovese G, et al. Association of trypanolytic ApoL1 variants with kidney disease in African Americans. *Science* 2010; 329:841–845. doi: 10.1126/science.1193032
3. Julian BA, et al. Effect of replacing race with apolipoprotein L1 genotype in calculation of kidney donor risk index. *Am J Transplant* 2017; 17:1540–1548. doi: 10.1111/ajt.14113
4. Burdick JF, et al. Organ sharing—present realities and future possibilities. *Transplantation* 1991; 51:287–292. PMID: 1994519
5. Cooper D, et al. Will the pig solve the transplantation backlog? *Annu Rev Med* 2002; 53:133–147. doi: 10.1146/annurev.med.53.082901.103900
6. Porrett PM, et al. First clinical-grade porcine kidney xenotransplant using a human decedent model. *Am J Transplant* 2022; 22:1037–1053. doi: 10.1111/ajt.16930
7. Palsson R, et al. The association of calcium oxalate deposition in kidney allografts with graft and patient survival. *Nephrol Dial Transplant* 2021; 36:747. doi: 10.1093/ndt/gfy364 [Erratum to *Nephrol Dial Transplant* 2020; 35:888–894. doi: 10.1093/ndt/gfy271].

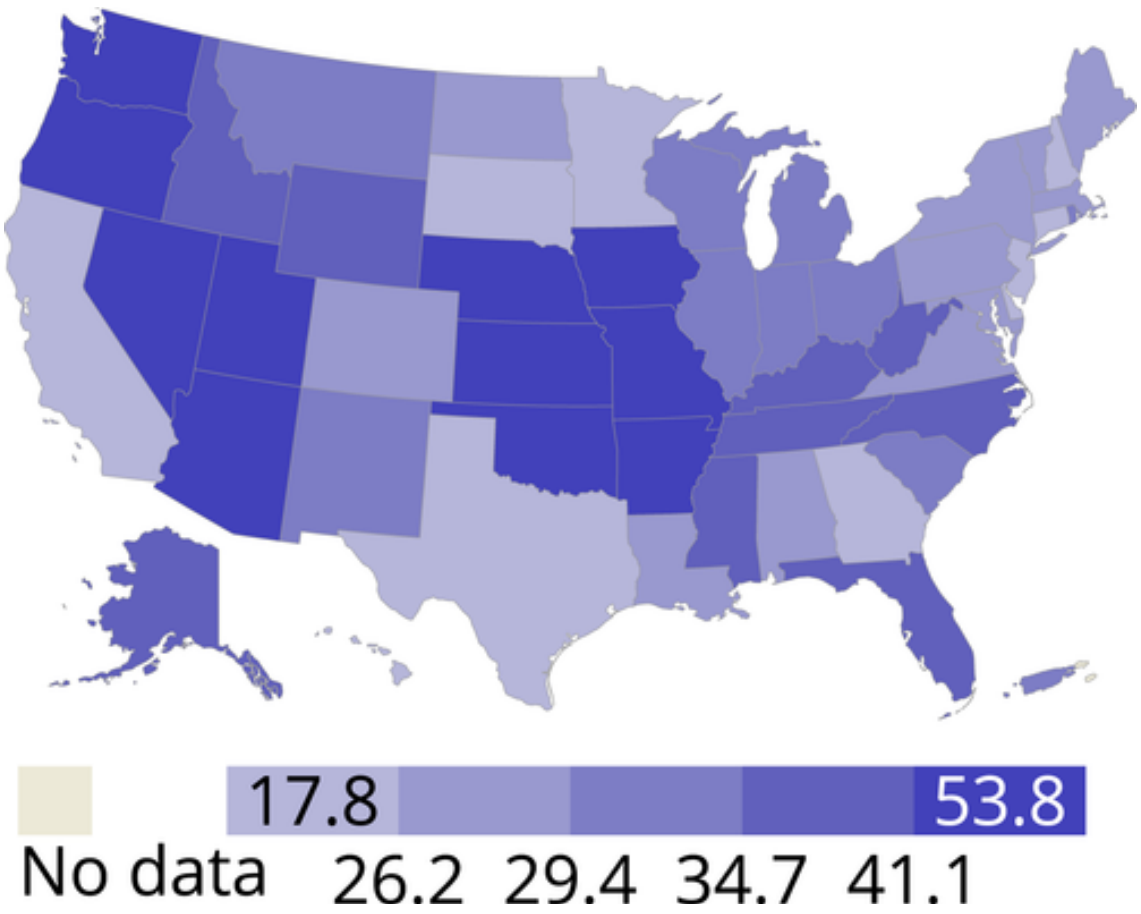
The New Kidney Transplant Allocation System

By John Vella

The kidney allocation policy within the United States was initially established in 1987 to promote the equitable and utilitarian distribution of deceased donor kidneys (1). The policy, managed by the United Network for Organ Sharing (UNOS)/Organ Procurement and Transplantation Network (OPTN), was extensively revised in 2014 to increase the utilization of available kidneys, reduce regional variability in access to transplantation, and improve posttransplant outcomes. Major changes at the time included the introduction of the Kidney Donor Profile Index (KDPI) and Estimated Post Transplant Survival (EPTS) scores as estimates of kidney quality and projected recipient survival, respectively, and also the elimination of regional allocation rule variations. Kidneys were allocated locally first, then regionally, and then nationally, although exceptions were made for zero-mismatched kidneys and for highly sensitized candidates. The major benefits of the change in the kidney allocation policy included a marked increase in the number of transplants for highly sensitized patients and also a decrease in the number of age-mismatched kidneys. Unfortunately, the longer cold ischemic time associated with a higher rate of delayed graft function, necessitating dialysis within the first week after transplantation. This, in turn, associated with small, although significant, decreases in allograft longevity (2–4).

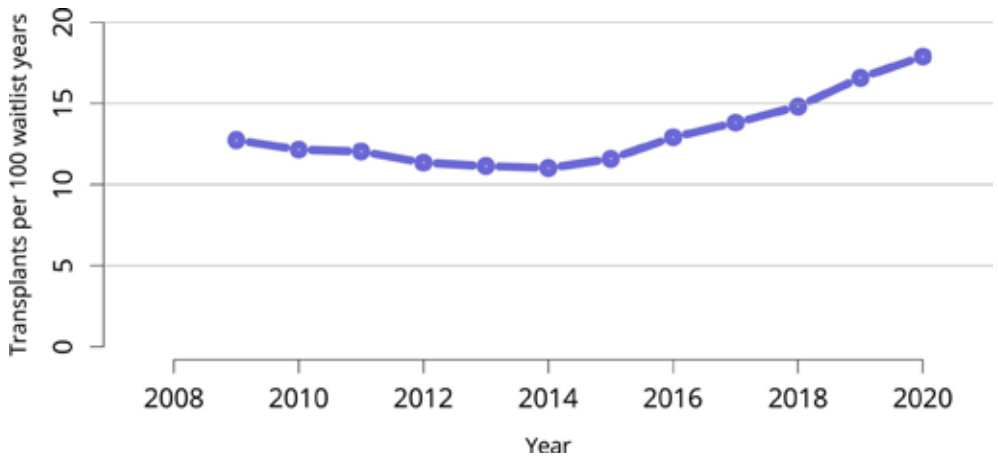
Persistent inequities in regional access and waiting times for transplantation combined with high kidney discard rates prompted the Department of Health and Human Services to require UNOS to further refine the policy to specifically address such issues (Figure 1).

Figure 1. Regional disparity in deceased donor kidney transplant rates



Percentage of adults who underwent deceased donor kidney transplant within 5 years of listing, 2015, by state. Candidates listed at more than one center are counted once per listing. State is candidate's home state. Reproduced from OPTN/SRTR 2020 Annual Data Report (5).

Figure 2. Increasing numbers of deceased donor kidney transplants



Overall deceased donor kidney transplant rates among adult waitlist candidates. Transplant rates are computed as the number of deceased donor transplants per 100 patient-years of wait time in a given year. Individual listings are counted separately. Reproduced from OPTN/SRTR 2020 Annual Data Report (5).

UNOS embarked on an exhaustive and, at times, acrimonious process, which culminated in the current kidney allocation system (KAS) implemented in March 2021. The biggest change was the elimination of donor service areas in which kidneys procured within a region were primarily allocated within the same region. This has been replaced with the concept of kidney allocation prioritization within a 250-nautical mile radius of the organ procurement center, similar to that previously implemented for the allocation of liver and lung allografts.

So here we are now, more than 15 months later: How has this change gone? The early experience has been somewhat mixed. Most programs initially experienced a marked increase in the volume of organ offers, which at times, has stressed existing resources. This has dissipated as UNOS revamped its electronic systems to incorporate more accessible offer filters. Rohan et al. (6) reported an increase in the number of deceased donor kidneys transplanted, although with longer waiting time and higher KDPIs, which have increased the delayed graft function rate. It will take time before a broader sense of the impact of the KAS is seen. It should be noted that the increasing number of deceased donor transplants performed in the United States predates the current iteration of allocation policy (Figure 2).

UNOS is now seeking public input and commentary on the concept of continuous distribution, which combines all matching factors into a single composite score to allocate deceased donor organs, similar to that already implemented for lung allocation (7). If implemented, this would be the fourth major iteration of the KAS. ■

John Vella MD, FRCP, FACP, FASN, FAST, is Director of Transplantation and of the Division of Nephrology, Maine Medical Center, Portland, ME. Dr. Vella is also Associate Medical Director of Maine Medical Partners Nephrology and Associate Professor of Medicine with Tufts University School of Medicine.

The author reports no conflicts of interest.

References

1. Burdick JF, et al. Organ sharing—present realities and future possibilities. *Transplantation* 1991; 51:287–292. PMID: 1994519
2. The Organ Procurement and Transplantation Network, United Network for Organ Sharing. Kidney Allocation System (KAS) "Out-of-the-Gate" Monitoring Report. February 19, 2015. http://optn.transplant.hrsa.gov/media/1158/kas_report_02-2015.pdf
3. Massie AB, et al. Early changes in kidney distribution under the new allocation system. *J Am Soc Nephrol* 2016; 27:2495–2501. doi: 10.1681/ASN.2015080934
4. Stewart DE, et al. Changes in deceased donor kidney transplantation one year after KAS implementation. *Am J Transplant* 2016; 16:1834–1847. doi: 10.1111/ajt.13770
5. Organ Procurement and Transplantation Network (OPTN) and Scientific Registry of Transplant Recipients (SRTR). OPTN/SRTR 2020 Annual Data Report. Published 2022. Accessed April 4, 2022. In: Lentine KL, et al. OPTN/SRTR 2020 Annual Data Report: Kidney. *Am J Transplant* March 10, 2022; 22:21–136. https://onlinelibrary.wiley.com/doi/10.1111/ajt.16982
6. Rohan VS, et al. Early assessment of national kidney allocation policy change. *J Am Coll Surg* 2022; 234:565–570. doi: 10.1097/XCS.0000000000000096
7. United Network for Organ Sharing (UNOS). Community update: Policy development based on continuous distribution. August 11, 2021. https://unos.org/news/community-update-continuous-distribution-policy-development/

APOL1 in Kidney Transplantation
The APOLLO Study

By Barry I. Freedman, Lijun Ma, and Marva M. Moxey-Mims

Discovery of the genetic association between *apolipoprotein L1* (*APOL1*) gene kidney-risk variants and chronic kidney disease in individuals with recent African ancestry dramatically altered the landscape in nephrology (1). This observation accounted for much of the threefold higher incidence rate of end stage kidney disease (ESKD) in African Americans (AAs) compared with other populations. *APOL1* genotypes also underlie a portion of the disparity in outcomes after deceased donor kidney transplantation (DDKT). Kidneys transplanted from deceased donors with African ancestry fail more rapidly than those from non-African ancestry donors (2). A series of retrospective reports revealed that donor *APOL1* genotype, not race, contributed to the more rapid failure (3, 4). *APOL1* genotypes are also associated with reduced kidney function after live kidney donation in AAs and may contribute to their higher rates of post-donation ESKD (5).

APOL1 is a prime example of how genotype-based precision medicine may better serve patients and physicians than "race-based" risk assessments. In DDKT, "donor race" is 1 of 10 characteristics used to compute the quality of donor kidneys in the Kidney Allocation System, called the Kidney Donor Risk Index (KDRI) (6). Despite the explicit bias of using donor race, the KDRI plays a critical role in allocation of kidneys for transplantation. Kidneys with presumed lower quality may be more likely to be discarded. Julian et al. (7) reported improved accuracy of the KDRI by replacing donor race with *APOL1* genotype. These results showed that KDRI quality scores would improve dramatically in ~85% of AA donor kidneys with *APOL1* low-risk genotypes and dramatically worsen in ~15% of kidneys from *APOL1* high-risk genotype donors. More accurate assessment of kidney quality from AA deceased donors would likely reduce the discard rate of kidneys from donors with *APOL1* low-risk genotypes. This should lead to more transplants, better matching of donors with recipients, improved outcomes, and lower health care costs (7).

These data led the National Institutes of Health to develop the *APOL1* Long-term Kidney Transplantation Outcomes (APOLLO) Consortium in 2017 (8). The intent is to prospectively follow outcomes of large numbers of kidneys transplanted from AA donors based on *APOL1* genotypes and determine the safety of live AA kidney donation (Figure 1). *APOL1* is an ambitious study with the potential to alter the current KDRI by replacing donor race with the *APOL1* genotype. The primary outcome is to determine time-to-death-censored kidney allograft failure in recipients of AA deceased donor kidneys based on *APOL1* genotypes. Secondary outcomes include the rate of loss of kidney function based on change in outpatient estimated glomerular filtration rate, rate of change in outpatient serum creatinine concentration, and time to development of sustained proteinuria in recipients of a DDKT from AA donors based on *APOL1*.

APOLLO works closely with the United Network for Organ Sharing (UNOS) and the Association of Organ Procurement Organizations and has collected biosamples from deceased donors at 52 organ procurement organizations and 59 human leukocyte antigen (HLA) labs. Recipients and live donors have been recruited from more than 120 US transplant programs. The consortium includes the largest central institutional review board (IRB) in the IRB Reliance Exchange and has an engaged Community Advisory Council guiding its scientists (9).

Despite the COVID-19 pandemic, APOLLO is currently following outcomes in UNOS from more than 3733 DDKT from 2028 deceased donors with DNA for *APOL1* genotyping. Many of these recipients have been recruited to determine effects of recipient *APOL1* genotypes on outcomes (10, 11). Donors and recipients provide blood for DNA, and the vast majority provide serum and urine. Biosamples are stored at the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) Biorepository.

To date, approximately 25% of AA deceased donors eligible for APOLLO had both kidneys discarded. It is hoped that rapid *APOL1* genotyping in deceased donors at the time of HLA typing and hepatitis B, hepatitis C, and HIV testing can be included in the kidney allocation process. Approximately 87% of AA in the general population lack *APOL1* high-risk genotypes, and many of these kidneys will be good quality for transplantation. The quality of donor kidneys should not be calculated based on donor race when causative gene variants underlying nephropathy are known. APOLLO is a groundbreaking study. It has the potential to change clinical practice in transplant medicine. Recruitment is expected to be complete in early 2023, and results will follow after suitable follow-up. ■

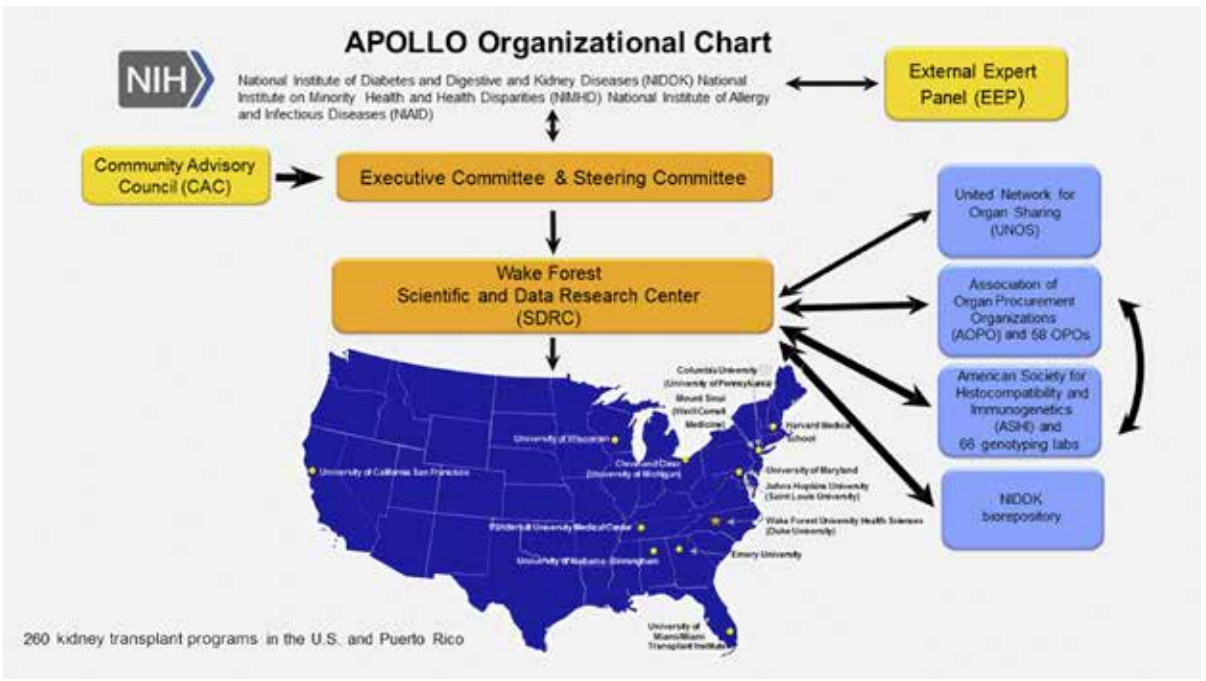
Barry I. Freedman, MD, and Lijun Ma, MD, PhD, are with the Section on Nephrology, Wake Forest School of Medicine, Winston-Salem, North Carolina. Marva M. Moxey-Mims, MD, is with the Division of Nephrology, Children's National Hospital, and Department of Pediatrics, The George Washington University School of Medicine and Health Sciences, Washington, DC.

Dr. Freedman and Wake Forest University Health Sciences have rights to a US patent related to *APOL1* gene testing (https://www.apol1genetest.com). Dr. Freedman is a consultant for AstraZeneca, RenalytixAI, and XinThera and receives research support from AstraZeneca and RenalytixAI. Drs. Ma and Moxey-Mims report no conflicts of interest.

References

1. Genovese G, et al. Association of trypanolytic ApoL1 variants with kidney disease in African Americans. *Science* 2010; 329:841–845. doi: 10.1126/science.1193032
2. Swanson SJ, et al. Effect of donor factors on early graft survival in adult cadaveric renal transplantation. *Am J Transplant* 2002; 2:68–75. doi: 10.1034/j.1600-6143.2002.020112.x
3. Reeves-Daniel AM, et al. The *APOL1* gene and allograft survival after kidney transplantation. *Am J Transplant* 2011; 11:1025–1030. doi: 10.1111/j.1600-6143.2011.03513.x
4. Freedman BI, et al. *APOL1* genotype and kidney transplantation outcomes from deceased African American donors. *Transplantation* 2016; 100:194–202. doi: 10.1097/TP.0000000000000969
5. Doshi MD, et al. *APOL1* genotype and renal function of Black living donors. *J Am Soc Nephrol* 2018; 29:1309–1316. doi: 10.1681/ASN.2017060658
6. Israni AK, et al. New national allocation policy for deceased donor kidneys in the United States and possible effect on patient outcomes. *J Am Soc Nephrol* 2014; 25:1842–1848. doi: 10.1681/ASN.2013070784
7. Julian BA, et al. Effect of replacing race with apolipoprotein L1 genotype in calculation of kidney donor risk index. *Am J Transplant* 2017; 17:1540–1548. doi: 10.1111/ajt.14113
8. Freedman BI, et al. *APOL1* Long-term Kidney Transplantation Outcomes Network (APOLLO): Design and rationale. *Kidney Int Rep* 2019; 5:278–288. doi: 10.1016/j.ekir.2019.11.022
9. Iltis AS, et al. Improving kidney disease research in the Black community: The essential role of Black voices in the APOLLO study. *Am J Kidney Dis* 2022; 79:750–753. doi: 10.1053/j.ajkd.2021.09.006
10. Lee BT, et al. The *APOL1* genotype of African American kidney transplant recipients does not impact 5-year allograft survival. *Am J Transplant* 2012; 12:1924–1928. doi: 10.1111/j.1600-6143.2012.04033.x
11. Zhang Z, et al. Recipient *APOL1* risk alleles associate with death-censored renal allograft survival and rejection episodes. *J Clin Invest* 2021; 131:e146643. doi: 10.1172/JCI146643

Figure 1. APOLLO organizational chart



Reproduced with permission from Freedman et al. (8).

Xenotransplantation

By A. Cozette Killian, Paige M. Porrett, Jayme E. Locke, and Vineeta Kumar

In 1964, the first kidney xenotransplant from a chimpanzee to human was performed successfully (1). Although the recipient survived 9 months, subsequent animal-to-human transplants were limited by immunologic barriers and the need for a sustainable organ source (2). Pigs soon became the ideal organ source because they produce large litters and mature rapidly, and availability is virtually unlimited (2, 3). Pigs have organs comparable in size and function with humans and lower risk of zoonoses, and their hormones and tissues are already used, suggesting positive public opinion (2, 3). The primary limitation of using pigs for xenotransplantation was the cross-species immunologic barrier (2, 4). The development of novel gene-editing technology to "humanize" the pig organ, however, has enabled successful pig-to-non-human primate (NHP) models and a return to animal-to-human experimentation (5–7).

The pig-to-decedent, or Parsons, model demonstrated important safety and feasibility features of kidney xenotransplantation (5). First, no hyper-acute rejection occurred, consistent with the negative pre-transplant pig-to-human crossmatch. Second, relative hemodynamic stability was maintained intraoperatively, and vascular anastomotic integrity was maintained at the higher human blood pressures. Third, no porcine endogenous retrovirus transmission was observed. Given the physiologic derangements of the brain-dead recipient (8), however, this pre-clinical model was not designed to assess xenotransplant physiologic function. Notably, although the kidneys made urine, they did not clear creatinine.

Given the complex, systemic functions performed by the human kidney, including filtration, electrolyte balance, volume status, blood pressure, and stimulation of erythropoiesis, xenograft physiologic compatibility requires evaluation (Figure 1). Although phase 1 clinical trials are needed, the physiologic findings from pig-to-NHP models, as previously reviewed by Iwase et al. (9), can be leveraged to hypothesize which kidney functions may be normal or altered in living human xenotransplant recipients (10).

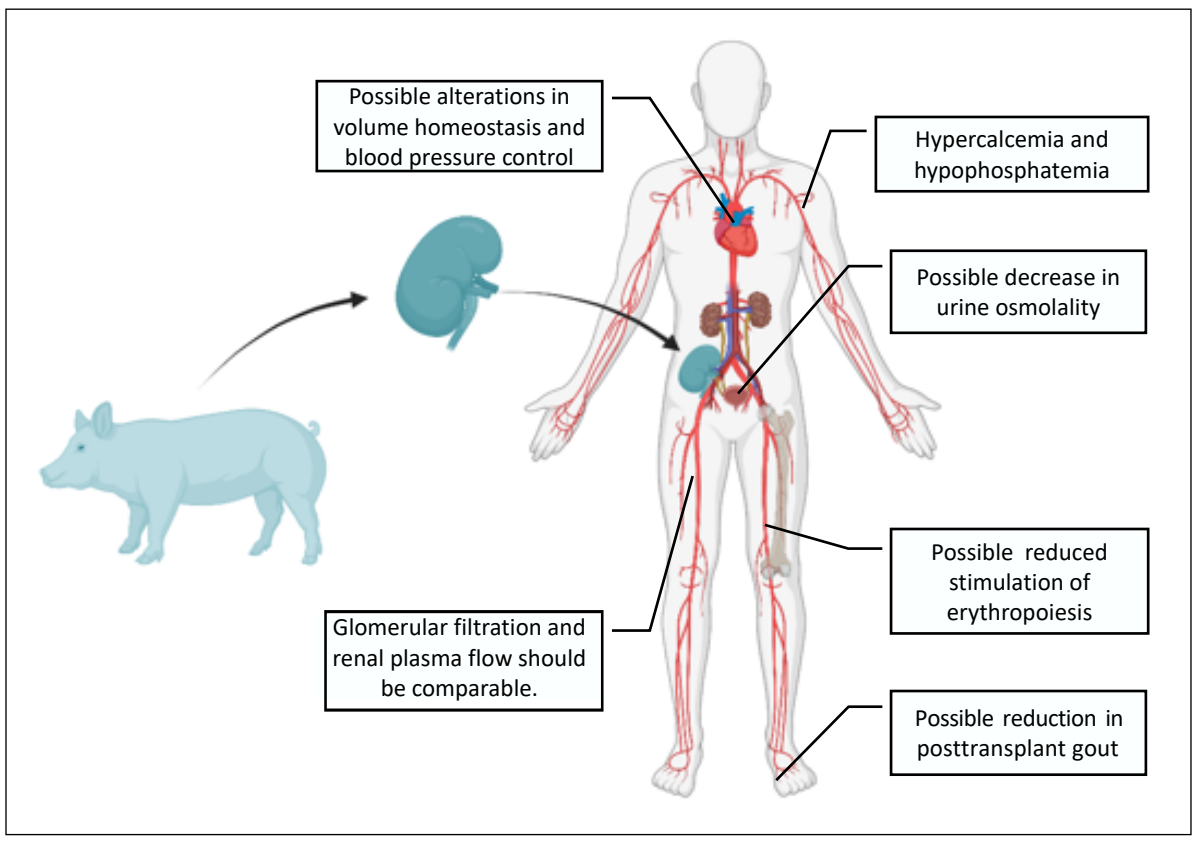
There are several aspects of renal physiology likely to be normal in human xenotransplant recipients. First, renal blood flow and glomerular filtration rate are similar in pigs and humans (human, 4 mL/min/g vs. pig, 3–4 mL/min/g; human, 130 mL/min/70 kg vs. pig, 126–175 mL/min/70 kg, respectively) (3, 10). Serum creatinine remained within normal human ranges, and proteinuria has not been observed in recent pig-to-NHP experiments (9, 10). Assuming immune-mediated rejection is prevented, these data suggest glomerular filtration should occur normally in living humans (8). Second, xenotransplants may enhance uric acid elimination, as they filter as well as secrete uric acid, perhaps protecting recipients from posttransplant gout (9).

Although pig-to-NHP models suggest that some aspects of renal xenograft physiology may differ from the human kidney, these differences may be successfully managed. Although most serum electrolyte concentrations remained within normal human limits in NHP recipients, gradual and mild hypercalcemia and late hypophosphatemia have occurred (9). Similar to allotransplantation, this could be managed with increased non-dairy dietary intake and oral phosphorus supplementation. Additionally, anemia among NHP recipients has been reported (9). This may be secondary to immunosuppression, blood draws, or incompatibility of NHP and pig erythropoietin (9, 10). Although a high degree of homology has been noted between human and pig erythropoietin (10), incompatibility could be managed with recombinant human erythropoietin, a common practice for anemia among patients with chronic kidney disease.

Pig xenografts may be incompatible with other aspects of human renal physiology. Intermittent hypovolemia has been noted among NHP xenograft recipients, although oral intake was not increased in a compensatory manner (9). Whereas saline infusions resolved this issue, and normal fluid balance was otherwise maintained, some hypothesize that these abnormalities may be related to incompatibilities in antidiuretic hormone (ADH) or the renin-angiotensin-aldosterone system, which may affect human recipients (9, 10). Pig ADH differs from NHP or human ADH, which may result in a decreased ability to concentrate urine in human recipients (10). However, the ability to concentrate urine was preserved in NHP experiments (urinary osmolarity pre-transplant, 296 ± 133 vs. posttransplant, 405 ± 102 mOsm/kg; p = 0.22) (11). Additionally, human angiotensinogen cannot be cleaved by pig renin. This could be countered by the observed normal renin levels in many end stage kidney disease patients from native kidney renin production (12). Furthermore, with optimization of oral fluid and salt intake, as is needed early after allotransplantation, volume regulation and blood pressure control may not be major issues in human xenograft recipients but will need to be carefully monitored (9, 12).

The primary immunologic hurdle has been overcome, and xenotransplantation may be rounding that "very long corner" (1). Kidney xenograft physiology requires greater understanding to ensure that functional compatibility with human recipients can be maintained or managed (10). Clinical trials are a suitable next step to move kidney xenotransplantation forward as a solution to the organ shortage. ■

Figure 1. Possible alterations in renal physiology in human renal xenograft recipient



Created with Biorender.com.

A. Cozette Killian, MD, MPH; Paige M. Porrett, MD, PhD; Jayme E. Locke, MD, MPH, FACS, FAST; and Vineeta Kumar, MD, FAST, are with the Comprehensive Transplant Institute, The University of Alabama at Birmingham.

Drs. Killian and Kumar report no conflicts of interest. Drs. Porrett and Locke receive grant salary support from United Therapeutics.

References

1. Cooper DKC, et al. A brief history of clinical xenotransplantation. *Int J Surg* 2015; 23(Pt B):205–210. doi: 10.1016/j.ijsu.2015.06.060
2. Cooper D, et al. Will the pig solve the transplantation backlog? *Annu Rev Med* 2002; 53:133–147. doi: 10.1146/annurev.med.53.082901.103900
3. Sachs DH. The pig as a potential xenograft donor. *Vet Immunol Immunopathol* 1994; 43:185–191. doi: 10.1016/0165-2427(94)90135-x
4. Cooper DKC, et al. The role of genetically engineered pigs in xenotransplantation research. *J Pathol* 2016; 238:288–299. doi: 10.1002/path.4635
5. Porrett PM, et al. First clinical-grade porcine kidney xenotransplant using a human decedent model. *Am J Transplant* 2022; 22:1037–1053. doi: 10.1111/ajt.16930
6. Rabin RC. In a first, man receives a heart from a genetically altered pig. *The New York Times*, January 10, 2022. https://www.nytimes.com/2022/01/10/health/heart-transplant-pig-bennett.html
7. Rabin RC. In a first, surgeons attached a pig kidney to a human, and it worked. *The New York Times*, October 19, 2021. https://www.nytimes.com/2021/10/19/health/kidney-transplant-pig-human.html
8. Wood K, et al. Care of the potential organ donor. *N Engl J Med* 2004; 351:2730–2739. doi: 10.1056/NEJMra013103
9. Iwase H, et al. Physiologic aspects of pig kidney transplantation in nonhuman primates. *Comp Med* 2018; 68:332–340. doi: 10.30802/AALAS-CM-17-000117
10. Hansen-Estruch C, et al. Physiological aspects of pig kidney xenotransplantation and implications for management following transplant. *Xenotransplantation* [published online ahead of print March 16, 2022]. doi: 10.1111/xen.12743; https://onlinelibrary.wiley.com/doi/10.1111/xen.12743
11. Soin B, et al. Physiological aspects of pig-to-primate renal xenotransplantation. *Kidney Int* 2001; 60:1592–1597. doi: 10.1046/j.1523-1755.2001.00973.x
12. Gross E, et al. Effect of spironolactone on blood pressure and the renin-angiotensin-aldosterone system in oligo-anuric hemodialysis patients. *Am J Kidney Dis* 2005; 46:94–101. doi: 10.1053/j.ajkd.2005.03.005

Using Social Determinants of Health Data to Address Racial Disparities in Kidney Transplantation

By Norine W. Chan and Lisa M. McElroy

Structural racism is a root cause of health inequities. The term structural racism refers to differential access by racial group to opportunities, resources, and societal well-being and is mediated through complex health care systems (1). To undergo kidney transplant, patients must navigate a multistep, conditional process that requires multiple health system and clinician interactions. This process exerts a differential burden on patients from marginalized groups. Studies in recent decades have demonstrated that racial minority groups experience lower rates of kidney transplant listing and transplant compared with patients of White race (2, 3). Patients of Black race are four times more likely than patients of White race to have kidney diseases but only half as likely to undergo kidney transplant (3). Even when listing occurs for racial minority groups, these individuals are more likely to be hospitalized while waitlisted, decreasing their overall likelihood of undergoing a transplant (4).

Social determinants of health (SDOH)—social conditions with broad-ranging effects on individuals' health, functioning, and quality of life—have significant impact on kidney transplant outcomes (5). Current data infrastructures for SDOH in transplant, however, are insufficient in quality and accuracy. SDOH data are collected at a basic level across transplant-specific registries, and inclusion of transplant patients in SDOH-focused national databases is limited by population sampling or exclusion criteria (6). Patient-level SDOH data in electronic health records (EHRs) are also poorly standardized, inadequately quality assured, and difficult to extract for analysis due to variability in data entry (7).

As social deprivation is disproportionately concentrated within racial minority groups (1), the absence of expanded SDOH infrastructure leaves kidney care professionals with only a superficial understanding of the root causes of racial disparities among their transplant patients. Race is a unique SDOH, in that it is often used as a proxy for biological differences within clinical decision-making algorithms. Known as race essentialism, these algorithms can promote racial prejudice and perpetuate structural racism in diagnosis and treatment eligibility (8). For example, inclusion of the race coefficient in estimated glomerular filtration rate calculations has historically overestimated kidney function in people of Black race, leading to delayed consideration for transplant referral (9). Efforts to improve equity in access to kidney transplant must mitigate these pitfalls of essentialism through enhanced understanding of how SDOHs mediate specific clinical outcomes. This is an essential prerequisite to development of interventions targeted to root causes of inequities at specific stages of the transplant selection process.

Improving availability and efficacy of SDOH data requires national standards for SDOH data collection, incentives through financial or quality metrics, and research that measures the impact of detailed collection (7). To address racial disparities in kidney transplant, kidney care professionals must be strong advocates for thorough and rigorous expansion of SDOH data infrastructure. Primary care, nephrology, or dialysis clinics are excellent sites for early adoption of EHR strategies for standardized and robust SDOH collection. In these settings, areas of social need for racial minority groups (e.g., lack of insurance, unemployment, and food insecurity) can be rapidly classified and addressed through targeted referral to community resources and care coordination. It is important to incorporate these practices early in the disease course when patients first begin treatment and consider repeated visits to the clinic as opportunities to bridge information gaps in EHRs regarding patients' social environments. If your health system does not currently collect or use expanded SDOH data, become a proponent for policy change by evaluating opportunity within current workflows, partnering with your colleagues on advocacy actions, and meeting with health system leadership to offer perspectives on disparities within your kidney transplant populations.

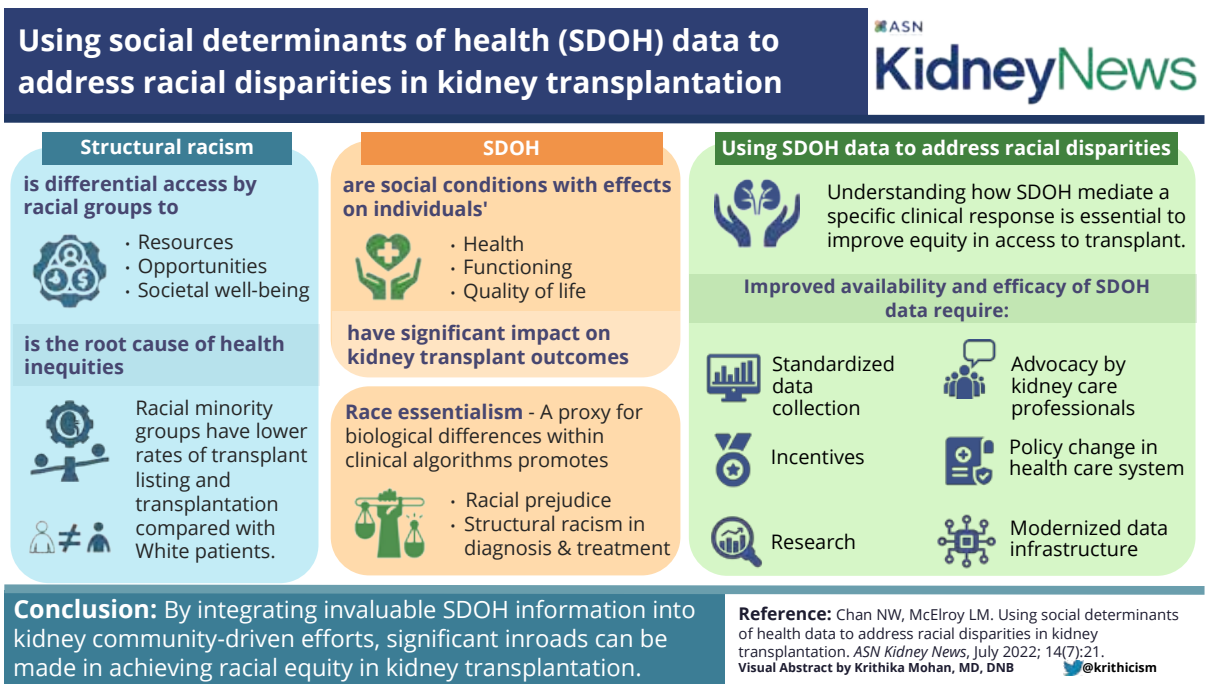
Earlier this year, the National Academies of Sciences, Engineering, and Medicine published a report regarding the establishment of an equitable, transparent, and effective organ allocation system (10). Its recommendations align with our suggestions for improving SDOH data to address racial disparities in transplantation, with a focus on modernizing data infrastructure and standardizing quality improvement. We must be conscientious about the value of early and culturally compassionate kidney transplant education for racial minority groups and deliberate about supporting community-, culture-, and faith-based networks that partner with patients to address social needs (e.g., racial-affinity discussion groups; patient and provider collaboration to lead transplant education workshops; and local resources for housing, transportation, and childcare). By integrating invaluable SDOH information into kidney community-driven efforts, significant inroads can be made in achieving racial equity in kidney transplantation. ■

Norine W. Chan and Lisa M. McElroy, MD, are with the Division of Abdominal Transplant, Department of Surgery, Duke University School of Medicine, Durham, NC.

The authors report no conflicts of interest.

References

1. Gee GC, Hicken MT. Structural racism: The rules and relations of inequity. *Ethn Dis* 2021; 31(Suppl 1):293–300. doi: 10.18865/ed.31.S1.293
2. Ng Y-H, et al. Does racial disparity in kidney transplant waitlisting persist after accounting for social determinants of health? *Transplantation* 2020; 104:1445–1455. doi: 10.1097/TP.0000000000003002
3. Taber DJ, et al. Twenty years of evolving trends in racial disparities for adult kidney transplant recipients. *Kidney Int* 2016; 90:878–887. doi: 10.1016/j.kint.2016.06.029
4. Newman KL, et al. Racial/ethnic differences in the association between hospitalization and kidney transplantation among waitlisted end-stage renal disease patients. *Transplantation* 2016; 100:2735–2745. doi: 10.1097/TP.0000000000001072
5. Wesselman H, et al. Social determinants of health and race disparities in kidney transplant. *Clin J Am Soc Nephrol* 2021; 16:262–274. doi: 10.2215/CJN.04860420
6. Massie AB, et al. Big data in organ transplantation: Registries and administrative claims. *Am J Transplant* 2014; 14:1723–1730. doi: 10.1111/ajt.12777
7. Cantor MN, Thorpe L. Integrating data on social determinants of health into electronic health records. *Health Aff (Millwood)* 2018; 37:585–590. doi: 10.1377/hlthaff.2017.1252
8. Mandalaywala TM, et al. Essentialism promotes racial prejudice by increasing endorsement of social hierarchies. *Soc Psychol Personal Sci* 2017; 9:461–469. doi: 10.1177/1948550617707020
9. Vyas DA, et al. Hidden in plain sight—reconsidering the use of race correction in clinical algorithms. *N Engl J Med* 2020; 383:874–882. doi: 10.1056/NEJMms2004740.
10. National Academies of Sciences, Engineering, and Medicine. Research Council. Realizing the promise of equity in the organ transplantation system. Consensus Study Report. 2022. https://nap.nationalacademies.org/catalog/26364/realizing-the-promise-of-equity-in-the-organ-transplantation-system



Oxalate Nephropathy in Kidney Transplantation

By Sambhavi Krishnamoorthy

Introduction

Oxalate or oxalic acid is a dicarboxylic acid formed in the human body from exogenous dietary sources and endogenous metabolism of ascorbic acid and some amino acids. It is essentially a terminal metabolic product that is produced by the liver, absorbed by the intestine from dietary sources, and freely filtered by the kidneys (Figure 1) (1). There is no human enzyme that can degrade it further.

Hyperoxaluria is divided into two types: primary hyperoxaluria (PH), which results from increased production in the liver, and secondary or enteric hyperoxaluria, due to increased absorption of oxalate in the gut, increased dietary consumption, or decreased metabolism by gut bacteria (Table 1). Individuals with PH have higher oxalate levels for any given glomerular filtration rate compared with enteric hyperoxaluria and stone formers. Similarly, enteric hyperoxaluria also has significantly higher plasma oxalate levels compared with urinary stone formers (2). End stage kidney disease (ESKD), by itself, leads to higher-than-normal oxalate levels, the degree of which depends on frequency and intensity of kidney replacement therapy. Following kidney transplantation, the allograft is exposed to higher plasma oxalate levels, leading to a risk of deposition of calcium oxalate with variable adverse outcomes depending on the clinical scenario. Calcium oxalate crystals in the kidney allograft are observed as transparent crystals, best seen under polarized light (Figure 2) (3).

Case 1

The patient is a 45-year-old female with a history of simultaneous liver-kidney transplant due to alcoholic cirrhosis and hepatorenal syndrome. She underwent gastric bypass surgery 6 years before her transplants. After 1 year of transplantation, she presents with malabsorptive diarrhea and acute kidney injury. An allograft kidney biopsy shows oxalate nephropathy with a serum oxalate level of 77 µmol/L, and she remains dialysis dependent after 4 weeks.

Multiple cases of allograft oxalate nephropathy have been reported in patients with enteric hyperoxaluria. As a part of pre-transplant evaluation, it is important to identify patients with cystic fibrosis, pancreatic insufficiency, bariatric surgery, inflammatory bowel disease, short gut syndrome, or celiac disease who are at risk of fat malabsorption, which leads to increased oxalate absorption. Pre-transplant oxalate levels can help guide changes in diet and intensity of dialysis, leading to a decrease in systemic oxalate load (4). Modification of post-transplant care focused on decreasing the supersaturation of calcium oxalate in the urine, decreasing dietary oxalate, use of calcium-based binders, and intensive dialysis in the setting of delayed graft function (DGF) can lead to successful outcomes (4).

Case 2

The patient is a 39-year-old female with a history of ESKD of unknown etiology. At the age of 2, she developed urinary symptoms, and between the ages of 2 and 5, she had multiple kidney stones. Genetic workup confirms PH type 1. She is approved for simultaneous liver-kidney transplantation. Her preoperative oxalate level is 102 µmol/L.

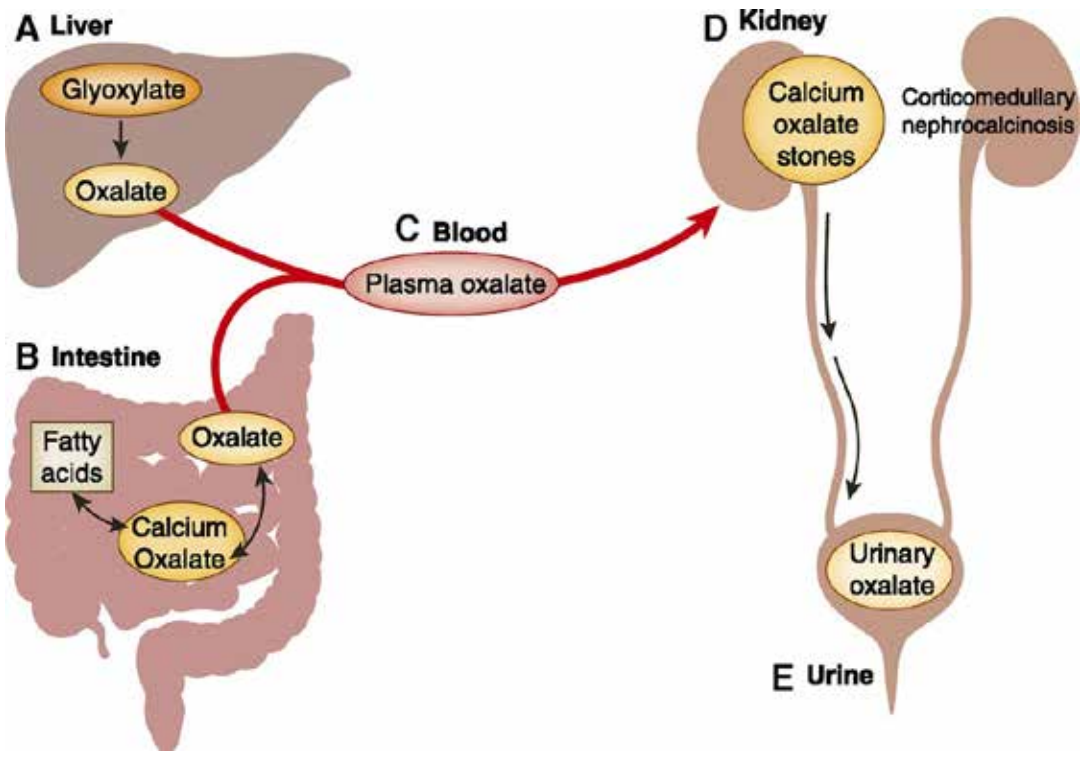
PH is a rare autosomal-recessive disorder that results from one out of three genetic defects in the liver metabolism of glyoxylate or hydroxyproline. Individuals with PH type 1 and type 2 are at a higher risk of developing chronic kidney disease, ESKD, and systemic oxalosis due to higher plasma oxalate levels, whereas PH type 3 causes a milder dysfunction. It is important to screen patients with a childhood history of nephrocalcinosis/nephrolithiasis for these genetic mutations before transplantation. A kidney-alone transplant has a high risk of recurrence of oxalate nephropathy, leading to allograft failure due to the continued overproduction of oxalate by the liver. Only a subset of patients who respond to pyridoxine therapy can undergo successful kidney-alone transplantation. Currently, liver-kidney transplantation is the gold standard of therapy. Even with successful reduction of hepatic oxalate production with transplantation or via use of pyridoxine, recurrent oxalate deposition due to early transient hyperoxaluria from mobilization of systemic stores does occur. Hence, it is important to individualize care posttransplant with intensive dialysis, calcium binders, and volume expansion with monitoring of plasma oxalate levels in these patients for the best long-term outcomes (5). Newly emerging therapies using RNA interference, such as lumasiran, which have shown successful reduction in hyperoxaluria, may eliminate the need for transplantation (6).

Case 3

The patient is a 64-year-old male with a history of ESKD attributed to diabetes mellitus type 2, with recent deceased donor kidney transplantation (DDKT). The patient develops delayed graft function (DGF) without resolution at 4 weeks after DDKT, and allograft is biopsied showing acute tubular injury and calcium oxalate deposition of unclear clinical significance.

Oxalate deposition in kidney allografts with DGF is common, seen in 4%–53% of biopsies, as described in various retrospective studies (7–10). This effect was particularly seen in patients with longer time on dialysis, higher serum creatinine, and diabetes. The presence of calcium oxalate deposition in allografts is also associated with DGF and worse patient outcomes at 5 years posttransplant. Whether calcium oxalate deposition is causative or a marker of allograft dysfunction remains unclear (7). ■

Figure 1. Regional disparity in deceased donor kidney transplant rates



Hepatic metabolism and dietary oxalate absorption generate plasma oxalate, which is then primarily excreted by kidneys into urine. Figure 1 and part of legend are reprinted from Witting et al. (11).

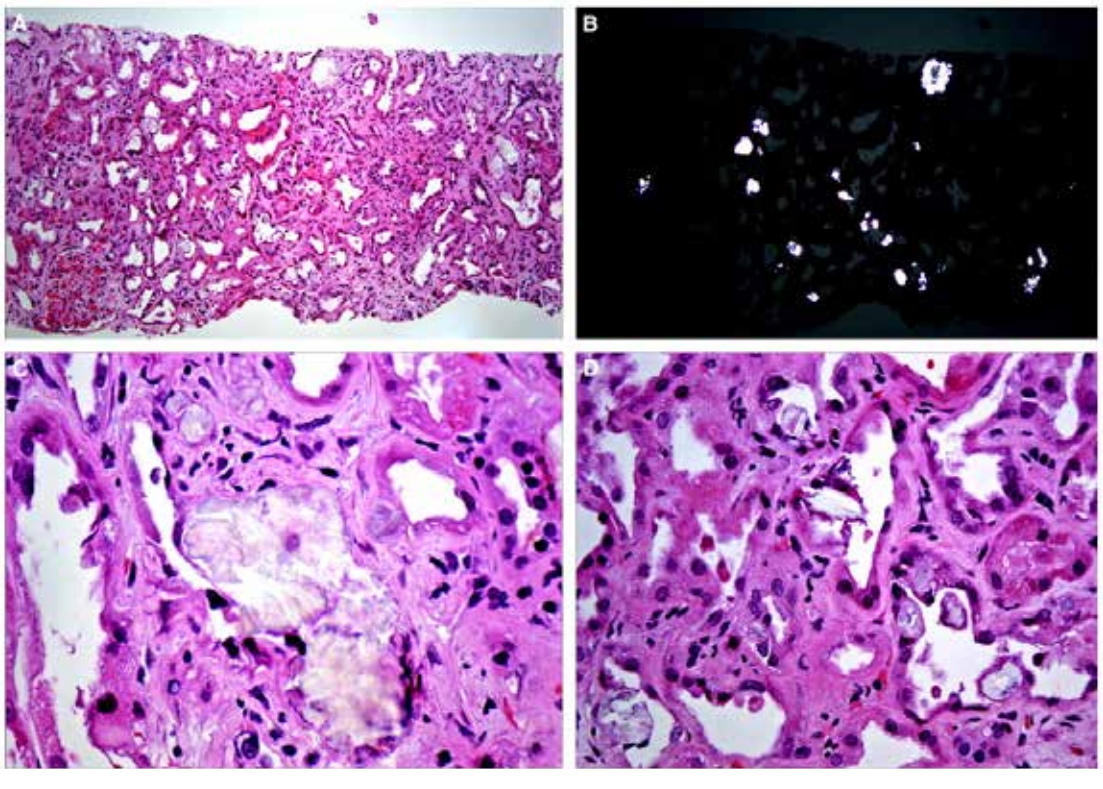
Sambhavi Krishnamoorthy, MD, is with the Division of Nephrology, University of Chicago Biological Sciences Division, Chicago, IL.

The author reports no conflicts of interest.

References

1. Alshaikh AE, Hassan HA. Gut-kidney axis in oxalate homeostasis. *Curr Opin Nephrol Hypertens* 2021; 30:264–274. doi: 10.1097/MNH.0000000000000690
2. Perinpam M, et al. Plasma oxalate in relation to eGFR in patients with primary hyperoxaluria, enteric hyperoxaluria and urinary stone disease. *Clin Biochem* 2017; 50:1014–1019. doi: 10.1016/j.clinbiochem.2017.07.017
3. Nasr SH, et al. Oxalate nephropathy complicating Roux-en-Y gastric bypass: An underrecognized cause of irreversible renal failure. *Clin J Am Soc Nephrol* 2008; 3:1676–1683. doi: 10.2215/CJN.02940608
4. Roodnat JI, et al. A successful approach to kidney transplantation in patients with enteric (secondary) hyperoxaluria. *Transplant Direct* 2017; 3:e331. doi: 10.1097/TXD.0000000000000748
5. Cornell LD, et al. Posttransplant recurrence of calcium oxalate crystals in patients with primary hyperoxaluria: Incidence, risk factors, and effect on renal allograft function. *Am J Transplant* 2022; 22:85–95. doi: 10.1111/ajt.16732
6. Garrelfs SF, et al. Lumasiran, an RNAi therapeutic for primary hyperoxaluria type 1. *N Engl J Med* 2021; 384:1216–1226. doi: 10.1056/NEJMoa2021712
7. Palsson R, et al. The association of calcium oxalate deposition in kidney allografts with graft and patient survival. *Nephrol Dial Transplant* 2021; 36:747. doi: 10.1093/ndt/gfy364 [Erratum to *Nephrol Dial Transplant* 2020; 35:888–894. doi: 10.1093/ndt/gfy271].
8. Truong LD, et al. Calcium oxalate deposition in renal allografts: Morphologic spectrum and clinical implications. *Am J Transplant* 2004; 4:1338–1344. doi: 10.1111/j.1600-6143.2004.00511.x
9. Pinheiro HS, et al. Early presence of calcium oxalate deposition in kidney graft biopsies is associated with poor long-term graft survival. *Am J Transplant* 2005; 5:323–329. doi: 10.1111/j.1600-6143.2004.00684.x
10. Bagnasco SM, et al. Oxalate deposits in biopsies from native and transplanted kidneys, and impact on graft function. *Nephrol Dial Transplant* 2009; 24:1319–1325. doi: 10.1093/ndt/gfn697
11. Witting C, et al. Pathophysiology and treatment of enteric hyperoxaluria. *Clin J Am Soc Nephrol* 2021; 16:487–495. doi: 10.2215/CJN.08000520

Figure 2. Pathologic findings in oxalate nephropathy



(A) A low-power view shows diffuse tubular degenerative changes with numerous intracellular and intraluminal tubular calcium oxalate deposits. A normal-appearing glomerulus also is present (hematoxylin and eosin [H&E]). (B) The same field as (A) is shown under polarized light. The calcium oxalate crystals are more easily identified (H&E). (C) At high magnification, the calcium oxalate deposits form intraluminal translucent crystals (H&E). (D) In this field, the calcium oxalate crystals are smaller and lie within the cytoplasm of the tubular epithelium. Tubules exhibit prominent degenerative changes, including luminal ectasia, cytoplasmic simplification, and loss of brush border (H&E). Original magnifications, ×40 (A and B); ×400 (C and D) (3).

Table 1. Causes of secondary hyperoxaluria

Bariatric surgery
Roux-en-Y gastric bypass
Jejunoileal bypass
Bowel resection/short gut syndrome
Trauma
Crohn's or ulcerative colitis
Mesenteric ischemia
Increased dietary intake
Excess green smoothie/vegetable juicing
Excess cashew nut/cashew apple intake
Excess vitamin C intake
Malabsorption
Pancreatic insufficiency
Cystic fibrosis
Celiac disease

Policy Update

ASN Supports Healthcare Workforce Resilience Act; KidneyX Receives Bipartisan Funding Nod

The US health care workforce is facing a shortage impacting those seeking kidney care. In 2019, the Association of American Medical Colleges projected that demand for physicians will continue to outpace supply, and the United States will see a shortage of up to 122,000 physicians by 2032 (1). Although this threat facing the US health care workforce has been exacerbated by the COVID-19 pandemic, the kidney care workforce is already facing shortage challenges. Just one practicing nephrologist is available for every 3427 people living with kidney diseases in the United States. As a talented and diverse kidney care workforce is vital to the nation's kidney health (nearly one-half of practicing nephrologists are international medical graduates) (2), ASN is advocating for multiple bipartisan and bicameral efforts introduced in the 117th Congress that will alleviate the constraints that the kidney care workforce confronts.

ASN supports the Healthcare Workforce Resilience Act (S. 1024, H.R. 2255), which directs the US Citizenship and Immigration Services to "recapture" previously unused immigrant visas and make them available to nurses and physicians who petition for such a visa before 90 days after the end of the COVID-19 public health emergency (which was renewed on April 12, 2022, and is expected be renewed again this summer). Up to 40,000 visas are available, with 25,000 reserved for nurses and 15,000 for physicians. Certain family members may accompany the principal beneficiary of a visa provided under this bill and will not count against the 40,000 cap. These recaptured visas would also not be subject to "country caps," expanding the qualified applicant pool, as they would be drawn from a pool of unused employment-based visas that Congress has previously authorized. This bill would release the commitment and talent of foreign-born medical professionals across the nation providing needed reinforcements to our health care workers who are on the front lines in the fight against COVID-19 and ensure that kidney care professionals are able to meet the needs of their patients.

ASN also supports the Conrad State 30 and Physician Access Reauthorization Act (S. 948, H.R. 3541), which incentivizes foreign physicians to serve in underserved rural communities. The bill waives the typical requirement—that individuals under a J-1 nonimmigrant visa to receive medical training must leave the country and reside for 2 years abroad before being eligible to apply for an immigrant visa or permanent residence. The waiver is provided if the individual meets certain qualifications, including serving for a number of years at a health care facility in an underserved area. In addition to extending the statutory authority for the program for 3 years upon enactment, the bill allows for the number of waivers that each state may obtain in the next fiscal year (FY) to increase from 30 to 35 if a certain number of waivers were used the previous year.

Congress must ensure that there is a robust pathway for kidney health care professionals and invest in the needs of all Americans living with kidney diseases and kidney failure. These bills would bolster the US health care workforce while addressing the nation's kidney care needs, especially among citizens living in rural areas. Updates on progress made to address the challenges facing the kidney care workforce will be provided in subsequent issues of *Kidney News* and in real time via @ASNAdvocacy on Twitter.

KidneyX Receives Bipartisan Support in the 2023 Funding Cycle

Kidney Innovation Accelerator (KidneyX) continues to receive bipartisan support as lawmakers prepare legislation to fund the federal government in FY 2023. In two letters (3, 4), led by Representatives Suzan DelBene (D-AL), Larry Bucshon (R-IL), Terri Sewell (D-AL), and Neal Dunn (R-FL) in the House and by Senators Ben Cardin (D-MD) and Todd Young (R-IN) in the Senate, congressional champions of KidneyX call for a total of $25 million to be provided for the program in FY 2023.

Citing the past record of success of KidneyX in accelerating innovation, including supporting 67 innovators across five prize competitions since its establishment in 2018, members of Congress note that a full $25 million in funding will allow KidneyX to expand the scale and scope of its Artificial Kidney Prize competition and run competitions in areas such as refining the diagnosis of kidney diseases and developing tools to prevent kidney diseases altogether.

The call for increasing investment in KidneyX comes as negotiations on federal spending for FY 2023 unfold. Facing an election in November, members of Congress are under pressure to continue to address COVID-19, as well as hot-button issues, such as inflation and gun violence. Although final funding levels will reflect these debates, bipartisan support for increased investment in KidneyX is essential for focusing attention on the need for accelerating innovation in kidney health. ■

References

1. Association of American Medical Colleges. New findings confirm predictions on physician shortage. April 23, 2019. https://www.aamc.org/news-insights/press-releases/new-findings-confirm-predictions-physician-shortage
2. Association of American Medical Colleges. Physician specialty data report. Active physicians who are international medical graduates (IMGs) by specialty, 2017. December 2017. https://www.aamc.org/data-reports/workforce/interactive-data/active-physicians-who-are-international-medical-graduates-imgs-specialty-2017
3. DelBene SK, et al. Letter to Chairwoman DeLauro and Ranking Member Cole. Congress of the United States. April 27, 2022. https://www.asn-online.org/policy/webdocs/FY23KidneyXAppropriationsHouse.pdf
4. Cardin BL, et al. Letter to Chair Murray and Ranking Member Blunt. United States Senate. May 25, 2022. https://www.asn-online.org/policy/webdocs/FY23KidneyXAppropriationsSenate.pdf

Improve Adoption of Home Hemodialysis in People with Kidney Failure

By Lori Hartwell

As the health care community looks to home hemodialysis to improve the quality of life and overall management of patients with kidney diseases, all work should start by centering patient experiences and realities. I was diagnosed with kidney failure at the age of 2 in 1968 and luckily fell into the care of pioneer pediatric nephrologist Richard Fine, MD, who saved my life more than once with his innovative spirit. I was the first child to experience peritoneal dialysis in California, and I successfully managed my own home dialysis for 10 years. I have since founded the Renal Support Network (RSN) to empower patients with kidney diseases to become proactive in their care and hopeful about their future. After 13 years of dialysis and now living with my fourth kidney transplant, embracing the right treatment option has been key to my survival.

RSN consistently promotes home dialysis on its website through interviews and podcasts with health care professionals, nephrologists, and patients who are succeeding in this mode of care. The organization's educational materials and support groups start by laying a foundation of realistic assessments and expectations for the full range of treatments, from transplant to home hemodialysis.

The goal laid out by the Centers for Medicare & Medicaid Services (CMS) in the End-Stage Renal Disease (ESRD) Treatment Choices (ETC) payment model is to have 80% of new ESRD beneficiaries dialyze at home or have a transplant by 2025. This is a huge hurdle, as less than 15% of dialysis patients are currently on home dialysis. Patients need to overcome several barriers to be approved for home dialysis, and they should not be approved if they are not prepared to succeed. I have found it very valuable to educate them about the treatment details and help them to gain insights from other patients who are managing well on home hemodialysis and to interact with peers to build confidence so they can manage their care and thrive.

Barriers to home dialysis

Some common barriers to home hemodialysis include lack of space in the home and relational/family assistance, trepidation about self-administering, and resistance to having medical supplies in the home. There are more barriers that arise after patients are at home with equipment and a schedule, such as fear of the unknown, feeling unwell and overwhelmed, and having a low energy level.

Often, people crash into dialysis and do not feel well. It can take time to adjust and feel better as nephrologists help patients stabilize and get their numbers back into an acceptable range. These experiences are all very real, and transitioning patients into managing their own life-saving treatment quickly may prove to be difficult. It is known that depression is very high when one's kidneys fail, and one needs to rely on a machine to live. I often found it hard to self-manage when I was depressed or ill, and during those times, it helped to have a caregiver around to help me.

At RSN, we do not want patients to be placed on home dialysis to check off a box or to be rushed into home dialysis if they just minimally meet the requirements but are not fully committed to their own care. Patients can then end up failing on the treatment. This is not in the spirit of this initiative. Starting *and successfully retaining* people on home dialysis should be the goal.

In the September 2021 issue of *Kidney News*, Innovate Kidney Care suggested changes to CMS Conditions for Coverage and related guidance to lower costs of care and increase adoption of home hemodialysis (1).

I suggest regulations be changed to allow for a paid caregiver or for respite care when needed. This will increase home dialysis numbers. Also, because the bundled payment includes funds for staff, RSN requests a pilot to see if incentivizing patients with a monthly fee or some financial means (e.g., to reduce or waive the Medicare fee) can increase their adoption of home dialysis. Motivating patients with payments will allow them extra funds to get the help or space they need to be successful with home dialysis. A bill, the "Improving Access to Home Dialysis Act," which has been introduced in the US House of Representatives by Reps. Bobby L. Rush (D-IL) and Jason Smith (R-MO) and would provide reimbursements through Medicare, is a step in the right direction.

Home dialysis training and support should be expanded and delivered in a variety of health care settings. If we want the overwhelming majority of new patients with ESRD to receive dialysis at home or via in-center self-care by 2025, then CMS regulations must incentivize service providers to address the physical, social/familial, economic, psychological, and situational barriers to care; provide real incentives for those modalities considered optimal; and increase access to home health care worker visits and/or telehealth.

The following are some of the barriers I have witnessed among my peers regarding home hemodialysis:

- Home environment not sterile enough, large enough, or appropriate for maintenance or storing items
- Anxiety and stress issues of the dialysis process
- Fear of self-cannulation
- Inadequate home wiring or plumbing for use of machine
- Family not trustworthy; worries about damaging or misplacing equipment
- Cost of missing work, for either the patient or caregiver, for training
- No one to help; fear of doing it alone
- Lack of family support or fear of family response to having the illness in the home
- Fear of a serious medical incident
- Physical issues, such as the inability to lift medical equipment, move supplies, and hang bags
- Fear of robbery because needles and medical supplies are in the home
- Fear of burnout or guilt about the time and energy caregivers provide
- Unstable health or cognitive issues
- Homelessness or unstable home situation
- Plan of care is to be transplanted, and catheter placed in abdomen is not a medical recommendation by transplant team.
- Lack of self-confidence/self-discipline in keeping to a treatment regimen
- Insecurity about learning the procedures and executing them properly
- Feeling isolated at home vs. the socialization of a dialysis facility, which reduces anxiety

Many of these obstacles can be overcome. I have recorded success stories and posted them online to encourage our patient community. Education and preparation are critical, and these require personal interaction and support.

When home hemodialysis is still difficult to manage, I recommend an intermediate option: Self-care in-center dialysis could provide many of the advantages of home-based dialysis and remove many of the barriers that prevent patients from choosing to undertake dialysis at home. Self-care in-center dialysis is a real step to help people get more comfortable with caring for themselves, and every avenue should be explored to incentivize this treatment option as well.

Home hemodialysis is a focus now for many reasons. Studies of patients managing home dialysis have shown them to be generally healthier, needing fewer mediations, and requiring much less frequent hospitalization. I have seen that successful home hemodialysis helps people living with kidney diseases to live the life they were meant to live. We all need to work to make this happen. ■

Lori Hartwell is the Founder and President of the Renal Support Network.

Reference

1. Campaign aims to expand home dialysis. *Kidney News* September 2021; 13:21. https://www.asn-online.org/publications/kidneynews/archives/2021/KN_2021_09_sep.pdf

Dialysis Initiation in Patients with Chronic Coronary Artery Disease and Advanced Chronic Kidney Disease in the ISCHEMIA-CKD Trial

By Benjamin Lidgard and Nisha Bansal

In patients with advanced chronic kidney disease (CKD), the decision to pursue invasive strategies for treatment of coronary artery disease involves careful consideration. Data from the International Study of Comparative Health Effectiveness with Medical and Invasive Approaches (ISCHEMIA)-CKD trial may better inform these decisions. The National Heart, Lung, and Blood Institute (NHLBI)-funded ISCHEMIA-CKD trial was a randomized clinical trial that included 777 patients from 30 countries, predominantly in the United States, Russia, Poland, India, and China. Inclusion criteria included aged ≥21 years, kidney failure on maintenance dialysis or estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2, and at least moderate ischemia on a pharmacologic or exercise stress test (1). The trial found no difference in cardiovascular events with a strategy of coronary angiography and revascularization versus conservative goal-directed medical therapy.

A post hoc analysis of a subset of 362 participants in the ISCHEMIA-CKD trial investigated risk of subsequent dialysis initiation in both treatment groups (2). Despite comparable eGFR at randomization, participants in the invasive arm had shorter times to dialysis initiation (6 versus 18 months in the conservative arm), although overall risk of dialysis initiation was equal between groups at a median follow-up of 23 months. There was no statistical difference in rates of post-procedure acute kidney injury (AKI) between the two treatment groups (7.8% vs. 5.4%; p = 0.26), so AKI is an unlikely explanation for these findings. Further work is needed to understand other factors that may explain this association.

The study had several strengths, including study of a trial population. However, some limitations should be acknowledged. Several risk factors for CKD progression, including previous rate of progression, proteinuria, and CKD etiology, were unknown and potentially affected risk of dialysis initiation. Post-procedural follow-up and the decision to initiate dialysis were not protocolized; it is possible, given the non-blinded design, that providers were biased toward early dialysis initiation in participants in the invasive arm.

In summary, findings from the ISCHEMIA-CKD trial provide important new data on cardiovascular procedures in patients with advanced CKD. It will be interesting to see how these findings are translated into clinical care, including counseling patients on the risks versus benefits of cardiovascular procedures, as well as pre-kidney transplant evaluations. ■

Benjamin Lidgard, MD, and Nisha Bansal, MD, MAS, are with the Division of Nephrology, University of Washington, Seattle.

The authors report no conflicts of interest.

The ISCHEMIA-CKD trial was funded by NHLBI grants U01HL117904 and U01HL1179050, and the primary findings were published in April 2020.

Effect of treatment strategies on the timing of dialysis initiation in patients with chronic coronary artery disease and advanced CKD

KidneyNews

ISCHEMIA

ISCHEMIA-CKD
(International Study of Comparative Health Effectiveness with Medical and Invasive Approaches-Chronic Kidney Disease)

Non-dialysis-requiring CKD at baseline n = 362

23 months (IQR 25-175; 14-32 months)

RANDOMIZATION

Coronary disease management strategy on dialysis initiation	Initiated dialysis	Time to dialysis initiation (median) *months*	Procedural AKI
Invasive strategy	18.9%	6 (IQR 3-16)	7.8%
Conservative strategy	16.9%	18.2 (IQR 12.2-25)	5.4%
	p = 0.22	p = 0.004	p = 0.26

Baseline clinical factors associated with earlier dialysis initiation

- 2.08 (1.72-2.56) *p<0.001* — Lower baseline eGFR asso. with a 5-unit decrease
- 2.30 (1.28-4.13) *p=0.005* — Diabetes
- 7.97 (1.09-58.21) *p=0.041* — Hypertension
- 2.34 (1.22-4.47) *p=0.010* — Hispanic ethnicity

Conclusion: In participants with non-dialysis-requiring CKD in ISCHEMIA-CKD, randomization to an invasive chronic coronary artery disease management strategy (relative to a conservative chronic coronary artery disease management strategy) is associated with an accelerated time to initiation of maintenance dialysis for kidney failure. IQR, interquartile range.

Briguori C, et al. Dialysis initiation in patients with chronic coronary disease and advanced chronic kidney disease in ISCHEMIA-CKD. *J Am Heart Assoc* 2022; 11:e022003. doi: 10.1161/JAHA.121.022003

Visual Abstract by Edgar Lerma, MD, FASN

References

1. Bangalore S, et al. Management of coronary disease in patients with advanced kidney disease. *N Engl J Med* 2020; 382:1608–1618. doi: 10.1056/NEJMoa1915925
2. Briguori C, et al. Dialysis initiation in patients with chronic coronary disease and advanced chronic kidney disease in ISCHEMIA-CKD. *J Am Heart Assoc* 2022; 11:e022003. doi: 10.1161/JAHA.121.022003

Findings

Apixaban Reduces Bleeding Risk in Dialysis Patients with Atrial Fibrillation

For dialysis patients with nonvalvular atrial fibrillation (AF), anti-coagulation with apixaban—at both standard and below-label doses—lowers the risk of bleeding events compared with warfarin, concludes a study in the *American Journal of Kidney Diseases*.

Using US Renal Data System data from 2013 to 2018, the researchers identified 17,156 Medicare beneficiaries with nonvalvular AF receiving maintenance hemodialysis. All patients (12,517) had a new prescription for warfarin, and 2382 patients had apixaban at a label-concordant dose of 5 mg twice daily, or 2257 patients had apixaban at a lower dose of 2.5 mg twice daily. Outcomes, including stroke or systemic embolism, major bleeding events, and death from any cause, were compared between apixaban groups. The mean age of patients was 66 years, and 38% of patients were women, 68% were White, and 28% were Black. The percentage receiving warfarin decreased from 86% in 2014 (the year apixaban was approved) to 42% in 2018.

Risk of stroke or systemic embolism was similar across treatment groups: approximately 2 per 100 patient-years with approaches designed to simulate intention-to-treat (ITT) analysis and to incorporate censoring at drug switch or discontinuation (CAS). However, apixaban was associated with a lower rate of major bleeding events. In the ITT analysis, hazard ratios (HRs) were 0.67 with label-concordant dosing and 0.68 with below-label dosing. In the CAS analysis, HRs were 0.53 and 0.562, respectively. Label-concordant apixaban was also associated with lower all-cause mortality: HR was 0.85 with both ITT and CAS analyses. There was no difference in mortality with below-label apixaban versus warfarin.

Nonvalvular AF is common in dialysis patients, and anti-coagulants are prescribed to reduce the risk of stroke. In this group of patients, the direct oral anti-coagulant apixaban is sometimes given at below-label doses to reduce bleeding risks. There are limited data to guide anti-coagulant treatment in dialysis patients with AF.

This analysis suggests that apixaban reduces the risk of major bleeding, compared with warfarin, in dialysis patients with nonvalvular AF. Bleeding risk is similar for label-concordant and below-label dosing, whereas the standard dose appears to be associated with lower mortality. The investigators conclude, "Label-concordant apixaban dosing may therefore provide the best tradeoff of benefits and risks among the treatment approaches assessed" [Wetmore JB, et al. Apixaban dosing patterns versus warfarin in patients with nonvalvular atrial fibrillation receiving dialysis: A retrospective cohort study. *Am J Kidney Dis*, published online ahead of print April 22, 2022. doi: 10.1053/j.ajkd.2022.03.007; https://www.ajkd.org/article/S0272-6386(22)00621-7/fulltext]. ■

Improving Our Understanding of Long-Term Kidney Outcomes after Allogeneic Stem Cell Transplant

By Matthew Abramson and Priya Deshpande

Although allogeneic hematopoietic stem cell transplant (HSCT) is the curative treatment for many patients with hematologic conditions, these patients are at a higher risk of acute kidney injury (AKI) and chronic kidney disease (CKD) as a result of conditioning therapies, exposure to radiation therapy, and chronic treatment with calcineurin inhibitors (Figure 1). CKD and albuminuria increase the risk of hypertension and end stage kidney disease, which ultimately impact mortality (1, 2). Many studies have evaluated the incidence of CKD post-HSCT, and the incidence of CKD ranges from 4% to 66% (3–9). However, some studies have yielded conflicting results regarding overall mortality in patients who develop CKD after HSCT (10–12). In a recent article in the *Clinical Kidney Journal*, Pelletier et al. (6) sought to determine the prevalence and risk factors for developing CKD and assess the impact of CKD on 1-year overall survival, relapse-free survival (RFS), transplant-related mortality (TRM), relapse risk, and graft-versus-host disease (GVHD)-free/RFS (GRFS) in a retrospective single-center analysis of 408 adults with hematologic malignancies who underwent HSCT in Toronto, Ontario, Canada.

Pelletier et al. (6) found that 64% of patients developed AKI (defined and staged based on the Kidney Disease Improving Global Outcomes) at 100 days post-HSCT. Nine percent of patients developed CKD (defined using the CKD-Epidemiology Collaboration equation by an estimated glomerular filtration rate of <60 mL/min/1.73 m^2) 100 days post-HSCT. Nineteen percent of patients developed CKD 1 year post-HSCT. Patients who developed CKD at 1 year experienced AKI within 100 days of transplant, were older, and were female. The patients who developed CKD after 1 year had a twofold increase in mortality as compared with patients who did not, even after adjustment for covariates. CKD at 1 year was associated with worse GRFS but had no effect on RFS, TRM, and relapse risk.

This study highlights the need for a multidisciplinary approach between the oncology and nephrology teams to care for HSCT patients, particularly those who are at higher risk for developing CKD. In the right clinical context, these patients may benefit from renin-angiotensin aldosterone system blockade (13–15). ■

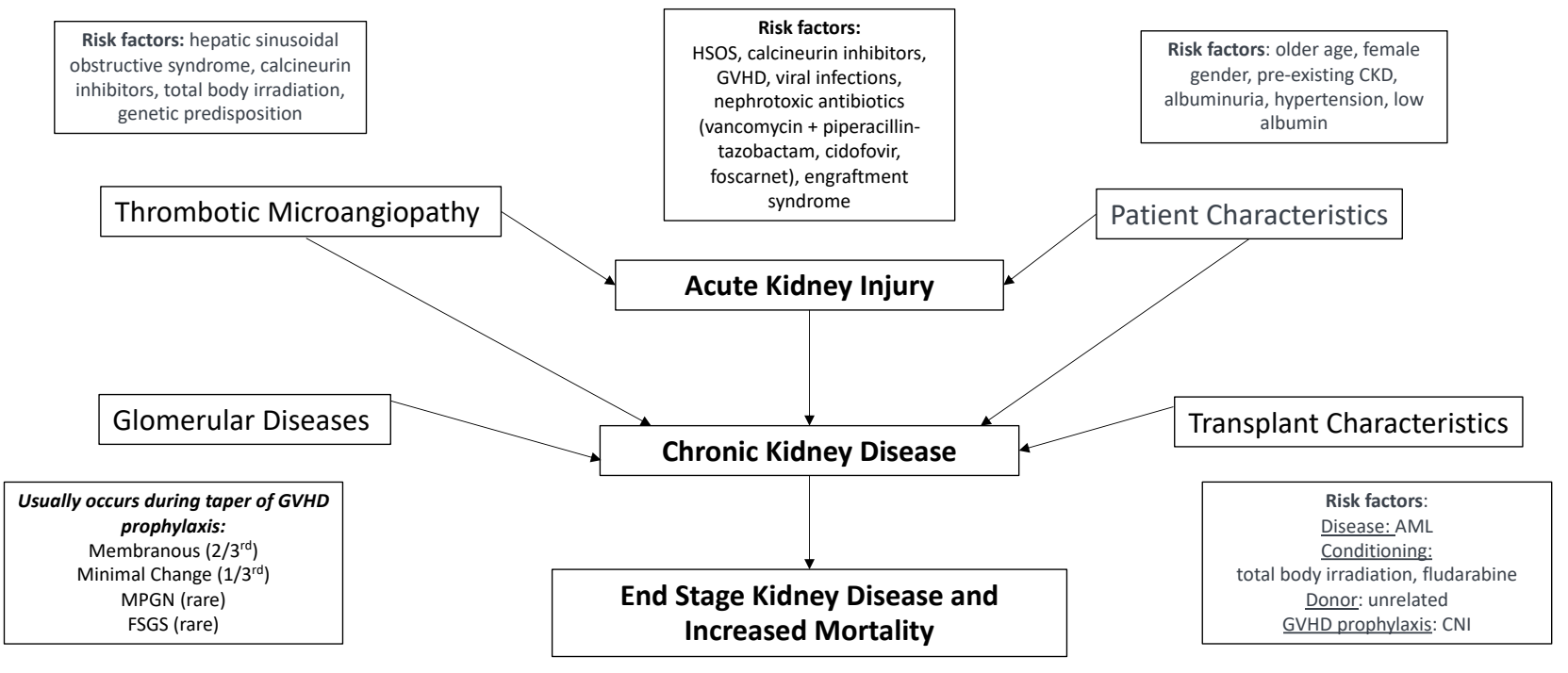
Matthew Abramson, MD, and Priya Deshpande, MD, are with the Division of Nephrology, Icahn School of Medicine at Mount Sinai, New York, NY.

The authors report no conflicts of interest.

References

1. Cockwell P, Fisher L-A. The global burden of chronic kidney disease. *Lancet* 2020; 395:662–664. doi: 10.1016/S0140-6736(19)32977-0
2. Hingorani S, et al. Urinary cytokines after HCT: Evidence for renal inflammation in the pathogenesis of proteinuria and kidney disease. *Bone Marrow Transplant* 2014; 49:403–409. doi: 10.1038/bmt.2013.197
3. Zhou W, et al. Long-term renal outcome after allogeneic hemopoietic stem cell transplant: A comprehensive analysis of risk factors in an Asian patient population. *Clin Transplant* 2017; 31:e12920. doi: 10.1111/ctr.12920
4. Weiss AS, et al. Chronic kidney disease following non-myeloablative hematopoietic cell transplantation. *Am J Transplant* 2006; 6:89–94. doi: 10.1111/j.1600-6143.2005.01131.x
5. Saddadi F, et al. Chronic kidney disease after hematopoietic cell transplantation: Frequency, risk factors, and outcomes. *Transplant Proc* 2009; 41:2895–2897. doi: 10.1016/j.transproceed.2009.07.093
6. Pelletier K, et al. Chronic kidney disease, survival and graft-versus-host-disease/relapse-free survival in recipients of allogeneic hematopoetic stem cell transplant. *Clin Kidney J* [published online April 7, 2022]. https://academic.oup.com/ckj/advance-article/doi/10.1093/ckj/sfac091/6564752?login=false
7. Ellis MJ, et al. Chronic kidney disease after hematopoietic cell transplantation: A systematic review. *Am J Transplant* 2008; 8:2378–2390. doi: 10.1111/j.1600-6143.2008.02408.x
8. Ando M, et al. Chronic kidney disease in long-term survivors of myeloablative allogeneic haematopoietic cell transplantation: Prevalence and risk factors. *Nephrol Dial Transplant* 2010; 25:278–282. doi: 10.1093/ndt/gfp485
9. Abramson MH, et al. Acute kidney injury in the modern era of allogeneic hematopoietic stem cell transplantation. *Clin J Am Soc Nephrol* 2021; 16:1318–1327. doi: 10.2215/CJN.19801220
10. Jo T, et al. Chronic kidney disease in long-term survivors after allogeneic hematopoietic stem cell transplantation: Retrospective analysis at a single institute. *Biol Blood Marrow Transplant* 2017; 23:2159–2165. doi: 10.1016/j.bbmt.2017.08.016
11. Touzot M, et al. Long-term renal function after allogenic haematopoietic stem cell transplantation in adult patients: A single-centre study. *Nephrol Dial Transplant* 2010; 25:624–627. doi: 10.1093/ndt/gfp529
12. Hingorani S, et al. Changes in glomerular filtration rate and impact on long-term survival among adults after hematopoietic cell transplantation: A prospective cohort study. *Clin J Am Soc Nephrol* 2018; 13:866–873. doi: 10.2215/CJN.10630917
13. Sedhom R, et al. Mini-review of kidney disease following hematopoietic stem cell transplant. *Clin Nephrol* 2018; 89:389–402. doi: 10.5414/CN109276
14. Osugi Y, et al. Treatment with candesartan combined with angiotensin-converting enzyme inhibitor for immunosuppressive treatment-resistant nephrotic syndrome after allogeneic stem cell transplantation. *Int J Hematol* 2006; 83:454–458. doi: 10.1532/IJH97.05183
15. Abboud I, et al. Chronic kidney diseases in long-term survivors after allogeneic hematopoietic stem cell transplantation: Monitoring and management guidelines. *Semin Hematol* 2012; 49:73–82. doi: 10.1053/j.seminhematol.2011.10.008

Figure 1. The interrelationship of patient-related and disease-related risk factors causing AKI and CKD in HSCT patients



AML, angiomyolipoma; CNI, calcineurin inhibitor; FSGS, focal segmental glomerulosclerosis; HSOS, hepatic sinusoidal obstruction syndrome; MPGN, membranoproliferative glomerulonephritis.

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

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

KidneyNews

Free Subscriber Service Request Card

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

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

Name

Address

City State Zip

Telephone Fax

Email Address

Signature Date

Title/Position

- ☐ Physician
- ☐ Researcher
- ☐ RN, CNN, NM, LPN, APN, PA
- ☐ Dialysis Center Director
- ☐ Administration
- ☐ Clinic Manager/Coordinator
- ☐ Social Work
- ☐ Other

Specialty Area

- ☐ General Nephrology
- ☐ Transplantation
- ☐ Dialysis
- ☐ Laboratory
- ☐ Other

Institution

- ☐ Hospital <100 beds
- ☐ Hospital 100-250 beds
- ☐ Hospital 251-500 beds
- ☐ Hospital > 500 beds
- ☐ Dialysis Center
- ☐ Clinical Lab
- ☐ Other

Please Circle Degree:

MD MD/PhD DO
PhD MBA RN MS
BS Other_____

ASN American Society of Nephrology

Return the completed form to:
Bob Henkel, 1401 H Street NW, #900, Washington, DC 20005
or Fax: 202-403-3615 or Email: bhenkel@asn-online.org

Index to Advertisers

Amgen . . . . . Pages 13–15
Baxter . . . . . Page 11
Horizon . . . . . Pages 2–5
Outset Medical . . . . . Page 7

BRCU
Board Review Course & Update

Face the Boards with Confidence

JUL. 31 – AUG. 2, 2022
Fairmont Chicago, Millennium Park

Time is running out for you to register for ASN's Board Review Couse & Update (BRUC). During this three-day in-person course, you will explore case discussions, interactive quizzes and games, and challenging "ask the professor" sessions. Taught by leading experts in the field, this course will reinforce key nephrology concepts while preparing you for the American Board of Internal Medicine (ABIM) nephrology certification and recertification exams.

Register today at www.asn-online.org/brcu

BRCU Highlights:

- Exam-focused curricula, patterned after the ABIM nephrology blueprint.
- Opportunity to interact with expert faculty.
- Interactive case-based studies and games.
- Complimentary access to all on-demand lectures in early July to jump start your preparation.
- Course ebooks and flashcards to continue study beyond the course.
- Access to course content for three years.
- Online practice questions with approximately 300 case-based, board-style questions.
- Up to an estimated 65.5 CME Credits and MOC Points.
- Central location in downtown Chicago.
- BRCU Study Pearls emailed to you weeks leading up to the ABIM exam in November.